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ABSTRACT BOOK



FROM EVIDENCE *to* ACTION

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SMALL-SCALE RELEASE OF NON-GENE DRIVE MOSQUITOES IN BURKINA FASO: FROM ENGAGEMENT IMPLEMENTATION TO ASSESSMENT, A LEARNING JOURNEY

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Innovative tools are needed to complement the existing approach for malaria elimination. Gene drive mosquitoes are one potential new technology in the control of malaria vectors. Target Malaria is one of the research projects developing this technology, and in July 2019, the project proceeded to an important step for this evaluation pathway: the small-scale release of non-gene drive sterile male mosquitoes in a village in Burkina Faso. In addition to the entomological and laboratory work to prepare for this important milestone, significant community and stakeholder engagement work was done. This study provides a review of engagement activities relevant to field trials on non-gene drive genetically-modified mosquitoes as well as an assessment framework—using both qualitative and quantitative studies as well as an audit procedure. The latter was implemented to evaluate whether the release activities could proceed with the appropriate level of agreement from the community. This paper shows the importance of this first phase of work to innovate and learn about engagement processes for responsible research in the field of genetic approaches for malaria vector control. The function of these assessments is crucial for the learning agenda. The assessments demonstrated ways to increase understanding and ensure effective progress with field studies and, therefore, the pathway for responsible research. In conclusion, gene driven technology is increasingly considered as a promising approach to control vector borne diseases, in particular malaria. Stakeholders' involvement in this research process is one of the recurring requirements in international guidance documents. With this paper Target Malaria offers an opportunity to explore the practical achievements and challenges of stakeholder engagement during early phases of a technology evaluation, and in particular how it implemented an assessment framework to learn from its experience.

5001

ACCELERATING MALARIA ELIMINATION IN CAMBODIA: ANALYSIS OF IMPACT OF THE"LAST MILE" INTENSIFICATION PLAN

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The Greater Mekong Subregion countries are preparing to enter the final phase of malaria elimination. To maintain this momentum, more nuanced, and targeted approaches are required. Cambodia's National Center for Parasitology, Entomology, and Malaria Control (CNM) and partners are implementing an intensification plan called the "last mile" strategy to accelerate progress. This comprises a focalized aggressive set of interventions including house-to-house fever screening (AFS), targeted bed and hammock net distribution, chemoprophylaxis of forest goers (IPTf) and target drug administrative (TDA). Implementation is supported by village and mobile malaria workers and health centres with outreach to remote communities. Analysis of routine malaria data was done to measure the impact of the last mile strategy and guide future plans. From 25th December 2020 to 1st March 2023, last mile had been implemented in 123 villages (population 75,195). Village mean and median malaria annual parasite index (API) during the 12 months prior to implementation were 1.075 and 0.258 (IQR: 0, 0.036), respectively. In the 12 months after the intervention, these were 0.178 and 0 (IQR: 0, 0). The paired difference of the village median APIs was compared using the Wilcoxon signed-rank test giving a p-value of < 0.0001. To compare the declining rates, an interrupted time series analysis was performed using segmented regression. Before the last mile implementation, mean and median declining incidence rate ratio were -0.106 and -0.114 (IQR: -0.152, -0.061), respectively, compared to -0.503 and -0.547 (IQR: -0.576, -0.511) after the intervention, p < 0.0001. Overall cases in these villages decreased by 52% from 1806 in 2020 to 863 in 2022, despite the number of malaria tests performed remaining steady. The reduction in cases was even higher among mobile populations at 59%. Although this initial result suggests the last mile intervention significantly reduced malaria cases in implementation villages, implementation is ongoing and the final analysis will be presented. Lessons learned and implications for other countries aiming for elimination will be discussed.

5002

MALARIA TREND AND IDENTIFICATION OF RISK GROUPS IN AN ELIMINATION SETTING, 2019-2022

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Zanzibar has achieved significant progress in reducing malaria transmission over the past fifteen years; however, elimination has not yet been achieved. In elimination settings, malaria infections tend to occur in older age groups and cluster in certain households and subpopulations. The latter clustering is often related to certain risk factors, such as occupation or mobility, which place these individuals at higher risk of malaria infection relative to others. We extracted malaria surveillance data from 2019-2022 available in the Coconut system (Zanzibar malaria surveillance system) to assess malaria case trends over time and identify risk factors across sub-populations using logistic regression to inform development of a Reactive Drug Administration (RDA) strategy in Zanzibar. Malaria cases recorded in the Coconut system were identified passively through microscopy or malaria Rapid Diagnostic Test (mRDT) at the health facility or through the subsequent mRDT testing at household level as part of routine Reactive Case Detection. There was a notable decrease (62.2%) in malaria cases from 11,613 cases in 2019 to 4,389 cases in 2022. Overall, 60% of cases were classified as imported throughout the years. Districts with a high proportion of local cases were Micheweni (45%), Mjini (33%), Wete (30%), and Magharibi B (30%). In all years, a high risk of malaria was seen in males compared to female [OR=1.6; 95% CI 1.5-1.7] and in individuals aged 15-45 years compared to those below 15 years [OR=2.1; 95% CI 1.9-2.1]. Since the 15-45 years age group is the working class in most communities, the findings suggest there may be behavioral or occupational exposure such as being fishermen, night watchmen, and students that are associated with malaria transmission outside of the household. A further investigation to better characterize the high-risk populations, including occupational risks and social behaviors, is recommended to guide the deployment of appropriate interventions, such as RDA and targeted vector control in this elimination setting.

5003

EFFECTIVENESS OF THE EXPANDED ROLE OF COMMUNITY HEALTH WORKERS IN MALARIA ELIMINATION IN MYANMAR: AN OPEN STEPPED-WEDGE CLUSTER-RANDOMISED CONTROLLED TRIAL

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The network of malaria volunteers in the Greater Mekong Subregion have significantly contributed to progress towards the goal of malaria elimination by 2030. As Mekong countries approach malaria elimination, the motivation and social role of malaria volunteers, and malaria testing rates, have declined in parallel with decreasing malaria burden. To address this issue, the Community-delivered Integrated Malaria Elimination (CIME) model was developed from an evidence-base and field-tested in Myanmar to evaluate its effectiveness and cost-effectiveness. An open stepped-wedge cluster-randomised controlled trial randomised at the village level was conducted in 72 villages in Yangon Region from 1 November 2021 to 17 April 2022 (24 weeks) to evaluate the CIME model that integrates services for malaria, dengue, tuberculosis, childhood diarrhoea and non-malaria fever compared to the existing malaria volunteer model. One-off and continuous implementation costs of the Models were calculated. Compared to the existing integrated malaria volunteer model, a 23% relative increase in village rapid diagnostic testing for malaria after the introduction of the CIME model was observed in both *intention-to-treat* (adjusted incidence rate ratio = 1.23, 95%CI = 1.01, 1.50, p= 0.036) and *as-treated* analyses (adjusted incidence rate ratio = 1.23, 95%CI = 1.01, 1.49, p=0.042), adjusting for time and season. Among the 2,540 visits suspected of dengue, tuberculosis, childhood diarrhoea and febrile illness, the CIME volunteers provided initial treatment and referral services to 12% (307/2,540) of them. The total cost per volunteer per one-, three- and five-year period was USD 2,992 USD 8,893 and USD 14,794 respectively for the CIME model, and USD 1,168 USD 3,492 and USD 5,816 respectively for the existing malaria volunteer model. Although the CIME model is associated with additional costs for providing health services for common tropical diseases, it is effective in increasing the annual blood examination rate required for malaria elimination accreditation compared to the existing malaria volunteer model.

5004

MALARIA CASE-BASED SURVEILLANCE FOR THE INTERRUPTION OF LOCAL MALARIA TRANSMISSION IN TANZANIA MAINLAND

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Tanzania mainland is implementing the 2021- 2025 National Malaria Strategic plan. This is hand in hand with the stratification of sub-national levels in malaria risk strata and the introduction of tailored intervention according to epidemiolocal risk strata as suggested by the Global Technical Strategy (GTS) for malaria 2016-2030. Malaria Case-Based Surveillance (mCBS) is among interventions in councils with very low malaria transmission risk and aims to interrupt malaria transmission contributing to the local elimination of malaria in active foci. The implementation is organized according to Health facilities' malaria disease burden defined as confirmed malaria cases diagnosed per month per health facility. Malaria Case Based Surveillance is implemented in Arusha, Iringa, Kilimanjaro, Manyara, and Njombe regions. There are six steps in conducting mCBS triggered by the passive detection of a malaria case at a health facility. This involves passive case detection, case classification, and notification, case follow-up and reactive case detection, proactive case detection, focus identification and classification, focus investigation, and focus response. All steps are done by trained healthcare workers and Region/Council Health Management Teams using the mCBS protocol under the guidance of the National Malaria Control Programme. A total of 5,250 passive cases were detected at both the private and public health facilities in Arusha 2,806 cases, Kilimanjaro 1,173 cases, Njombe 309 cases, and Manyara 962 cases. Among these detected passive cases 2,149 were classified as local cases (diagnosed within the same council where transmission occurred) and 3,101 were classified as imported cases (diagnosed in a council where transmission did not occur). Most of the local cases were from peasants, children, pastoralists, and infants. All local passive cases were followed up, 1647 were tested and only 65 cases (3.9%) tested positive and were treated. Malaria Case Based Surveillance is pivotal in the detection of asymptomatic cases that are missed at health facilities and provides a better understanding of risk factors in transmission foci.

5005

ENHANCED ACTIVE CASE DETECTION TO ELIMINATE MALARIA IN YALA PROVINCE, THAILAND

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Thailand's malaria elimination strategy includes several active case detection (ACD) methods, both proactive and reactive. In Yala Province, where there is intermittent civil unrest, malaria cases declined from 1,592 in fiscal year 2015 (FY15) to 57 in FY22. In FY16, following a successful pilot project among military personnel, local authorities expanded ACD to include civilian populations, relying on community health workers to navigate the unique context. This study used routine surveillance data to examine ACD yield (i.e., confirmed cases among total screened) and trends among all 821,334 blood draws and 14,855 confirmed cases in Yala from FY15-FY22. T-tests were run for mean differences, and spatial trends were assessed using intercept-only generalized linear regression models. Over the study period, ACD screenings represented 58.3% of all blood draws in Yala (compared to 74.1% nationally). Among 478,708 ACD blood draws, 1,328 cases were detected, representing a yield of 0.28% (range 0.01%-0.92%, compared to 0.07% nationally). In FY18, local authorities replaced other proactive methods with special case detection (SCD), which used a small team to screen every village member, in an effort to reduce costs and optimize ACD. As a result, SCD screenings increased from 1,769 in FY17 to 15,546 in FY18; however, SCD yield significantly decreased from 0.73% in FY17 to 0.10% in FY18 and down to 0.01% by FY22 ($p < 0.05$). Yield for reactive case detection was higher in the first 6 years compared to the last two years (0.39% compared to 0.004%, $p < 0.05$), consistent with declining malaria incidence. Geospatial results showed that subdistricts with higher ACD yield clustered in the center of the province. Although ACD yield in Yala is higher than elsewhere in Thailand, these results show that there is an opportunity to further refine targeting and methods to make efficient use of resources. Epidemiological data could help quantitatively define high-risk populations and areas. Thailand plans to use these results and further analyses to develop standard operating procedures to accelerate malaria elimination among these at-risk populations in Yala.

5006

A PROGRAM EVALUATION OF REACTIVE FOCAL DRUG ADMINISTRATION IN NORTHERN SENEGAL

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In 2016, Senegal's Programme National de Lutte contre le Paludisme began conducting reactive focal drug administration (rFDA), the presumptive treatment of index case compound members, in 10 low transmission districts. This controlled interrupted time-series analysis used routine surveillance data from 2015 to 2020 to estimate the impact of rFDA on passively detected malaria case incidence in 157 health facility catchment areas (HFCAs) receiving rFDA with > 60% coverage. Ninety-four HFCAs receiving the standard intervention package were used as a comparator, and 2015 through 2016 taken as baseline. Negative binomial regression models were stratified by transmission intensity and time period and adjusted for rainfall, vegetation index, temperature, month, urbanicity, outpatient visits, community health worker density, and bednet and indoor residual spraying coverage. Among facilities with baseline annualized incidence rates of < 10 cases per 1,000 population and high intervention coverage through 2020, incidence rates were similar across groups (IRR = 0.97, 95% BCI = 0.67, 1.42), as were monthly declines in incidence rates (IRR = 1.00, 95% BCI = 0.98, 1.42) following rFDA roll-out, possibly reflecting the prevailing impact of universal bednet distributions in 2016 and 2019. In contrast, from roll-out through September 2018, incidence rates were estimated to be 36% lower in areas receiving rFDA (IRR = 0.64, 95% BCI = 0.45, 0.91), with a 3% greater decline in slope each month in rFDA areas than in control areas compared to baseline (IRR = 0.97, 95% BCI = 0.94, 1.00). Among facilities with baseline incidence rates of ≥ 10 cases per 1,000 population, incidence rates were not statistically significantly different between rFDA and comparison groups (IRR = 0.77, 95% BCI = 0.48, 1.24) from roll-out through September 2018, when intervention coverage remained high, nor were monthly declines in incidence rates (IRR = 0.97, 95% BCI = 0.93, 1.01). RFDA was not associated with sustained, lower incidence rates compared to the standard intervention package; however, the use of incomplete routine surveillance data may have influenced these findings.

5007

PREGNANT WOMEN EXCLUSION IN CLINICAL TRIALS FOR MALARIA, TUBERCULOSIS, AND COVID-19: A REVIEW OF TRIAL REGISTRY DATA

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Clinical trials are critical in establishing the safety, efficacy, dosing, and target population of new interventions, yet they often exclude pregnant women. The extent of exclusion of pregnant women in clinical trials is not well-described. This systematic review aimed to describe the extent of exclusion of pregnant women in clinical trials for malaria, tuberculosis, and COVID-19 vaccine. We searched clinicaltrials.gov for trials targeting adult females for malaria, tuberculosis, and COVID-19 vaccine between the years 2000 and 2021. We conducted separate searches for each condition and performed descriptive analysis to report the proportion of studies that included pregnant women. We also examined and reported the clinical development pathway (trial phases). As of December 18, 2021, clinicaltrials.gov listed 399,532 studies, of which 1,173 met our search criteria. Of these, 1,116 studies verified pregnancy criteria and were eligible. 95% (1,064) of the eligible studies excluded pregnant women. Of the 52 (5%) that included pregnant women, 90% (47) were specifically pregnancy trials. Among them, 65% (34) were Phase III, 10% Phase II/III, 10% Phase II, 12% Phase I, and 4% Phase I/II. A total of 45 malaria, 5 TB, and 2 COVID-19 vaccine trials included pregnant women. Our findings confirmed a high exclusion of pregnant women from the clinical product development pathway. This is attributed to the protectionist ethic. However, we argue for an urgent paradigm shift to more inclusion as exclusion prevents the collection of data that informs assessments of safety, efficacy, and therapeutic dosage, thereby precluding adequate information for informed decision-making in pregnancy. It is crucial to tip the clinical development pathway in favor of pregnant women to ensure their safety and provide better therapeutic options.

5008

NODDING SYNDROME CLINICAL CHARACTERISTICS, RISKS FACTORS, ACCESS TO TREATMENT, AND PERCEPTIONS IN GREATER MUNDRI AREA, SOUTH SUDAN

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Nodding syndrome (NS) is a neurodegenerative disease of unknown etiology, affecting poor people in Tanzania, South Sudan, Uganda, the Democratic Republic of Congo, Cameroon, and the Central African Republic. It presents with head nodding and other seizures; often associated with debilitating complications, including impaired cognitive and physical development and delayed sexual maturity. Previous attempts to identify a potential cause have focused on infections, nutrition, toxins, autoimmunity, hormonal and metabolic derangements, and genetic factors, but all were inconclusive. Control of onchocerciasis and its vector, the blackfly, by community-directed treatment with ivermectin and larviciding of rivers were proposed to prevent new cases. However, certain communities in the affected areas believe that NS is transmitted from person-to-person and thus can be prevented by isolation of cases from other family members or peers. To further unravel the many unknowns of NS, we conducted a house-to-house survey and case-control studies in Mundri County, South Sudan to investigate the clinical characteristics, risk factors, access to treatment and perceptions about NS. In total, 224 cases with median age of seizure onset 10 years were identified. Head nodding only was reported in 22.3%, and head nodding plus other types of seizures in 77.7% cases. Wasting, stunted growth, delayed sexual development and speech and behavioural abnormalities were observed in 23.6%, 22.2%, 17.3%, 19.4% and 5.6% cases, respectively. The consumption of rat-meat, but not other bushmeat was associated with an increased risk of NS (OR 9.31, 95% CI 1.27–406.51). Cases were more likely to have taken ivermectin in the last 5 years (OR 2.40, 95% CI 1.33–4.43), and were less likely to share a bedroom with other children (OR 0.06, 95% CI 0.02–0.16) or adults (OR 0.27, 95% CI 0.13 0.56). In conclusion, rat-meat consumption is an unlikely risk factor for NS, and ivermectin intake was more common among NS cases than controls. Importantly, we documented that children with NS are stigmatized because of the misconception that NS is transmitted through direct contact.

5009

DIABETES-ASSOCIATED MAJOR LIMB AMPUTATION IN SOLOMON ISLANDS: EPIDEMIOLOGICAL CHARACTERISTICS AND CLINICAL MANAGEMENT

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Solomon Islands is classified as a UN "Least Developed Country" and faces the 9th highest prevalence of diabetes globally. Limited resources, poor infrastructure, and challenging geography make medical and surgical delivery difficult. This retrospective study aims to describe the characteristics and clinical management of patients undergoing diabetes-associated major limb amputation. It is the first study on major limb amputation in Solomon Islands. Demographic and clinical data was abstracted from charts belonging to patients with diabetic ulcers who underwent major limb amputation at four surgical centers. Summary statistics were gathered from this dataset. Over a 5-year period (2018-2023), 338 adults underwent major limb amputation secondary to diabetes-associated infections. Of these, 285 patients had medical records available for data abstraction. The median age for these patients was 55 years (range: 18-83), 50.5% (N=144) were male. The most common known cause of initial ulceration was general trauma (N=93). The second most common cause was rat bites (N=15). The mean Wagner's classification score was 3.59. 97.5% (N=278) of patients experienced delay in accessing amputation. Late presentation was also common with 33% (N=93) waited 30 or days before seeking medical attention. Blood sugar levels were controlled in only 1.4% (N=4) of patients during hospital stay. The mean wait time between recommendation of amputation and operation was 7 days (range: 0-86). Among all patients who underwent major limb amputation, 12% (N=41) died prior to discharge. In conclusion, major limb amputation is a costly and radical procedure which contributes to severe disability in the local context. Earlier presentation, effective diagnosis of foot/limb infection, aggressive management of infection, and earlier access to surgical care are likely to prevent limb loss. This research shows the importance of investing in diabetes prevention to prevent downstream complications. Future research should investigate locally modified and sustainable methods to improve limb salvage and preventative foot care.

5010

LEVERAGING PARTICIPATORY MAPPING AND FINE-SCALE GEOSPATIAL ANALYSES TO OPTIMIZE COMMUNITY-BASED HEALTHCARE PROGRAMS AND POLICIES

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In rural communities, where geography is often the main barrier to access primary healthcare, community health workers (CHWs) provide essential primary health services. Sophisticated geospatial data and analyses are transforming health systems; however, these approaches are rarely developed to serve community health programs and policies. As an integral part of the public health system, there is a critical need to develop evidence-based decision making tools (e.g data dashboards, hotspot mapping, and precision health) at local scales relevant for community health programs. A set of high-resolution geospatial data, analyses and decision-making tools are being integrated into community health programs in Ifanadiana, a rural district of Madagascar. The backbone of this initiative was the collection of high-quality geospatial data for the district via participatory mapping in OpenStreetMap, resulting in the mapping of over 100,000 buildings and 20,000 km of footpaths. This data enabled us to accurately estimate field-derived travel times to primary care facilities for each household in the district and identify geographic distance as a major barrier to primary care use. We then demonstrated that geographic barriers persist at the community health level and we developed a spatial algorithm to optimize the location of community health sites within each CHW catchment, the results of which are embedded in an online data dashboard. Finally, we are using this dataset to optimize the planning and implementation of proactive CHW programs, estimating optimal routes for CHWs to visit every household in a catchment, contributing towards universal access to healthcare. All of these geospatial analyses are publicly available as e-health tools to guide programs. Our work highlights how high-resolution geospatial analyses can be integrated into existing community health programs to address spatial inequalities and barriers to achieving universal health coverage. Scale-up of these tools could contribute to optimizing community health systems globally, in line with the 2018 guidelines from the World Health Organization.

5011

WHO IS MISSED IN A COMMUNITY-BASED SURVEY: DIFFERENCES IN SOCIO-DEMOGRAPHIC ERISTICS AND HEALTHCARE SEEKING AMONG MISSED AND SAMPLED INDIVIDUALS FOR A SEROSURVEY IN ZAMBIA AND IMPLICATIONS FOR BIASED ESTIMATES OF HEALTHCARE SEEKING, VACCINATION COVERAGE, AND SEROPREVALENCE

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As serological assessments play an increasing role in measuring disease burden, identifying population immunity gaps, and guiding vaccination strategies globally, understanding the impact of sampling biases on outcomes of interest is increasingly important. In Zambia, a serological survey was conducted in two districts using residual samples from health facilities and validated by comparison with a concurrent community-based serosurvey. We conducted a follow-up study to assess differences in characteristics of households and individuals excluded from the sampling frame of the community-based serosurvey (23% of households) compared to those included and evaluated the magnitude of the bias in healthcare seeking, vaccination coverage, and measles seroprevalence. The initially missed households were smaller, less likely to have children, and were 15% to 29% more likely to be headed by women. Missed individuals came from less wealthy households, with imbalances in adults for sex and occupation, and were more likely to seek care at health facilities. Nevertheless, simulating a survey in which missed households were included in the sampling frame did not result in significant differences in the outcomes of interest, i.e., coverage of a second dose of measles vaccine, healthcare seeking, and measles seroprevalence, with less than a 5% difference in these outcomes. Two of the clusters had evidence of geographical clustering of missed households. Simulations of enumeration strategies in which additional households were enumerated until a specified threshold was reached resulted in a reduction in the estimated bias. These findings underscore that, even as community-based studies are upheld as the gold standard study design in assessing immunity gaps and underlying community health characteristics, results from these studies should be interpreted in the context of the study methodology and challenges during implementation, which include likely gaps in establishing accurate and up-to-date sampling frames. Failure to account for these gaps may result in biased estimates and detrimental effects on decision-making.

5012

THE EFFECT OF COMMUNITY-BASED PACKAGE OF INTERVENTIONS ON IMPROVING INSTITUTIONAL DELIVERY CARE SERVICES UTILIZATION IN ARBA MINCH HDSS, SOUTHERN ETHIOPIA: A CLUSTER-RANDOMIZED CONTROLLED TRIAL

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Regular utilization of maternal healthcare services reduces maternal morbidity and mortality. However, evidence shows that women do not use the existing services, especially institutional deliveries, with a substantial inequity between urban and rural areas. This study evaluated the effect of a package of community-based interventions on the improved institutional birth rate in rural Ethiopia. We conducted this cluster-randomized controlled trial (NCT05385380) from 2019 to 2021 at the Arba Minch Health and Demographic Surveillance System site. We randomly assigned six kebele clusters to the intervention and four to the control arm. We used a package of interventions, which included providing information on safe motherhood via videos or audiocassettes with a birth preparedness card for pregnant females, training for community volunteers and health extension workers, and improving maternity waiting home services. Women in the control arm received routine services only. We used generalized mixed-effects logistic regression models to evaluate the effect of the intervention on the outcome variables. We enrolled 727 pregnant females across the 10 clusters, with a 617 (84.9%) successful follow-up rate. The proportion of institutional deliveries in the intervention arm was increased by 16.1% from 36.4% (174/478) at the baseline to 52.5% (224/427) at the end line (Adjusted odds ratio [AOR] for McNemar's Test = 1.5; 95% confidence interval [CI]: 1.1 to 2; $p < 0.001$). However, the control arm had a 10.3% decrease in institutional deliveries (from 164/249 to 105/190). In addition, pregnant females who received the intervention were 2.8 times (AOR 2.8; 95% CI: 1.2, 6.4) likelier to give birth at a health institution than those in the control arm. This study demonstrates that an integrated community-based intervention package can increase utilization of institutional delivery care services in rural Ethiopia. Therefore, we recommend that functioning maternity waiting homes and audio-video-supported education for pregnant women be part of routine maternal healthcare to achieve the "leave no one behind commitment" in maternal health.

5013

IMPACT OF A MOBILE OBSTETRIC REFERRAL EMERGENCY SYSTEM (MORES) ON REDUCING CARE DELAYS IN RURAL LIBERIA

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Maternal mortality disproportionately affects low- and middle-income countries, including Liberia. Due especially to late presentation with infectious conditions, maternal mortality can be reduced with obstetric triage systems which are unavailable in Liberia. Mobile health interventions are a promising but underutilized method to reduce care delays for such patients. This study assessed the impact of a Mobile Obstetric Referral Emergency System (MORES) in rural Liberia. Front-line health providers working at 18 rural health facilities and 2 hospitals received training on obstetric triage and MORES. Data on 300 patients at three time points: 0, 6-months, and 12-months were collected to assess care delays and clinical outcomes. MORES usability data were recorded through WhatsApp messages and provider interviews. Baseline and midline results (N=200) are reported with endline data being collected. Results demonstrated a significant decrease in time from decision to incision for Cesarean section (n=60) from 482 minutes pre-training to 186 minutes post-training (M=296 min, 4.93 hours reduced). In total, 43 providers referred 359 patients with thousands of messages through MORES. Messages included infectious diagnoses, transfer rationale, time from rural facility to hospital, and patient outcomes. MORES was highly usable and acceptable and demonstrated components of health systems strengthening, including decreased transfer times, improved inter-professional dynamics, feedback mechanisms, exposing hidden delays, and establishing a preliminary electronic health record with follow-up for high-risk patients. MORES demonstrated high acceptability and improved clinical metrics, particularly reduced delay to C-section. Capacity building included patient tracking in a setting where electronic health records are unavailable, and where formal follow-up care is not standardized. Future studies should evaluate scalability throughout Liberia and mixed methods analysis of patient perceptions.

5014

DETECTING CIRCULATING MALARIA-INFECTED ERYTHROCYTES IN HUMANS WITHOUT A DROP OF BLOOD

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Highly-sensitive, novel point-of-care (POC) malaria diagnostics are necessary to address the limitations of current POC methods. We developed and tested a breakthrough, noninvasive photoacoustic (PA) flow cytometry (PAFC) device to detect hemozoin, a universal biomarker of blood-stage *Plasmodium* infection. Here, we present results of the first-in-human application of a novel PAFC device, the Cytophone, which uses high-pulse-rate lasers and an innovative ultrasound 16-transducer array to noninvasively detect circulating malaria-infected red blood cells (iRBCs) *in vivo*. Our technological design allows for the identification of iRBCs through the specific PA signal shapes, widths, and time delays of these cells compared to signals from uninfected blood, skin, and motion artifacts. We conducted a pilot diagnostic performance study in n=27 Cameroonian adults with uncomplicated malaria followed longitudinally for 5 visits over up to 37 days post-treatment. At each visit, participants underwent Cytophone, microscopy, a pan-species rapid diagnostic test, and highly-sensitive molecular testing. Compared to microscopy, Cytophone had a sensitivity, specificity, and receiver operating characteristic area under the curve of 90%, 69%, and 0.84, respectively, indicating excellent diagnostic performance. Using highly-sensitive *var*ATS qPCR as the gold standard, Cytophone had an optimal diagnostic detection cut-off at ≥ 7 parasites/μL and comparable performance to standard POC methods. Following treatment, we noted a clear trend in decreasing PA signals over the follow-up period, with the Cytophone showing similar relative rates of quantitative decrease as microscopy. Additionally, Cytophone detected PA peaks in 2/2 *P. malariae* mono-infection samples, demonstrating the device's ability to detect non-falciparum species. Overall, results of this first proof-of-principle clinical study conducted in an endemic setting demonstrate the potential to rapidly and noninvasively detect malaria infection *in vivo*. Additional device modifications and studies are underway to further optimize this innovative new diagnostic platform.

5015

DROPLET DIGITAL PCR AND SEQUENCING REVEALS CONCURRENT PFHRP2/3 GENE DELETIONS AND KELCH 13 MUTATIONS ACROSS ETHIOPIA

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Test-treat-track (TTT) approach to eradicate malaria relies on the detection of Histidine-Rich Proteins 2/3 (HRP2/3) through rapid diagnostic tests (RDTs), followed by treatment with artemisinin-combination therapies (ACT). However, data suggest that in the Horn of Africa alone *hrp2/3* deletions resulted in up to 50% of to be missed by RDTs. Recent reports of kelch13 mutations suggest resistance conferring single nucleotide polymorphisms are widespread. Our group was the first to document kelch13 R622I in Ethiopia in 2014. If these hrp2/3 deletions and kelch 13 mutations were to occur together this would jeopardize malaria elimination. To describe the interplay between diagnostic- and drug-resistance in *P. falciparum* species, 217 *P.falciparum* malaria infections randomly selected from 7 regions representative of Ethiopia were evaluated for *hrp2/3* deletions using qualitative PCR and quantitative by digital droplet PCR (ddPCR). Sequencing of *kelch13* was assessed to identify kelch 13 mutations associated with artemisinin-resistance. The preliminary results (n=42) demonstrate that with PCR, 11/42 (26%) were *hrp2* negative, 33/42 (79%) were *hrp3* negative and 11/42 (26%) were both *hrp2/3* negative. However, with ddPCR, 10/42 (23%) samples were negative for both *hrp2* exon 1 and 2, 32/42 (76%) negative for *hrp3*, while 9/42 (21%) were negative for both *hrp2/3*. 18/42 (43%) samples had 1 or more mutations in *kelch13*. 9/42 (21%) of infections contained either polyclonal infections or partial deletions by ddPCR. A significant proportion 9/42 (21%) of samples contained *hrp2/3* deletions combined with *kelch13* mutations ($P = 0.0573$). Further analysis of the remaining samples will confirm whether there is significant correlation between the deletions in *hrp2/3* and the *kelch13* mutations. Our study raises the spectre of co-selection of drug and diagnostic resistance in *P. falciparum* malaria. The completed study results will be presented at ASTMH.

5016

MULTIPLEX MICROFLUIDIC CARTRIDGE 'MICROLAMP' FOR MALARIA DETECTION AND SPECIATION

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In clinical settings, patients are often misdiagnosed and do not receive correct timely treatment. Rapid multiplexed tests comprising variants of the infectious diseases can be pivotal in identifying the infections and enhance the physician's ability to diagnose use appropriate treatment and avoid misusage of drugs. Point-of-care tests (POCTs) with rapid and accurate diagnosis are need. Loop mediated amplification (LAMP) significantly reduces detection time with a simplified sample preparation step and a rapid amplification step under isothermal conditions. For widespread usage, POCTs must be simple to perform with minimal technical expertise biosafety and provide diagnosis within 30 minutes. We have developed a microfluidic cartridge based POCT for malaria diagnosis. The cartridge is constructed with a multilayered architecture forming channels, reservoirs and integrating a porous lateral flow (LF) strip loaded with dry LAMP reagents in a closed system. The LF strip acts as a filter as well as provide passive flow of assay fluids (sample, buffer solutions). The cartridges are loaded on a companion battery-powered reader device comprising a heater for isothermal amplification. A combination of LEDs, optical filter and light-intensity sensors performs a real-time visual fluorescence readout of the LAMP products. A complementary smartphone app provides wireless control over the device components as well as recording the real-time LAMP data to improve diagnosis accuracy. This POCT platform dubbed "MicroLAMP" is coupled with a multiplexed panel for detection and differentiation of malaria parasites using a minimally invasive finger prick blood sample. The POCT tool is broadly applicable to multiple infectious diseases at a low cost.

5017

ACTIVE CASE DETECTION AND TREATMENT OF MALARIA IN PREGNANCY USING LAMP TECHNOLOGY (LAMPREG): A PRAGMATIC RANDOMIZED DIAGNOSTIC OUTCOMES TRIAL

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Malaria infection during pregnancy (MiP) leads to low birthweight which is a strong risk factor for neonatal and childhood mortality. Intermittent preventive therapy in pregnancy (IPTP) uptake in sub-Saharan African countries remains low. Diagnosis of MiP is challenged by sub-clinical presentation and low parasitemia. This clinical trial evaluated active detection of MiP using a molecular method for the detection of Plasmodium DNA by loop-mediated isothermal amplification (LAMP) during antenatal care (ANC) in Ethiopia where there is no IPTP. A pragmatic randomized diagnostic outcomes trial was conducted between 2020-3 at three rural hospitals and five health centres. Women are randomized to either the standard of care (SOC, 1/3) or the active case detection arm (LAMP, 2/3) at their first ANC visit and subsequently followed through to delivery. Malaria diagnosis is performed by microscopy and RDT in the SOC arm using Malaria-LAMP (Loopamp™, Human Diagnostica), microscopy, and RDT in the intervention arm. Treatment of women positive for malaria by any method was with Co-artem. In the interim analysis, 2,116 women were enrolled, 715 in the SOC arm and 1401 in the LAMP arm, with 1452 deliveries completed. Malaria detection was superior using LAMP detection with 219 positive (15.6%), compared to 129 (9.2%) and 114 (8.1%) for RDT and microscopy, respectively. In terms of outcomes, the average newborn weight was 47.0g higher in the LAMP arm (3,184g vs. 3,231g, p=0.12). The proportion of LBW newborns was 5.06% (SOC-arm) and 4.24% (LAMP-arm) (p=0.57). Newborn anemia was 3.85% in SOC versus 2.31% in LAMP (p=0.13). Significant reduction in prematurity (12.12% [SOC] versus 5.26% [LAMP], p=<0.0001) and improvement in 28-day newborn weight (4,121g [SOC] versus 4,331g [LAMP], p=<0.0001) was observed with LAMP. Molecular diagnosis of malaria with LAMP detected almost double the number of MiP compared to standard microscopy and RDT, resulted in improved absolute birth weight, lower incidence of LBW, less newborn anemia, less prematurity and improved 28-day newborn weight. Final results of this major clinical diagnostics trial will be presented at ASTMH.

5018

NEW THYMIDINE KINASE-IN DEPENDENT CLICK CHEMISTRY DNADETECT™ PROBES FOR ASSESSMENT OF DNA PROLIFERATION IN MALARIA PARASITES

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The alkyne modified thymidine analogue 5-ethynyl-2′-deoxyuridine (EdU) is a gold standard chemical probe for detection of DNA synthesis and proliferation in mammalian cells. EdU exploits the thymidine salvage pathway to incorporate into nuclear DNA, followed by detection via copper catalysed azide-alkyne cycloaddition (CuAAC) with a fluorescent azide. However, a limitation of EdU (and similar probes like BrdU) is that some organisms, including *Plasmodium* malaria parasites, lack the thymidine kinase enzyme that is essential for metabolism. While *P. falciparum* with

an introduced thymidine kinase from *Herpes simplex* virus has been successfully used in DNA labelling studies using BrdU and EdU, this approach may not be feasible for analysis different *Plasmodium* species, multiple laboratory lines and field isolates. To overcome this, we have designed and synthesised new thymidine-based probes that overcome the need for an endogenous thymidine kinase enzyme. Using CuAAC with a fluorescent azide and flow cytometry, we have shown that these DNADetect™ probes robustly label replicating asexual intraerythrocytic *P. falciparum* parasites, while EdU as a control failed to label parasites. The DNADetect™ chemical probes are synthetically accessible and thus have broad applicability as tools to further understand the biology of different *Plasmodium* species, including laboratory lines and clinical isolates.

5019

USE OF MINIMALLY INVASIVE TISSUE SAMPLING (MITS) TO DETERMINE THE CONTRIBUTION OF MALARIA INFECTIONS TO MORTALITY IN CHILDREN UNDER 5 YEARS OF AGE IN THE CHAMPS NETWORK

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Background Malaria remains a major killer of children globally, but accurately quantifying endemic country estimates is difficult as current tools lack sensitivity. Such estimates are needed to prioritize targeting of commodities and interventions.Methods Seven sites in Africa and Asia participating in Child Health and Mortality Prevention Surveillance (CHAMPS) collected comprehensive data from stillbirths and children <5 years of age within their catchment areas. Minimally invasive tissue sampling (MITS) was performed on those enrolled within 24 hours of death. Underlying, intermediate, and immediate causes of death (CoD) were assigned by local expert panels, utilizing sociodemographic, clinical, laboratory, and verbal autopsy data according to standardized protocols. The expert panel also determined if the death could have been prevented with existing, recommended measures. Analyses were conducted in 4 sites with high malaria endemicity (Mozambique, Kenya, Sierra Leone and Mali) to describe factors associated with malaria-related deaths, estimate malaria-specific mortality, and assess the proportion of preventable deaths in 1 to <60 month-olds.Findings Between 2016-2022, MITS was used to determine CoD for 773 infant and child deaths. Malaria played a significant role in the causal pathway in 237 (30.7%), 75.7% of which were aged 12-<60 months. Of all malaria deaths, 24.9% occurred in the community, 16.0% were medically unattended, and 98.7% were determined to be preventable. *P. falciparum* was the sole infecting pathogen in 164 (69·2%) of the malaria-related deaths: Bacterial co-infections were in the causal pathway of 24·5%, viral co-infections in 13.1%, and malnutrition in 30.5% of the cases. InterpretationMalaria remains a significant cause of childhood deaths in the malaria-endemic sites of CHAMPS despite available treatments and prevention measures. Importantly, one in 4 malaria deaths also had a bacterial co-infection, supporting the use of antibiotics in severe malaria patients.

5020

ALTERED IL-7/IL-7R SIGNALING IN CD4+ T CELLS FROM PATIENTS WITH ACTIVE VISCERAL LEISHMANIASIS

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CD4+ T cells play an important role in controlling L. donovani infection, through IFN-γ, required for activation of macrophages and killing of intracellular parasites. However, CD4+ T cell effector functions are hampered in visceral leishmaniasis (VL) patients. In a recent study that defined a transcriptional signature for CD4+ T cells from active VL patients, we found that expression of the IL-7 receptor (IL-7R, (CD127) was downregulated, compared to CD4+ T cells from endemic controls (ECs). Since IL-7/IL-7R signaling is critical for the survival and homeostatic maintenance of CD4+ T cells, we investigated the role of this signaling pathway in active VL patients, relative to ECs. CD4+ T cells were enriched from peripheral blood collected from VL and EC subjects and expression of IL7 and IL-7R mRNA was measured by real time qPCR. IL-7 signaling potential and surface expression of CD127 and CD132 on CD4+ T cell and various cell subsets was analyzed by multicolor flow cytometry. Plasma levels of soluble IL-7 and IL-7R were measured by ELISA. In line with previous findings, we found reduced IL7R mRNA expression in CD4+ T cells as well as reduced soluble IL-7R in plasma of VL patients. However, plasma levels of soluble IL-7 were higher in VL patients. Interestingly, expression of the IL-7R was higher on VL CD4 T cells as compared to EC, with activated CD38+ CD4+ T cells showing higher surface expression of IL-7R (CD127 and CD132), compared to CD38- CD4+ T cells in active VL patients. CD4+ T cells from VL patients had higher signaling potential after stimulation with recombinant IL-7 compared to EC, as measured by phosphorylation of STAT5. Thus, despite reduced IL7R mRNA expression in CD4+ T cell from VL patients, surface express of IL-7R was higher and increased phosphorylated STAT5 was seen following exposure to IL-7. Thus, despite lower IL-7mRNA expression, IL-7 signaling appears to be functional and even enhanced in VL CD4 cells and cannot explain the impaired effector function of VL CD4 T cell. The enhanced plasma IL-7 may have caused reduced IL7R transcription by CD4+ T cells as a part of homeostatic feedback mechanism.

5021

DECONSTRUCTING TRANSMISSION OF VISCERAL LEISHMANIASIS THROUGH ANALYSIS OF BLOOD FED SAND FLIES

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Visceral leishmaniasis (VL) is a vector-borne neglected parasitic disease transmitted by sand fly bites. VL causes up to 90,000 new cases per year and has a fatality rate of 95% without treatment. In India, VL is nearing elimination, yet disease outbreaks continue to occur. With many features of VL transmission not well understood, partly due to disease focality that is influenced by local environment, sand fly behavior, and human density and activity, in-depth analysis of field collected blood fed female sand flies can offer valuable insights into the dynamics of VL transmission. In addition to understanding host preference, we hypothesize that linking the source of the sand fly blood meal to *Leishmania* infection status and burden will shed light on the directionality of parasite transmission and point to potential infection reservoirs in a natural setting. To achieve this, we are developing tools using single sand flies experimentally fed on blood of various animals, spiked or not with *Leishmania donovani*. We dried the dissected midgut of individual blood fed female sand flies onto Whatman 903 protein saver card filters, used for specimen preservation in the field, and optimized DNA recovery to an average of 200-300ng per specimen; enough to run several concurrent assays. Using a sensitive Taq-Man probe-based

qPCR targeting kinetoplast DNA, we successfully detected and quantified *Leishmania* parasites from single infected guts. We also obtained strong amplification from single flies fed on human, goat, cow, pig, and dog blood using a multiplex PCR for blood meal analysis based on the mitochondrial cytochrome c oxidase subunit one gene, and we are currently testing others. After completing laboratory optimization, we will validate these tools in VL outbreak villages in India. This toolbox can be adapted to specific leishmaniasis foci for greater understanding of sand fly behavior in a field setting. Using established techniques to address epidemiologically relevant questions can enhance our understanding of leishmaniasis transmission within human communities and improve policy-making decisions towards better vector-control programs.

5022

NEUTROPHILS IN PATHOGENESIS OF POST KALA-AZAR DERMAL LEISHMANIASIS (PKDL), FRIEND OR FOE?

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Post Kala-azar Dermal Leishmaniasis, a sequel of apparently cured Visceral Leishmaniasis, presents in South Asia with papulonodular (polymorphic) or hypomelanotic lesions (macular). Neutrophils are the first line of defense in VL and facilitate disease establishment by serving as 'trojan horses'. However, knowledge regarding a biological role, if any, for neutrophils in PKDL is limited. This study aimed to delineate the status of neutrophils at the dermal lesions of PKDL, and their possible functionalities. Accordingly, the presence of lesional CD66b$^+$ neutrophils along with their functional status was assessed by immunofluorescence/ immunohistochemistry in terms of activation (CD66b$^+$/CD64$^+$), degranulation (CD66b$^+$/MPO$^+$), release of neutrophil elastase (NE) and matrix metalloprotease 9 (MMP9) along with their transcriptomic profile using the Visium (10X) platform. The levels of circulating neutrophil chemo-attractants CXCL8, CXCL1/2/5, CCL2 and 20, along with cytokines, IL-6, IFN-γ, IL-4, IL-10, TNF-α, IL-17 and IL-23 as markers for inflammation were evaluated by a multiplex assay. As compared to skin from healthy individuals, PKDL cases demonstrated an increased infiltration of activated neutrophils (increased CD64$^+$, MPO, NE). There was an increase in plasma levels of neutrophil chemo-attractants, along with pro-inflammatory and regulatory cytokines. Levels of MMP9 were elevated in both circulation and at lesional sites, with concomitant collagen I degradation. However, the tissue damage was moderate, perhaps owing to the concomitant increase in expression of *TIMP1.* The immune responses constituted a mixed Th1 (IFN-γ, IL-6), Th2 (IL-4) and Treg (IL-10) profile, with a conspicuous absence of the Th17 phenotype. The increased levels of CXCL8 and CXCL5 correlated with the proportion of infiltrated neutrophils; furthermore, this homing was IL-10 dependant. Taken together, in PKDL, a chronic dermatosis, the presence of activated neutrophils at lesional sites suggested its permissive role(s) in modulating the lesional landscape and facilitating disease progression.

5023

ALTERED PROFILE OF CD4+T CELLS CHEMOKINE RECEPTOR EXPRESSION DURING VISCERAL LEISHMANIASIS

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Robust Th1 cell responses, which activate macrophages to kill intracellular parasites, are required to control Leishmania infection. Yet, VL patients do not control the infection despite expansion of CD4$^+$ T cells and increased IFNγ expression in the spleen. Chemokines &/or chemokine receptors are involved in cellular migration & are critical in the inflammatory response. In a recent study that defined a transcriptional signature for CD4$^+$ T cells from active VL patients, we found several differentially expressed chemokine receptor genes compared to CD4$^+$ T cells of healthy endemic controls (HEC). Since CD4$^+$ T cell plays crucial roles in parasite clearance, there is need to understand the role of altered chemokine receptor expression on CD4$^+$ T cells & their different subsets. In this study, we validated the gene expression & surface protein expression of differentially expressed chemokine receptors found in human VL subjects compared to HEC by real-time qPCR and multicolor flow cytometry, respectively. We found elevated mRNA & surface protein expression of CCR5, while reduced CCR4 & CCR6 expression in VL patients CD4$^+$ T cells. CCR5 was upregulated on Th1 cell subsets indicating the expansion of CCR5$^+$ Th1 cells in peripheral blood that may be responsible for Th1 cells trafficking towards the infected tissue. CCR4 expression was reduced on regulatory T cells (Treg) & central memory T cells (Tcm) suggesting reduced frequencies of these cells in peripheral blood during VL. Our results suggest that VL patients possess unique chemokine receptor expression on their surface compared to healthy subjects. The implications of these finding have on VL pathogenesis & how the knowledge of these changes can provide direction for the development of new and improved therapeutic approach against VL is under investigation.

5024

A POTENTIAL ROLE FOR ADIPOCYTES IN VISCERAL LEISHMANIASIS

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Leishmaniasis is a chronic parasitic disease in which parasites are found in host macrophages throughout the reticuloendothelial organs. Recent data indicate that many cells not thought of traditionally as immune cells contribute to the cytokine/chemokine environment locally where the parasite survives, and to the systemic immune responses. Adipocytes are versatile cells whose functions in systemic energy homeostasis and as reservoir for excess energy are well documented. Adipocytes are present in subcutaneous tissues near the parasite inoculum, but their potential involvement in immunoregulation of leishmaniasis is unknown. To determine whether and how adipocytes interact with the *Leishmania* species, we differentiated human preadipocytes into adipocytes and incubated them with *L. infantum, L. major* or *L. braziliensis* promastigotes. We found that the *Leishmania spp.* parasites were taken up by human adipocytes and transformed morphologically to the intracellular amastigote form, but this occurred differently between the species. *L. infantum* was taken up by 20.0% of adipocytes, whereas *L. major* or *L. braziliensis* were taken up by 11.5 or 4.8% of adipocytes, respectively. None of the parasite species replicated intracellularly over 48 hrs. RT-qPCR for candidate immunoregulatory transcripts revealed up-regulation of the IL6 and PPARγ but down-regulation of genes involved in lipogenesis such as Adiponectin, Lipoprotein lipase and Leptin receptor. There were quantitative, but no apparent qualitative differences between the species. These data suggest a potential role for adipocytes in *Leishmania* spp. infection, although the roles may differ between different *Leishmania* species.

5025

IMMUNE MODULATION INDUCED BY LEISHMANIA EUKARYOTIC INITIATION FACTOR BEFORE LEISHMANIA INFANTUM INFECTION OF THP1 DERIVED MACROPHAGES

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Leishmaniases are a complex group of neglected infectious diseases of poverty, and serious public health problems. Development of novel control strategies remains a research priority. *Leishmania* Eukaryotic Initiation Factor (LelF) antigen is a natural Th1 type natural adjuvant that stimulates

cytokine expression in healthy and infected cells. We showed LelF induces resistance of J774 mice cells to *L. donovani* infection. We investigate here the effect of LelF on infection of human macrophages by *Leishmania infantum*. To model macrophage-parasite interaction *in vitro*, we used THP-1-derived macrophages (TDMs) and *L.infantum* strain. Infection conditions as multiplicity of infection, incubation and readout time were set by light microscopy. The optimal protein amount that was not cytotoxic and did not affect TDMs viability was selected based on LDH and MTT assays, respectively. Cells were treated before the infection with recombinant LelF protein and its effect on infection was measured on Giemsa-stained slides. The presence of microbicidal molecules such as Nitric Oxide and reactive oxygen species in culture supernatant was determined. Levels of secreted cytokines were quantified by multiplex flow cytometry. We found that a MOI of 10 parasites per cell leads to 70% of infected cells and up to 6 intracellular amastigotes/cell with an optimal infectivity at 24h time post infection. With LelF pre-treatment, infectivity of TDMs decreased to 39% and parasite load to a mean of 2 amastigotes/cell. Parasitic Index of untreated infected TDMs were found to be 420, this value decreased to 80 for LelF treated cells; the effect was shown to be specific to live parasites (vs killed parasites or latex beads). This result indicated that LelF induced cell resistance to *L.infantum* infection (80% parasitic index inhibition). Such an effect was proven to be associated with the accumulation of ROS and a significant release of pro-inflammatory cytokines such as IL-8, TNF-α, IL-6 and IL-1β. The study confirms the prophylactic potential of LelF in another pathogen-cell model and open ways to understand mechanisms involved in the cell response to LelF immune modulation.

5026

CATALASE IS DETRIMENTAL FOR LEISHMANIA VIRULENCE (WITH NOTES ON EVOLUTION OF CATALASES IN TRYPANOSOMATIDAE)

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Catalase is one of the most abundant enzymes on Earth. It decomposes hydrogen peroxide, thus protecting cells from dangerous reactive oxygen species. The catalase-encoding gene is conspicuously absent from the genome of most representatives of the family Trypanosomatidae. The exceptions are monoxenous relatives of *Leishmania* spp., and representatives of the genera *Blastocrithidia*, *Obscuromonas*, and *Vickermania.* In this work, we expressed the *Leptomonas seymouri*-derived catalase from the *Leishmania mexicana beta-tubulin* locus using a novel bi-cistronic expression system, which relies on the 2Apeptide of *Teschovirus A*. We demonstrated that catalase-expressing parasites are severely compromised in their ability to develop in insects, to be transmitted and to infect mice, and to cause clinical manifestation in their mammalian host. Taken together, our data support the hypothesis that the presence of catalase is not compatible with the dixenous life cycle of *Leishmania*, resulting in loss of this gene from the genome during evolution of these parasites. To complement these data, we ablated a catalase-encoding gene from the *Leptomonas seymouri* genome and established an add-back, where catalase was overexpressed from the 18S rRNA locus of *L seymouri*. Our study demonstrated that parasites' development and infectivity *in vivo* (in *Dysdercus peruvianus* model) depends on the expression level of this enzyme. These studies were further complimented by biochemical characterization of three independently-acquired catalases (of *Blastocrithidia*, *Leptomonas*, and *Vickermania*) *in vitro*, which showed that the enzyme of *Blastocrithidia nonstop* is cyanide-resistance, an unprecedented feature among all investigated monofunctional catalases.

5027

GEOSPATIAL ANALYSIS OF THE DISTRIBUTION OF HYMENOLEPIS NANA INFECTION AMONG CHILDREN'S HOUSEHOLDS AND SCHOOLS OF THE PROVINCE OF ANTA, PERU

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Hymenolepis nana is an emergent parasitosis in the Cusco region associated with morbidity in children of rural communities. We used data from a cross-sectional study evaluating children for gastrointestinal parasites in the Anta province in Peru. We geographically tagged the children's residences and respective schools. Stool was evaluated by rapid sedimentation and Kato Katz microscopy. Local distribution patterns of infection were identified via Anselin local Moran's I and Getis-Ord Gi* statistics. A total of 2961 children were included from 51 schools. The mean age was 9.7 years old (± 3.55), 1479 (50%) were female, and the median HAZ was -1.4 (IQR -2 to -0.8). The median H. nana prevalence per school was 15% (IQR 3.61 - 24.20), 915 (30.9%) children were infected with > 1 parasite, and 420 (14.4%) of the households had at least one child infected with H. nana. Mapping of hymenolepiasis distribution of hot and cold spots (p< 0.10) geographically differed between schools and households. Logistic regression analysis showed that infected children residing in areas of high geospatial risk of infection had lower HAZ score (OR 2.725 95%CI 1.162-0.828, p= 0.016) and had mothers with fewer years of education (OR 0.859, 95% CI 0.744 - 0.992, p=0.039) compared to uninfected children residing in similar areas. When comparing schools located in hot vs cold spots, children attending schools in hot spots locations were younger (OR 0.882, 95% CI 0.812-0.958, p= 0.003), were more likely to have anemia (OR 1.873, 95% CI 1.198-2.928, p=0.006), had lower HAZ score (OR 0.795, 95% CI 0.669-0.944, p=0.009), lived at higher altitudes (OR 1.009, 95%CI 1.007-1.011, p = < 0.001), had fathers with fewer years of education (OR 0.928, 95%CI 0.866 - 0.973, p= 0.002), and had other parasitic infections (OR 1.513, 95% CI 1.099- 2.085, p= 0.011). Our data demonstrated clustering of H. nana infections in schools and residences suggesting school and household transmission. Information provided could be used for local health authorities to develop strategies for infection control.

5028

ACUTE KIDNEY INJURY IN CHILDREN WITH SICKLE CELL ANEMIA IS LINKED TO TUBULOINTERSTITIAL INJURY AND MICROCIRCULATORY DYSFUNCTION

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Acute kidney injury (AKI) is common in hospitalized children, including patients with sickle cell anemia (SCA). AKI is a diverse clinical syndrome and the pathophysiology of AKI in children with SCA associated AKI is not well understood. Here we investigated immune pathways associated with AKI in 185 children with SCA hospitalized for a vaso-occlusive pain crisis and 65 children with SCA in steady state as controls. AKI was defined in hospitalized children using the KDIGO definition as ≥ 1.5-fold change in creatinine within seven days or an absolute change of ≥ 0.3 mg/dl within 48 hours excluding children with a 1.5-fold change in creatinine from 0.2 mg/dL to 0.3 mg/dL. Using ELISA, we measured serum levels of markers of kidney structure and function (cystatin C, neutrophil gelatinase associated lipocalin [NGAL], renin), tubulointerstitial stress and inflammation (tissue inhibitors of metalloproteinases 1 [TIMP-1], interleukin-18 [IL-18]) and microcirculatory dysfunction (P-selectin, angiopoietin-2 [Angpt-2], and

soluble fms-like tyrosine kinase 1 [sFlt-1]). The median age of children enrolled was 8.9 years (IQR, 2.7 to 11.8) and 42.8% of participants were female. Compared to steady state controls, children hospitalized with a pain crisis had higher levels of NGAL, increases in markers of tubulointerstitial stress (TIMP-1) and microcirculatory dysfunction (Angpt-2 and sFlt-1) ($p< 0.0001$ for all) but no changes in markers of kidney function or inflammation. Among the 36.2% of children with AKI, there were significant increases in all biomarkers except for P-selectin. Similarly, all biomarkers except P-selectin increased with the severity of AKI (p trend <0.001) and were elevated among children who died ($p<0.05$). Children with SCA hospitalized with a pain crisis exhibit increases in markers of tubulointerstitial stress and structural kidney injury as well as endothelial activation. These pathways are further elevated in children with AKI, increase with worsening kidney function, and are associated with mortality. Additional studies are needed to develop kidney-protective interventions within this at-risk population.

5029

TEMPORAL TRENDS OF BLOOD GLUCOSE IN CHILDREN WITH CEREBRAL MALARIA

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Hypoglycemia, defined as a blood glucose <2.2 mmol/L, is associated with death in pediatric cerebral malaria (CM). The optimal duration of glucose monitoring in CM is unknown. We collected data from 1674 hospitalized Malawian children with CM to evaluate the association between hypoglycemia and death or neurologic disability in survivors. We assessed the optimal duration of routine periodic measurements of blood glucose. Children with hypoglycemia at admission had a 2.87-fold higher odds (95% CI: 1.35-6.09) of death and, if they survived, a 3.21-fold greater odds (95% CI: 1.51-6.86) of sequelae at hospital discharge. If hypoglycemia was detected at 6 hours but not at admission, there was a 7.27-fold higher odds of death (95% CI: 1.85-8.56). The presence of newly-developed hypoglycemia after admission was not independently associated with neurological sequelae in CM survivors. 94.7% of all new episodes of blood sugar below a treatment threshold of 3.0 mmol/L occurred within 24 hours of admission. In those with blood sugar below 3.0 mmol/L in the first 24 hours, low blood sugar persisted or recurred for up to 42 hours. Hypoglycemia at admission or 6 hours afterwards is strongly associated with mortality in CM. Children with CM should have 24 hours of post-admission blood glucose measurements. If a blood glucose less than the treatment threshold of 3.0 mmol/L is not detected, routine assessments may cease. Children who have blood sugar values below the treatment threshold detected within the first 24 hours should continue to have periodic glucose measurements for 48 hours post-admission.

5030

NEUROLOGICAL SYMPTOMS IN SICK CHILDREN PRECEDING DEATH AND CORRELATION WITH POSTMORTEM DIAGNOSIS: RESULTS FROM CHAMPS MORTALITY SURVEILLANCE NETWORK

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Neurological manifestations are common among ill children in low-income countries. We investigated the prevalence and characteristics of neurological manifestations in neonatal, infant, and child deaths in low-resource settings. The study used data collected as part of Child Health and Mortality Prevention Surveillance (CHAMPS) from December 2016 - July 2022, including clinical information, tissue specimens, and laboratory results to systematically determine the causes of death in under-5 children in Bangladesh, Ethiopia, Kenya, Mali, Mozambique, Sierra Leona and South Africa. A total of 3303 deaths underwent minimally invasive tissue sampling through July 2022. After excluding stillbirths, we assessed 2127 neonatal, infant and child deaths. Over 50% of cases with available clinical information presented with at least one neurological sign or symptom prior to their death, with seizures being the most frequent manifestation in all age groups (40% of children and 30% of neonates). The most common diagnoses were hypoxic events and meningoencephalitis in neonates, and malaria and meningoencephalitis in infants and children. However, the sensitivity of each group of signs and symptoms to predict specific diagnoses was overall very poor (with the highest sensitivity of 31.8% for seizures predicting hypoxic events in neonates), and diagnostic tests, such as lumbar punctures (LP), were only performed in a 17.8% of cases with a final diagnosis of meningoencephalitis. Overall, deaths were considered as potentially preventable in 84.8% of hypoxic events, 85.1% of meningoencephalitis and 97% of cerebral malaria cases. In conclusion, neurological manifestations are very common among sick children prior to death, and clinical presentations overlap significantly among the most common diagnoses in all age groups. Diagnostic tools, such as LPs, are rarely performed in our settings. Innovative tools to assess children with neurological manifestations and the improvement of healthcare systems in low-income countries are necessary to prevent under-5 mortality related to neurological emergencies.

5031

SOLUBLE TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS 1 (STREM-1) TO RISK-STRATIFY CHILDREN PRESENTING WITH FEBRILE ILLNESS IN SOUTHERN MOZAMBIQUE

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Febrile illnesses are a leading reason for pediatric medical consultations. Most febrile children attending primary care facilities have uncomplicated and self-limited infections, but a small proportion may progress to life-threatening conditions requiring prompt and advanced care. However, early in the course of illness, it is difficult to identify which children are at risk for severe and fatal infections. In resource-constrained settings, this is further complicated by limited health care providers and laboratory services. Here we tested the hypothesis that quantifying plasma biomarkers of immune and endothelial activation at clinical presentation may enhance risk-stratification of febrile children. This study was conducted in the Mozambican pediatric cohort of the FIEBRE study. Between December 2018 and February 2021, febrile children aged 2 months - <15 years were enrolled. We measured plasma levels of Angpt-2, CHI3L1, IL-6, IL-8, sFlt-1, sTNFR1, sTREM-1, suPAR, PCT, and CRP at presentation using Luminex and ELISA. Standard clinical and laboratory parameters were assessed at enrollment, and clinical outcomes were evaluated up to 28 days later. A total of 1,040 children were enrolled and had a plasma sample taken for biomarker measurement. 531 (51.1%) were outpatients and 509 (48.9%) were inpatients. Of these, 19 children died within 28 days. sTREM-1 was associated with 28-day mortality (p<0.001) and showed the best discrimination with an AUROC of 0.840 (95% CI: 0.761 to 0.920). sTREM-1 prognostic accuracy for 28-day mortality was superior to PCT (p=0.045), CRP (p<0.001) and lactate (p=0.011). Combining sTREM-1 with some clinical severity scores or definitions (e.g., LODS, LqSOFA, WHO danger signs) improved their prognostic accuracy. sTREM-1 was also associated with 7-day mortality and length of hospital stay. These findings add evidence for sTREM-1 as a promising biomarker for risk-stratification of febrile illnesses in children in resource-constrained settings.

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EFFECT OF POINT-OF-CARE RAPID DIAGNOSTIC TESTS ON ANTIBIOTIC PRESCRIPTION IN PRIMARY HEALTH CARE SETTINGS IN TWO PERI-URBAN DISTRICTS IN GHANA

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The management of febrile illnesses is challenging in low-resource countries. It contributes to antibiotic resistance through inappropriate use from diagnostic uncertainty and limited numbers of point-of-care diagnostic tests. This study aimed to assess the impact of rapid diagnostic tests, clinical algorithms, and communication on clinical outcomes and antibiotic prescriptions, compared to standard-of-care practices, of acute febrile illness at outpatient clinics in Shai-Osudoku and Prampram districts in Ghana. This was an open-label, centrally randomized controlled trial in four health facilities. Participants aged 6 months to 18 years old, with acute febrile illness were randomized to either intervention or control arm. A set of point-of-care diagnostic tests and clinical algorithms were used to guide prescribers in antibiotic prescriptions in the intervention arm while a standard-of-care approach per the Ghana National guidelines was used in the control. Clinical outcomes and adherence to prescriptions were assessed in both arms on day 7 follow-up. A total of 1512 patients were randomized to either the intervention (n=761) or control (n=751) arm. The majority were children under 5 years (76.3%) and male (53.5%). The median age was 2 years and the majority presented with fever (94.4%) and/or cough (64.0%). Overall, the intervention reduced antibiotic prescriptions by 4.7%. In children under 5 years, it reduced by 14.5% (RR 0.855 [0.748, 0.978]); 14.8% in non-malaria cases (RR 0.852 [0.754, 0.963]), and 16% in patients with respiratory symptoms (RR 0.840 [0.732, 0.962]). Almost all participants had favorable outcomes (99.7% vs 99.4%) and high adherence (95.5% vs 96.9%) on day 7 follow-up. In conclusion, the combination of point-of-care diagnostics, clinical algorithms, and communication messages can be used at the primary healthcare level to reduce antibiotic prescriptions among children with acute febrile illness.

5033

ASSESSING THE PORTABILITY OF A PEDIATRIC TELEMEDICINE AND MEDICATION DELIVERY SERVICE TO THE GHANAIAN SETTING: A PILOT STUDY

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The impact of an intervention relies on its portability to novel settings. A telemedicine and medication delivery service (TMDS) model has worked to improve pediatric access to nighttime care in Haiti; however, the success of the intervention cannot be extrapolated to novel contexts. To establish portability, the TMDS model, known as MotoMeds, must be evaluated in settings with distinct healthcare infrastructures and burdens of disease. Our objective was to implement MotoMeds TMDS in Ghana to assess the model's operational feasibility and clinical safety in a setting with a nationalized emergency medical service and a high burden of malaria. The TMDS was launched in Ghana on November 16th, 2022, in the low-resource communities of Jamestown and Usshertown in Accra. When children ≤10 years became sick at night, their guardians called MotoMeds and reached National Ambulance Service (NAS) Emergency Medical Technicians (EMTs). EMTs asked the guardians questions per WHO-derived decision-support tools. Severe cases were referred to NAS or hospitals. Non-severe cases were further explored; EMTs gathered histories, symptoms, and exam findings over the phone to determine treatment plans. Treatment plans included rapid diagnostic testing for malaria, medications, fluids, and clinic follow-up. EMTs traveled to households to perform parallel in-person examinations and provide testing and treatment. EMTs consulted local on-call physicians as needed. Follow-up phone calls were performed at 10 days. In the first 3 months, 184 cases were enrolled, and 157 household visits were conducted. Common complaints at the call center included fever (150, 82%), cough (91; 49%), and skin problems (62, 34%). An on-call physician was consulted for 22% (41) of cases. 174 cases (95%) were reached for follow-up. At 10 days, 85% (148) of cases were "Well", 11% (19) of cases were "Improved", 2% (4) were the "Same", and 2% (3) of cases were "Worse". No severe adverse events occurred. Findings to date support the operational feasibility and clinical safety of the TMDS in Ghana; thus suggesting the portability of the TMDS model. Implementation and data collection are ongoing.

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SEROLOGIC EVIDENCE OF MARBURG VIRUSES AND A BUNDIBUGYO VIRUS-LIKE EBOLAVIRUS IN MADAGASCAN ROUSETTE BATS

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Ebolaviruses and marburgviruses are causative agents of viral hemorrhagic fever diseases with a high case fatality in humans. Historically, outbreaks of marburgviruses have occurred in Central and South Africa, connected to mining or cave-tourism activities in caves where the reservoir species, Egyptian rousette bats (ERBs; Rousettus aegyptiacus), roost. Recent Marburg virus disease outbreaks in Equatorial Guinea, Guinea, and Ghana have highlighted gaps in our current knowledge of Marburg virus (MARV) distribution and at-risk areas for spillover. On Madagascar, a single species of rousette bat, Madagascan rousette, resides. We conducted serology-based biosurevillance to assess whether ebolaviruses and marburgviruses circulate enzootically in Madagascan rousettes. Serum samples from 559 Madagascan rousettes and two other species of fruit bats were tested by a multiplex microsphere-based immunoassay for immunoglobulin (Ig) G reactivity against soluble envelope glycoprotein (GP) ectodomain trimers of filoviruses. Antigen-antibody complexes were detected via Luminex xMAP-based technologies, with IgG levels reported as a median fluorescence intensity. Seropositivity cutoffs were determined with a three-sigma-rule (99.7%) probability distribution of naïve ERB sera and latent cluster analysis of field-collected Madagascan rousette sera. We detected IgG binding antibodies against MARV (7.6%; 43/559), Ravn (RAVV) (13.4%; 74/559), and Bundibugyo virus GP (4.8%; 27/559). Interestingly, 5.5% (31/559) were co-positive for IgG against MARV and RAVV. Serological profiles of Madagascan rousettes suggest the presence and co-circulation of uncharacterized ebolaviruses and marburgviurses. Specific serological footprints in Rousettus species native to Madagascar extends our understanding of the host reservoir-pathogen dynamics, implicating the bat genus Rousettus as a reservoir for marburgviruses. Future research is necessary to determine possible evidence of viral chatter between bats and other wildlife or domestic animals, and spillover risk to humans.

5035

EXPOSURE OF EGYPTIAN ROUSETTE BATS (ROUSETTUS AEGYPTIACUS) AND A LITTLE FREE-TAILED BAT (CHAEREPHON PUMILUS) TO ALPHAVIRUSES IN UGANDA

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The reservoir for zoonotic o'nyong-nyong virus (ONNV) has remained unknown since this virus was first recognized in Uganda in 1959. Building on existing evidence for mosquito blood-feeding on various frugivorous bat species in Uganda, and seroprevalence for arboviruses among bats in Uganda, we sought to assess if serum samples collected from bats in Uganda demonstrated evidence of exposure to ONNV or the closely related zoonotic chikungunya virus (CHIKV). In total, 652 serum samples collected from six bat species were tested by plaque reduction neutralization test (PRNT) for neutralizing antibodies against ONNV and CHIKV. Forty out of 303 (13.2%) Egyptian rousettes from Maramagambo Forest and 1/13 (8%) little free-tailed bats from Banga Nakiwogo, Entebbe contained neutralizing antibodies against ONNV. In addition, 2/303 (0.7%) of these Egyptian rousettes contained neutralizing antibodies to CHIKV, and 8/303 (2.6%) contained neutralizing antibodies that were nonspecifically reactive to alpha-viruses. These data support the interepidemic circulation of ONNV and CHIKV in Uganda, although Egyptian rousette bats are unlikely to serve as reservoirs for these viruses given the inconsistent occurrence of antibody-positive bats.

5036

SPATIAL VARIATION IN NIPAH VIRUS SEROPREVALENCE AMONG PTEROPUS MEDIUS BATS IN BANGLADESH

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The Indian flying fox, Pteropus medius, is the known reservoir for the Nipah virus (NiV) in Bangladesh, causing spillovers into humans every year. Previous studies of bat roost nearby human cases demonstrated that viral shedding is rarely detected and that prevalence of IgG antibodies against NiV in these flying foxes varied from 14-60%. Many questions remain about the ecology of this virus, including whether spatial and temporal differences in spillover are associated with differences in transmission or behaviors among reservoir hosts. During 2019-2022, we investigated seroprevalence and NiV shedding among flying foxes in Bangladesh at four roosts: one large roost (Cox's Bazar>2000) outside NiV spillover areas, and one large (Faridpur>2000) and two smaller roosts (Naogaon and Rangpur<1000) nearby spillover sites. Once per month, we collected throat and urine swabs and a blood sample from 100-200 bats. We used a multiplex immunoassay to detect antibodies against the receptor-binding protein from NiV virus and four other species of Henipavirus (Hendra, Cedar, Mojang, and Ghana virus) and rRT-PCR to detect viral shedding in swabs. We sampled 3023 bats; overall, NiV seroprevalence was 14% and 5 bats (<0.01%) were found to be actively shedding NiV. Seroprevalence was similar between the two large roosts (17% vs 19%), nearby and far away from spillover sites. However, two smaller roost sites nearby spillover areas had much lower seroprevalence (6% in Naogaon and 5% in Rangpur) than larger roosts, suggesting that NiV transmission within bat roosts may be influenced by population size. Investigations into bat movement between roosts and bat feeding behavior differences by roost size could further explain how roost size may contribute to these patterns. Although none of the other henipaviruses included in the immunoassay circulate in bats in Bangladesh, many individual bat antisera were co-positive with those antigen targets, suggesting that other unknown henipaviruses may circulate in these bats. Given the human health risks posed by NiV, describing the other henipaviruses that may circulate in these reservoir hosts should be a research priority.

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CENCURUT VIRUS: A NOVEL ORTHONAIROVIRUS FROM ASIAN HOUSE SHREWS (SUNCUS MURINUS) IN SINGAPORE

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Orthonairovirus is a genus of viruses in the family Nairoviridae, order Bunyavirales, with a segmented circular RNA genome. They typically infect birds and mammals and are primarily transmitted by ectoparasites such as ticks. Four of nine Orthonairovirus genogroups can infect humans, with Crimean-Congo hemorrhagic fever virus infections displaying case fatality rates up to 40%. Here, we discover and describe a novel Orthonairovirus as Cencurut virus (CENV). CENV was detected in 34 of 37 Asian house shrews (Suncus murinus) sampled in Singapore and in a nymphal Amblyomma helvolum tick collected from an infected shrew. Pairwise comparison of CENV S, M, and L segments had 95.0 to 100% nucleotide and 97.5 to 100% amino acid homology within CENV genomes, suggesting a diverse viral population. Phylogenetic analysis of the individual gene segments showed that CENV is related to Erve, Lamusara, Lamgora, and Thiafora viruses, with only 49.0 to 58.2% nucleotide and 41.7 to 61.1% amino acid homology, which has previously been detected in other shrew species from France, Gabon, and Senegal respectively. The high detection frequency suggests that CENV is endemic among S. murinus populations in Singapore. The discovery of CENV, from a virus family with known zoonotic potential, underlines the importance of surveillance of synanthropic small mammals that are widely distributed across Southeast Asia.

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EPIDEMIOLOGY AND GENETIC DIVERSITY OF NOVEL PARAMYXOVIRUSES RELATED TO LANGYA VIRUS IN RODENTS AND SHREWS IN BANGLADESH

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Rodents and shrews live in close proximity to humans and have been identified as critical hosts of zoonotic pathogens. As part of a broad One Health surveillance effort, we conducted surveillance for novel zoonotic viruses in wildlife, domestic animals, and people. Paramyxoviruses (PMV) were one of the priority viral groups targeted for the surveillance. Here, we report discovery of novel PMV in wild rodent and shrews in Bangladesh. We collected oral and rectal swab samples from rodents (n= 1019) and house shrews (n=186) twice a year, in the dry and wet seasons, from three districts in Bangladesh from 2016 to 2018. To detect known and novel paramyxovirus, we tested swab samples using consensus PCR assay targeting RDRP genes of paramyxovirid specific generate primers. Overall, 2.1% (25/1205; 95% CI: 1.3-3.0) animals was positive against PMV.The prevalence of PMV was similar in rodents (2.06%; 21/1019) and shrews (2.15%; 4/186). We detected 04 novel strains of PMV from 25 samples of 06 species of rodents and house shrew. The PMV was more prevalent in wet than dry seasons.We identified landscape, sex, and health conditions significantly associated with PMV shedding in multivariable logistic regression model.Phylogenetic analysis revealed that three PMV strains identified in rodents are genetically related to Jeilongvirus. The discovery of one PMV strain genetically related to the novel zoonotic Langya virus in shrews warrants further investigation. However, the whole genome and molecular characterization are required to ascertain the virus pathogenicity and similarity with Langya or a novel strain of PMV. This study discovered that diverse strains of paramyxovirus, including those related to Langya virus, are present in shrews and rodents in Bangladesh. Future studies in Bangladesh should continue to characterize PMV viral diversity, and Langya virus should be included as possible etiologies for humans at high-risk human-animal interfaces that test negative for common pathogens.

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INVESTIGATION OF RIFT VALLEY FEVER OUTBREAK ASSOCIATED WITH 'ABORTION STORMS' IN MBARARA DISTRICT, UGANDA 2023

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Rift valley fever (RVF) is a zoonotic disease of public health and economic importance. Uganda has reported sporadic acute human cases since 2016 and identified convalescent livestock herds. In January 2023, acute disease with high fevers was reported in cattle among one dairy farm in Mbarara district as well as presenting with classical 'abortions storms' that is stereotypically characterized RVF diseases in larger outbreaks in the East-African rift valley. The Mbarara district rapid response team supported by the national rapid response team together with partners responded to these reports and blood samples were collected and taken to the Uganda Virus Research Institute (UVRI) for testing and confirmation. We conducted both human and veterinary investigations following a one health approach where 90 human samples, 42 cattle samples, 5 goat samples, and 4 milk samples from the affected farm were collected and tested by PCR, IgM, and IgG ELISA at the UVRI Viral hemorrhagic fever laboratory. Next Generation Sequencing (NGS) is being conducted and ongoing. To date (20th March 2023), 27.7% (25/90) human cases have been confirmed by PCR and IgM ELISA with 3 deaths, 23.8% (10/40) cattle tested positive by PCR and 69% (29/42) were positive by IgG ELISA whereas 2 sheep tested positive by IgG and 2 milk samples tested positive by PCR. 30 animals had reports of abortions in a space of two months within the one farm. 96% (24/25) of human cases reported contact with livestock, and 80% (20/24) are males with an average age of 37.7. Most human cases are alive (88%) and only 2 had hemorrhagic symptoms with the predominant symptoms being fever and general body weakness. This was the first active infection in cattle and milk samples that has been detected in Uganda associated with a cluster of acute human cases. Animal movement control measures were instituted to limit the spread and provided health education for high-risk groups such as abattoir workers and herdsmen. Recommendations for public health and animal preventive measures included immunization, vector control and health education in the affected communities to mitigate the effects of RVF.

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GENETIC DIVERSITY AND AMINO ACIDS VARIATIONS AT VACCINE TARGET SITES IN RABIES VIRUSES COLLECTED FROM DIFFERENT HOST SPECIES IN MAKUENI AND SIAYA COUNTIES, KENYA

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Rabies, a viral disease that causes lethal encephalitis is endemic in Kenya and is transmitted to humans mainly by domestic dogs. Rabies kills an estimated 2000 people annually, despite there being effective vaccines for dogs and humans. This study characterized the genetic diversity of RABV

obtained from brains of suspected rabid animals from Makueni county, Eastern region and Siaya county, Western Kenya and determined variances within the antigenic sites of RABV vaccines currently in use in Kenya. Brain biopsies (165) confirmed positive for rabies with rapid kits were collected between July 2021 and August 2022 from dogs, cats, cows, sheep and goats and re-screened for RABV by qPCR. Whole genome sequences (WGS) and individual nucleoprotein (N) and glycoprotein (G) genes were used for phylogeny. The amino acid variances in the N and G genes antigenic sites were compared to three RABV vaccine sequences: Pitman-Moore L503 (PM), Challenge Virus Standard (CVS) and the Pasteur vaccine (PV) strains. Of the 165 brain samples, 156 were positive by qPCR and 141 (74 from Makueni and 67 from Siaya) produced useable sequences. Phylogenetic lineages drawn from WGS, individual N and G genes showed two geographical distinct lineages: The Eastern Kenya sequences overwhelmingly (n=69) clustered with the Africa 1b lineage, with only 3 in Africa 1a. In contrast, the Western Kenya sequences (n=64) clustered with Africa 1a with only 3 in Africa 1b. The nearest common ancestor of the Africa 1a traced to Sudan, while the Africa 1b traced to Tanzania. The percent amino acid homologies of the N gene to the RABV vaccines were at least 97.6% for PV, 97.8% for CVS and 98.5% for PM. The homology with the G gene were at least 93.0% for PV, 93.3% for CVS and 92.2% for PM. Our data confirm geographical isolation of RABV in Eastern and Western Kenya. The data suggests limited migration, probably through wild carnivore movement or translocation of domestic dogs by humans. The observed amino acid variances RABV vaccines antigenic sites would predict good vaccine efficacy, indicating that the RABV endemicity in Kenya is due limited programmatic vaccine coverage.

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A GUT COMMENSAL PROTOZOAN REMOTELY TUNES PULMONARY DISEASE SEVERITY

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The microbiome plays a crucial role in regulating the immune system. The bacterial composition of the microbiome, in particular, is known to alter eosinophil responses to various stimuli with certain bacterial profiles having been associated with increased susceptibility to the development of allergies and asthma. However, the precise role of the other microbial kingdoms within the microbiome, such as viruses, fungi, and protozoa, in modulating immune responses and susceptibility to disease is not yet fully understood. Commensal protozoa are an integral component of the vertebrate microbiota, yet they are vastly understudied compared to their pathogenic counterparts. While colonization with commensal protozoa is known to alter the local immune response in the intestine and aid in protection against enteric bacterial pathogens, it is unclear whether these organisms can also influence extra-intestinal immunity. Here, we show that the gut-dwelling commensal protozoan Tritrichomonas musculis (T. mu) can remotely shape the immune landscape in the lungs following colonization. Despite not directly affecting the health of the host, the presence of T. mu in the gut causes accumulation of eosinophils in the lungs and is dependent on the inter-organ migration of intestinal derived inflammatory group 2 innate lymphoid cells (iILC2). This sustained eosinophilia in the lungs also requires interaction between iILC2s, T cells, and B cells, which form a tripartite immune network that provides a specific niche for lung eosinophils. This network exacerbates allergic airway inflammation induced by house dust mite exposure while also limiting early bacterial dissemination following infection with Mycobacterium tuberculosis in mice colonized with T. mu. Collectively, this data indicates that commensal protozoa can tune the severity of multiple pulmonary diseases by triggering a lung immune network that enhances local eosinophilia which can have beneficial or detrimental effects on host fitness under different stimuli.

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HYPOXIA PROMOTES CYTOLYTIC ACTIVITY OF CD8 T CELLS AND PATHOGENESIS IN CUTANEOUS LEISHMANIASIS

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Leishmaniasis is a diseasecaused by protozoan parasites of the genus Leishmania and the mostcommon form of the disease is cutaneous leishmaniasis (CL). A fundamentalquestion in CL is what regulates the development of severe disease, informationthat is critical to develop therapies to ameliorate pathology. In a series ofstudies, we demonstrated CD8 T cell-dependent cytotoxicity as the main inducerof immunopathology in CL. This result was unexpected since IFN-γ production byCD8 T cells plays a protective role by promoting pathogen elimination. Toresolve this paradox, we studied the CD8 T cells in different anatomic sitesand found that the effector function of CD8 T cells in CL depends on theirlocation: while CD8 T cells are cytotoxic (GzmB+) and produce little IFN-γ inthe skin lesions, CD8 T cells in the draining lymph nodes (dLN) have theopposite profile. Importantly, GzmB- CD8 T cells from dLN quickly upregulateGzmB after injection into CL lesions. By transcriptional profiling, we foundthat CD8 T cells in lesions but not dLN have a hypoxic signature. In vivo, weobserved that leishmaniasis lesions are hypoxic using the Oxyphor G4 oxygenprobe and pimonidazole staining. In vitro, we found that induction of hypoxiawas sufficient to convert GzmB- into GzmB+ CD8 T cells, and significantlydecreased CD8 T cells production of IFN-γ. Together these data stronglyimplicate hypoxia as the key factor driving CD8 T cells to become pathogenic inthe skin lesion. In vivo, mice with CD8 T cell deficient in HIF-1α also produced significantly less GzmB in the skinlesions compared to wildtype counterparts. We will also utilize a mouse linewhich has Cre stabilized in low oxygen to specifically delete HIF in the lesionto further analyze how HIF impacts CD8 T cell function in vivo. Together, ourresults suggest that the hypoxic signaling through the transcription factor HIFin CL lesions is the necessary factor that converts protective CD8 T cells intopathogenic cytotoxic T cells in the skin lesion.

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CD30L EXPRESSION ON CD4+T CELLS IS REQUIRED FOR THE DEVELOPMENT OF ALLERGEN- AND HELMINTH-DRIVEN TYPE 2 INFLAMMATION IN THE LUNG

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Type 2 immune responses are associated with helminth infections but also drive allergic disorders. Transcriptomic analyses of house dust-mite (HDM) driven pulmonary type-2 inflammation revealed a marked upregulation in genes associated with the Th2 activation pathways (e.g.IL-4, IL-5, IL-9, IL-13, and IL-33), but also other important inflammatory mediators including TNFSF8 also known as CD30L. Additionally, single cell RNA sequencing on CD45+-sorted lungs cells showed marked expression of CD30L on lymphoid cells, but most noticeably on allergen-activated CD4+ T cells. To explore the role played by CD30L in Type 2 associated pulmonary inflammation, we used two experimental mouse models, including HDM-intranasal sensitization and Ascaris infection in the lungs. Flow cytometry analysis revealed that the effector memory Th2 cells, defined by TCRb+CD4+CD44+CD154+IL-13+ from both HDM-allergic and Ascaris-infected lungs showed a marked over-expression of CD30L, when compared with naive cells. Interestingly, repeated infection with Ascaris parasites increased even further the frequency of CD30L+ Th2 effector cells in comparison with primary infection. We next examined the role of CD30L in the CD4+ T cell differentiation in vitro. Naïve cells from CD30L

KO mice or from naïve WT mice following CD30L blockade during in vitro differentiation into Th2 cells demonstrated a significant impairment of Th2 cell differentiation (fewer IL-4 producing Th2 cells). Finally, to further examine the functional role of CD30L during the development of a pulmonary type-2 inflammation, our data demonstrated that CD30L KO mice following sensitization to HDM failed to induce an allergen-specific memory Th2 cell response in the lungs when compared with WT mice, based on the marked reduction in the frequency of allergen-specific IL-13 producing memory CD4 T cells. This in turn led to diminished HDM-specific IgG1 and IgE levels, as well as a reduction of eosinophils in the lung tissue. Taken together our preliminary findings suggests that CD30L expression on Th2 cells is required for the development of type-2 inflammatory immune responses in the lung tissue.

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HUMAN FILARIAL INFECTION DRIVES A DISTINCT SIGNATURE OF CD8+T CELL POPULATIONS AT HOMEOSTASIS AND IN RESPONSE TO CYTOMEGALOVIRUS (CMV) IN FILARIAL/CMV COINFECTIONS

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Characterization of the T cell responses in chronic filarial infections has focused largely on CD4+ subsets, with little information of CD8+ T cells. Because CD8+ T cells are central to viral-specific effector responses in most viral infections and because many occur in the context of coincident filarial infections, we sought to understand the nature of CD8+ populations and subpopulations in filarial/viral coinfections. We sought to characterize the heterogeneity and function of CD8+ T cells in filarial/cytomegalovirus (CMV) co-infected subjects through the use of multiparameter (26 color) flow cytometry to profile CD8+ subsets from PBMCs collected from 11 filarial-infected subjects (Fil+) and 6 filarial-uninfected controls (Fil-) at homeostasis and in response to cytomegalovirus (CMV) antigen (CD8 and CD4 megapools consisting of 345 peptides). We used a self-organizing map tool (FlowSOM) to profile CD8+ subsets driven by the filarial infection per se and by CMV. Based on the multidimensional profiling and clustering algorithms using data from PBMCs from all subjects at homeostasis (baseline), the Fil+ group had marked expansion of CD8+CD95+CD107a+PD-1+IFN-g+and CD8+CD45RA+CD107a+GranzymeB+IFN-g+ populations that reflect severe exhaustion and being pro-apoptotic. When stimulated with CMV antigen, the CD8+ T cells from Fil+ subjects expanded a population of CD8+GranzymeB+CD57+ cells compared to Fil- subjects ($p<0.03$) but failed to induce additional IFN-g and CD107a, both being important for viral control. Additionally, CMV antigen exposure induced a marked increase in the frequency of a memory CD3+CD8+ subset (CD8+CD45RA+CD161 +CD57+GranzymeB+Perforin+IL17+) whose function remains unknown. Our data suggest that filarial infection is associated with CD8+ T cell exhaustion and apoptosis; further when stimulated with viral antigen these CD8 subpopulations fail to produce the important cytokines necessary for viral control. These findings are likely important to understand the nature of bystander suppression of viral specific responses induced by chronic filarial infections.

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IL-11 REGULATES MUCOSAL RESPONSES IN ACUTE PULMONARY HELMINTH INFECTION

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Larval migration of helminth parasites through the lung drives an early neutrophil-associated inflammation before the establishment of an eosinophil-dominated type-2 immune response. Members of the IL-6 cytokine family, including IL-11, have been described to play a role in acute inflammatory responses. In a mouse model, we observed significantly elevated IL-11 levels in the lung tissue of mice following Ascaris spp. infection (2,196 pg/mL vs 968 pg/mL, $p<0.001$) at 8 dpi compared to naive mice. Flow cytometry and confocal imaging demonstrated that lung CD140a+ fibroblasts and EpCAM+ epithelial cells were major sources of IL-11 in the lungs of Ascaris-infected mice. Anti-IL-11 blocking antibodies during Ascaris infection markedly impaired the influx of neutrophils to the lung, whereas administration of rIL-11 not only induced high levels of G-CSF and CXCL1 but also increased neutrophil influx. By using Ascaris-infected IL-11Ra1 deficient mice, we observed a marked reduction in lung neutrophil influx (20.3 x 105cells vs 51.2 x 105cells, $p=0.030$) and a decrease of neutrophil-associated mediators (e.g., CXCL-1 and G-CSF) in the absence of IL-11 signaling when compared with WT Ascaris-infected animals. To elucidate whether IL-11 production by lung epithelial cells is elicited directly or indirectly, bronchial epithelial cell line (HBEC3-KT) grown in a monolayer on an extracellular gel matrix was shown to produce markedly increased (55% above baseline) amounts of IL-11 following exposure to Ascaris larvae. Moreover, HBEC3-KT cells stimulated in vitro with different recombinant cytokines, including IL-33, IL-1b, IL-1a, and TGF-β, revealed that TGF-β induces high levels of IL-11 in a dose dependent manner. Similar induction of IL-11 was observed in mouse fibroblast cell line (MM14. Lu) stimulated with TGF-β. Further pulmonary Ascaris larval migration drove a marked increase of TGF-β levels in vivo (1476.23 pg/mL vs 986.87 pg/mL, $p<0.001$). Taken together, our data suggests that IL-11 produced in the lung mucosa regulates a neutrophil-dominated inflammation in response to epithelial damage and TGF-β during acute lung helminth infection.

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RAPID INDUCTION OF CLINICAL TOLERANCE IN A PLACEBO-CONTROLLED CLINICAL TRIAL INVESTIGATING REPEATED CONTROLLED EXPOSURE TO SCHISTOSOMA MANSONI

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Epidemiological data from endemic settings suggests that (partial) immunity to schistosomiasis develops over time, and is likely enhanced by repeated infections and treatments leading to enhanced or prolonged antigen exposure. Moreover, animal studies have demonstrated that protection can be achieved after repeated immunisation with irradiated cercariae. In this study, we aimed to investigate the protective efficacy and safety of consecutive exposure-treatment cycles with Schistosoma mansoni (Sm) in healthy, schistosome-naïve participants using the single-sex controlled human Sm infection model. We enrolled 24 participants who were randomised (1:1) to either three (reinfection) or one (infection control) exposures to 20 male cercariae. The infection control group received two mock exposures first. Treatment with praziquantel (or placebo for infection controls) was given 8 weeks after the first and second (mock) exposure. All participants were treated with praziquantel 12 weeks after the third exposure. Throughout the study, adverse events were collected as well as serum to measure circulating anodic antigen (CAA) secreted by juvenile and adult worms to determine infection status. All but one participant completed follow-up. The percentage of participants with detectable infection after the final exposure (CAA ≥ 1.0 pg/mL) in the reinfection group was 82% (9/11) and 92% (11/12) in the infection control group. In the reinfection group, more related adverse events were reported after the first infection (45%) as compared to the second (27%) and third infection (28%). Severe acute schistosomiasis (AS) was observed in both groups after the first infection (2 out of 12 in reinfection group and 2 out of 12 in infection control group), but no AS was reported after the subsequent infections. In conclusion, repeated Sm infection led to clinical tolerance, but did not result in (sterile) protection. Further investigation into the underlying immune response will result in better understanding of immunity to schistosomes.

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COMPREHENSIVE ANTIBODY PROFILING IN SCHISTOSOMIASIS REVEALS IMMUNOLOGICAL SIGNATURES OF ACTIVE INFECTION

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Lack of accurate yet accessible diagnostics for neglected tropical diseases such as schistosomiasis is a critical bottleneck in their elimination. Antibody (Ab)-based tests, currently used for serological screening for schistosomiasis cannot distinguish past from current infection. We have developed a multiplexed 'Ab-omics' platform for deep biophysical characterization (both Fab & Fc ends) of a broad set of antigen-specific Abs including not only their isotype and subclass but also glycosylation, Fc receptor and complement binding. Machine-learning applied to this high-dimensional data can reveal unique Ab signatures predictive of disease state and outcome. Here, we apply the Ab-omics pipeline to Schistosoma mansoni infection. Sera from patients (n=88, from Minas Gerais, Brazil), previously screened for parasite eggs using the Kato-Katz technique, were characterized with the Ab-omics workflow using multiple S. mansoni antigens (SEA, SM25, MEG, CD63, Calumenin) and other helminth and non-helminth antigens. Antigen-coated barcoded beads were incubated with serum and probed with various fluorescently-labeled isotype and subclass probes, tetramerized Fc receptors and lectins. This revealed that SEA-specific IgG titers could not discriminate between individuals who were egg+ and those who were egg-. However, higher SEA and CD63-specific IgG4, Calumenin-specific Ab FcγR2A and SM25-specific Ab FcγR3B binding and antigen-specific Ab sialylation were found in egg+ individuals compared to egg- individuals. With a total of 324 measured features (18 Ab Fc characteristics x 18 antigens) from each patient, application of a new interpretable machine-learning approach (Essential Regression) revealed a complex interplay of proinflammatory (FcγR2A, FcγR3B) and anti-inflammatory (sialylation) Ab features and functions. Machine-learning (LASSO) based feature selection was able to identify a unique set of biomarkers to differentiate egg+ from egg- individuals (AuROC~0.9). Our findings suggest that a purely Ab-based biomarker can achieve accurate diagnosis of current versus past schistosome infection in endemic areas.

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MODELING TO SUPPORT DECISIONS ABOUT THE GEOGRAPHIC AND DEMOGRAPHIC EXTENSION OF SEASONAL MALARIA CHEMOPREVENTION IN BENIN

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Seasonal malaria chemoprevention (SMC) has been implemented in Benin since 2019 and targeted more than 400 000 children under 5 in the northern departments of Alibori and Atacora in 2021. The Benin National Malaria Control Program (NMCP) recently considered an extension of SMC, either demographically - children aged 5 to 10 in the same departments would also receive SMC, or geographically to children under 5 in new departments eligible according to WHO criteria. As neither extension had been tested before, the NMCP turned to modeling to estimate their impact. The model OpenMalaria was calibrated to represent the history of malaria interventions and transmission risk in Benin, as well as the age structure of the population. The future interventions which were already planned (mass net distribution campaigns, SMC in children under 5 in Alibori and Atacora, pilot projects of intermittent preventive treatment in infants) were simulated, together with the two extensions of SMC. The model predicted that the demographic extension of SMC could avert on average 4.6 severe cases per 1000 targeted children between 2024 and 2026, while the geographic extension could on average avert between 13 and 14.3 severe cases per 1000 children under 5, depending on the department. To be less cost-effective than the demographic extension, the geographic extension should thus be three times more expensive, when costs from the 2021 campaign indicate it would cost only 40% more. Numbers of severe cases averted per targeted child were similar between operational zones of departments considered for the geographic extension, probably due to similar transmission risks. These findings led to recommend targeting in priority highly populated zones, as SMC in the three most populated zones could avert as many severe cases as in the six other zones. Modeling allowed not only to choose the geographic over the demographic extension, but also to quantify their comparative impact. Modeling can be used to answer questions from decision-makers when they are closely associated to the process, from the refinement of the modeling question to the choice of epidemiological indicators.

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USING CAUSAL INFERENCE METHODS TO ACCURATELY ESTIMATE THE EFFECT OF INSECTICIDE TREATED NET USE ON THE RISK OF MALARIA INFECTIONS

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Although randomized trials concluded that insecticide treated nets (ITNs) use prevent malaria infections, some observational studies have found no effect or even an increased risk of malaria with ITN use. These conflicting results may be explained by time-varying confounding e.g. perceived malaria risk. Briefly, as transmission increases, subjects tend to increase their ITN use, hence incorrectly suggesting that ITN use is positively associated with the risk of infection in the next time point. When time-dependent confounders are affected by prior exposure, standard methods yield biased results. Marginal structural models (MSM) have been widely used to accurately estimate treatment effect in the presence of time-dependent confounders, but not in ITN use. We estimated the effect of ITN use on the risk of clinical and subclinical malaria infection using MSM with inverse probability of treatment weights (IPTW) and compared results with a regular longitudinal model based on generalized estimating equation (GEE). We analyzed data from a cohort conducted in Malawi where 962 participants (median age=13 years) were enrolled from 198 households and followed for one year (median 11.4 months) in monthly scheduled and unscheduled sick visits. ITN use and perceived malaria risk were collected at every 1-month interval. A total of 938 incident subclinical and clinical malaria infections were detected using qPCR. IPWTs were generated at each time based on logistic regression including history of previous ITN use and other variables associated with malaria exposure. Then, longitudinal GEE MSM with IPTW were fitted for subclinical and any malaria infection outcomes, apart from the regular GEE model. For any malaria infection, GEE MSM with IPTW yielded a non-significant stronger ITN protective effect (OR=0.82; 95%CI=0.63-1.09; P=0.17) compared to the standard GEE analysis (OR regular GEE =0.92; 95% CI: 0.76, 1.11; p=0.37) that underestimated the ITN effect. The MSM with IPTW showed that ITN is mainly effectively protective against subclinical (OR=0.71; 95% CI= 0.52-0.98; P=0.04). Therefore, MSM provides reliable estimates for evaluating ITN impact.

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MATHEMATICAL MODELLING TO SUPPORT STRATEGIC MALARIA PLANNING IN MOZAMBIQUE

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In setting the strategic plan for the period 2023 to 2030, the National Malaria Control Programme in Mozambique incorporated mathematical modelling to estimate the impact of four sub-national intervention plans. A ranking of geographic targets for seasonal malaria chemoprevention (SMC), perennial malaria chemoprevention (PMC), indoor residual spraying (IRS) and RTS,S vaccine from the 2020 stratification provided scenarios to be modelled. These were called "Business as Usual" (BaU) (insecticide treated nets, IRS), "Core" (BaU plus SMC and PMC, "Core Plus" (Core with SMC, PMC and the RTS,S vaccine) and "Ideal" (Core plus with more widespread SMC, PMC and the RTS,S vaccine), all with case management for simple and severe malaria. Using the OpenMalaria model, calibrated using historical data and transmission risk in Mozambique, the scenarios were simulated to assess impact on malaria. Modelled outputs included malaria prevalence, incidence, clinical cases and mortality. Each scenario was costed and cost-effectiveness analysis was used to assess what an optimal plan would entail, maximizing the number of cases averted in the under 5's and in the whole population. Comparing Plasmodium falciparum prevalence in 2030 vs in 2022 at the national level, the reduction in prevalence is 17% for the "Core" package, 19% for the "Core Plus" package and 20% for the "Ideal" package. When taking into consideration the cost of interventions, there exists an optimal plan that averts more cases than the "Ideal" package within the same budget. SMC and PMC appeared to be the most cost-effective interventions, with IRS and RTS,S only optimizing averted malaria cases with very large increments in the budget. Mathematical modelling provides a useful tool to support decision-making, specifically allowing for sub-national stratification. National strategic plans can be developed to optimize the number of malaria cases averted given a fixed budget envelope, and the potential long-term impact can be calculated.

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CAUSES OF UNDER-FIVE DEATH USING A PROBABILISTIC MODEL (INTERVA5) IN QUELIMANE DISTRICT, CENTRAL MOZAMBIQUE

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Community-based information on causes of stillbirths and under-five mortality is limited in many sub-Saharan countries. This is the case in Mozambique, where child mortality continues to be high despite a wide implementation and coverage of public health interventions with demonstrated impact. To understand why mortality levels remain high, we examine the underlying causes of death among stillbirths and children under the age of five years in Quelimane district, Central Mozambique. We aimed to include all stillbirths and under-5 deaths that occurred 12 months prior to the baseline census conducted from January to August 2022 in Quelimane district (population= 349,842). The main cause of death were computed using a computer algorithm InterVA-5. Only one cause of death was assigned for each case. The cause was chosen taking in consideration those with highest likelihood.Verbal autopsies were perform on 280 (79.1%) of a total 354 under-5 deaths identified through baseline census. The mean time between the date of death and verbal autopsy collection was 8.3 (SD, 5.36) months. Over half of the deaths (54.6.%) occurred at a health facility. Birth asphyxia was the most common cause of death among stillbirths and neonates (under 28 days of life), at 57.7% and 40.8% of deaths respectively, and it was more frequent among males. Diarrheic disease was the main cause of death among infants (1-11 months) at 46.0%. For older children aged 1- 4-years, malaria was the main cause of death among females (36.4%) and diarrheic disease was the most common cause in males (30.0%). Congenital malformations played an important role in childhood deaths up to the first year (4.3%). This study provided useful population-based insights on the causes of stillbirths and under-5 death and showed that most deaths occurred at health facilities and were related to preventable causes. Urgent strategic public health action targeting the health sector is needed to reduce facility deaths, including a redoubled attention to antenatal care, especially maximizing and improving the public health strategies currently available in order to save lives.

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INVESTIGATING THE ROLE OF HUMAN MOVEMENT ON DISEASES TRANSMISSION DYNAMIC IN KENYA, A TOOL FOR OUTBREAK PREPAREDNESS

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The spread of infectious diseases is influenced by human movement and its heterogeneity. Urban areas in high-income countries have been extensively studied in relation to human movement and infectious diseases, but there is a lack of research focusing on low-income countries. This study aims to describe the movement of people in two Kenyan urban settings and its impact on infectious diseases. From November to December 2021, we enrolled 200 participants representing the population of Ukunda and Kisumu, two urban settings in Kenya. We collected data on participant movement routines for two weeks through a semi-structured questionnaire. Each location listed by participants was geolocated. Spatial and network analysis were used to describe the movement patterns of participants. Using the results of the statistical analysis merged with data from Google Building, we built two synthetic populations of the study sites. The synthetic populations were used to build an individual-based model simulating a flu-like disease to identify individuals and locations with an important role in disease spread. We identified 702 locations across both sites with a median number of 4 people sharing a location in their routine (interquartile range [IQR]: 2-14 people). The median number of visited locations per person was 5 locations (IRQ: 4-6 locations). The most visited locations outside of individuals' homes were shops and markets, accounting for 42.6% of all listed locations. The distribution of visited locations among participants showed strong heterogeneity following a power-law distribution. The characteristics of movement routines recorded in the two sites were similar. The analysis of model results identified transmission hot-spot locations in the two cities and the fraction of the population which had an important role in disease spread. The results of our study demonstrate the feasibility of merging population surveys and freely available data to identify possible transmission hot-spots in low-income urban settings. The study method could be used to guide response interventions to mitigate and improve preparedness to handle disease outbreaks.

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IMPORTANCE OF COUNTRY PREPAREDNESS IN HANDLING HEALTH EMERGENCY, THE 2023 EBOLA OUTBREAK IN UGANDA

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In September 2022, an Ebola outbreak caused by the Sudan ebolavirus occurred in Uganda. The outbreak was declared resolved in January 2023 with a toll of 142 confirmed cases, 55 of whom later died. As no vaccine is available for the Sudan ebolavirus, Uganda response was based on a range of non-pharmaceutical interventions (NPIs), including case isolation, tracing of case contacts, and population lockdowns to reduce the spread of the virus. The aim of the analyses was to evaluate the impact of NPIs on the Sudan ebolavirus outbreak by simulating scenarios with different response effort. We built a spatially-explicit synthetic population of Uganda which included heterogeneity of human contact and movement. This synthetic population was then used to perform an individual-based model (IBM) to represent the spread of Sudan ebolavirus in Uganda from September 2022 onwards. A baseline model was created to reproduce the epidemic curve of the outbreak, including the adopted NPIs and the timing of their implementation. To assess the effectiveness of the outbreak response, the baseline model was compared to a scenario simulating the NPI response with a 5 months delay, and one with a less-controlled outbreak. The IBM results showed that scenarios with a late intervention response and with an out-of-control outbreak would have resulted in an Ebola outbreak like the one reported by countries affected by the West Africa in 2014-2016. The late response scenario projected an outbreak with 778 (95% confidence interval [CI]: 665-901) cases and 303 deaths (95% CI: 259-351), 5.5 times higher than the reported outbreak. The outbreak simulated using the less-controlled scenario resolved with 1,818 (95% CI: 811-4,774) cases and 709 deaths (95% CI: 316-1862), 12.8 times higher than the reported outbreak. Our results showed how Uganda's rapid response to the Ebola outbreak was able to drastically reduce the toll of the 2022 Sudan ebolavirus outbreak. Our study highlights the significance of preparedness to manage infectious disease outbreaks, as a crucial factor in mitigating the risk of a significant public health emergency

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THE GLOBALMIX PROJECT: COMPREHENSIVELY PROFILING SOCIAL CONTACT PATTERNS IN RESOURCE POOR COUNTRIES

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Social mixing data are the cornerstone of understanding the transmission and modeling the control of pathogens such as SARS-CoV-2, RSV, influenza, and measles that spread via close contact. However, there is a dearth of data on social contact patterns particularly from low-and-middle-income countries. Comparability is hampered with different study protocols, definition of a contact, tool design and data collection procedures and many modelers rely on European contact data projected onto low-and-middle-income country populations. To address this gap, we aimed to quantify social contact patterns in a total of 8 rural and urban sites of Mozambique, Guatemala, India, and Pakistan through The GlobalMix Study. For each country, 1,260 participants reported, in a paper diary, individuals with whom they had contact over two days, and characteristics of those contacts. In addition, members of 126 households carried wearable proximity sensors over 7 continuous days and concurrently kept a diary of all contacts over two of those days. Each sensor autonomously detects dyadic face-to-face (<6 feet separation) interactions between household members. We will present contact rates and matrices stratified by standardized definitions of age, sex, relationship, occupation, location, and duration of contacts for each site and country. We will quantify household and overall temporal network characteristics such as degree, number and duration of contacts, node loyalty and cosine similarity, and further compare these to contemporaneous diary data. We will present output from Mozambique and showcase the utility of our data. We report 8.8 (95% CI 8.4-9.2) and 6.3 (6-6.6) mean contacts per person per day in rural and urban areas, respectively. The highest median contacts were reported by 15-19-year-olds, and the highest assortativity by school children aged 10-14 years. These patterns are consistent with other studies in resource poor settings. An overarching value of The GlobalMix Study is to make the tools, methods, and data available to the scientific community for use in mathematical models of infectious disease transmission and control.

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TRANSMISSIBILITY OF LEISHMANIA DONOVANI FROM HUMAN TO SAND FLIES IN AN AREA ENDEMIC FOR VISCERAL LEISHMANIASIS IN INDIA

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On the Indian sub-continent, visceral leishmaniasis (VL) is a fatal form of leishmaniasis caused by the protozoan parasite Leishmania donovani, and transmitted by the bites of the vector sand fly, Phlebotomus argentipes. To achieve and sustain elimination of VL, the transmission potential of L. donovani exposed individuals from across the infection spectrum needs to be urgently addressed. We conducted direct xenodiagnosis on each of the active VL patients (n=77) and Post Kala-azar Dermal Leishmaniasis (PKDL) patients (n=26), before and after successful treatment, asymptomatic individuals (n=183) and HIV-VL patients (n=14). During xenodiagnosis, 30 - 35 female flies were exposed for 30 min on each site on the subject's forearm and lower leg, or the forearm only. Blood-engorged female flies were held in an environmental cabinet at 28°C and 85% humidity. At 60 -72 hours post- blood meal, flies were dissected and evaluated for L.donovani infection by microscopy as well as by quantitative polymerase chain reaction (qPCR). A subject was considered positive for infectivity to sand flies if promastigotes were observed in one or more individual flies by microscopic exam, or in one or more of the pools of flies by qPCR analysis. We found that 54.6% (42/77) and 77.9%(60/77) of active VL patients transmitted parasites to at least one fly or pools by microscopy and qPCR, respectively. Transmission of infection correlated with severity of VL disease. None of the drug cured VL patients were found xenodiagnosis positive by microscopy at 30 days post-treatment, although 7.7 %(6/77) were still positive by qPCR. Both nodular and macular PKDL patients were infectious to sand flies, with enhanced transmission when the flies were fed on nodular lesions. 92.8%(13/14) HIV-VL co-infected patients transmitted infection to flies. Importantly, none of the 184 asymptomatic subjects were infectious to sand flies. In conclusion, these findings confirm that active VL, PKDL and HIV-VL patients transmit L. donovani to the vector, but that early diagnosis and treatment will effectively remove these individuals as infection reservoirs.

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MOLECULAR IDENTIFICATION OF LEISHMANIA IN STAINED SLIDES FROM PATIENTS WITH CUTANEOUS LEISHMANIASIS IN SANTARÉM, PARÁ, BRAZIL

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Tegumentary leishmaniasis (TL) is an infectious disease caused by the protozoan Leishmania. The correct identification of the species of Leishmania is important epidemiologically and to adequate therapy. For the diagnosis of the disease, parasitological tests are used but they cannot identify species. The use of PCR (polymerase chain reaction) can be performed from different biological samples, such as stained smears stained on slides and previously examined by microscopy. As a target for PCR, the ITS-1 (internal transcribe space-1) region of the ribosomal RNA has an adequate number of polymorphisms for species-level distinction, in addition to conserved regions of diagnostic importance. Our objective was to identify Leishmania species from lesion smears from patients with suspected TL, residing in Santarém, Pará, Brazil. For the procedure, 40 lesion smears stained by Giemsa on microscopy slides, from 40 patients with suspected TL, were analyzed by microscopy (1000X) in the laboratory of the Núcleo Técnico de Vigilância em Saúde(NVTS)/Pará. These smears were subjected to DNA extraction using Qiamp DNA Mini (Qiagen) and the DNA was subjected to PCR, according to the amplification conditions used by GODOY et al, 2020. The amplified (320pb) product was submited to the Sanger sequencing. Our results showed that from 40 slides examined microscopically, 30 were positive and 10 were negative. Of the 10 negatives on microscopy, 100% (10/10) were negative on PCR. Of the 30 positives on microscopy, 83% (25/30) were positive on PCR-ITS-1. 18 samples from 25 submitted to sequencing showed the following results after alignment: 4 Leishmania (Viannia) lainsoni, 4 L. (Leishmania) amazonensis, 1 L. (V.) shawi, 2 L. (V.) guyanensis, 3 L.(V.) braziliensis, 1 L.(V.) naiffi ,1 L.(V.) panamensis and 2 L. panamensisi/guyanensis. Molecular investigation using ITS-1 as a target showed a specificity of 100% and a sensitivity of 83%.The sequencing of the ITS-1 intergenic region showed that there is a great diversity of Leishmania Viannia species in Santarém and L. (V.) braziliensis is not the most prevalent species in Santarém, Pará, as seen throughout Brazil.

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USEFULNESS OF ANTI A-GAL ANTIBODIES AS BIOMARKERS OF THERAPEUTIC RESPONSE IN CHAGAS DISEASE

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Assessment of parasitological cure in Chagas Disease (CD) relies on achieving consistent negative results in parasitological and conventional serological tests. However, conventional serological reagents were optimized for diagnosis. These are based on mixtures of native or recombinant Trypanosoma cruzi antigens and display suboptimal performance as post-therapeutic biomarkers with low specificity and a long period required for negativization after treatment (known as seroconversion). Novel biomarkers are urgently needed. The F2/3 antigenic fraction of T. cruzi tripomastigotes, whose major epitope is the α-Gal glycan (Galp(α1-3) Galp(β1-4) GlcNAc), has been proposed as biomarker of early treatment response. However, its standardization remains challenging as large quantities of live infective parasites are required to produce it. We recently developed a synthetic αGal antigen. Here, we evaluated the use of antibodies anti αGal antigen as a biomarkers of treatment efficacy in a cohort of T. cruzi-infected children. Serological responses against αGal antigen were evaluated using an in-house enzymelinked immunosorbent assay (ELISA) and compared to conventional ELISA (TcELISA). We included 71 children (0-16 years old) with 479 samples in total. At baseline, αGal antibody was reactive in 38/71 patients (53.5%). After treatment, in children < 1 year (n=15) αGal antibodies became negative earlier than TcELISA (median of 8 months [range 1 to 98] and 33.5 mo [range 7 to 99], respectively). In children 1 to 7 years old (n=12) the seroconversion was also earlier than with TcELISA (median of 48 months [range 2 to 107] and 113 months [range 46 to 107], respectively). Finally, in patients older than 7 years (n=11) the median time of negativization with αGal was 62 months [range 26 to 149] whereas TcELISA did not became negative. This is the first study that evaluates the performance of αGal as biomarker of treatment response in CD. Our results suggest that the antibodies anti αGal would shorten follow-up periods following CD treatment. Just as important, αGal would facilitate the implementation of clinical trials with new drugs, an urgent need in CD.

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CUTANEOUS LEISHMANIASIS DISEASE AWARENESS IN HIGH ENDEMIC, RURAL SRI LANKA: NEED FOR IMPROVED HEALTH PROMOTION

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Understanding community knowledge gaps in neglected tropical diseases is vital for planning context-specific prevention and control measures. Over 3000 cutaneous leishmaniasis (CL) cases are reported in Sri Lanka annually. We aimed to assess knowledge of CL among community in a disease-endemic region in Sri Lanka. We conducted a household survey in Anuradhapura district, Sri Lanka using a multi-stage cluster sampling method. The households' health-related decision-makers were the primary respondent. We used a semi-structured interviewer-administered questionnaire developed through a community engagement and involvement approach. Our sample included 1555 participants with a 98.4% response rate. Participants' mean age was 48.2 years (SD=13.8), and 1157 (74.4%) were females. Most had completed 11 years in school (n=634, 40.8%). Participants included housewives (n=637, 41.0%), farmers (n=301, 19.4%), self-employers (n=156, 10.0%) and others (n=461, 29.6%). Among participants, 1250 (80.4%) claimed they had heard of the disease (mostly the local name, 'sand fly or sand flea disease') while only 141 (11.3%) knew the term 'leishmaniasis'. Of those who had heard of the disease, 612 (49.0%) claimed they knew only the name. Among

the participants who knew more about the disease other than its name, 224 (35.1%) were aware that sand fly is the vector of leishmaniasis. The majority reported red (n=173, 27.2%), long-lasting (n=153, 24.0%), and pimples (n=378, 59.4%) as the main characteristics of early cutaneous leishmaniasis lesions. After excluding people with CL, 475 (77.4%) believed they are susceptible to leishmaniasis mainly due to having a family member or neighbor with leishmaniasis and the abundance of Maana in the surrounding area (an invasive grass belonging to the genus Glyceria). Notably, 518 (81.2%) believed leishmaniasis is curable, and 313 (49.1%) knew they should reach the district hospital for treatments. We identified community knowledge gaps related to the vector, clinical manifestations and treatment facilities for leishmaniasis, and public awareness programs should be tailored to address these identified gaps.

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A COST-EFFECTIVE LAMP-PCR FOR SCREENING AND MONITORING CHAGAS DISEASE

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The standard treatment for Chagas disease is efficient during the acute phase but only 1% of patients are treated because of poor early diagnosis. Most currently available PCR-based diagnostic methods are expensive, not portable, and do not consider the genomic variability of the parasite. A more specific, sensitive, and cost-effective tool is urgently needed to improve the early screening for Chagas disease in low-income endemic regions. A loop mediated isothermal amplification (LAMP-PCR) was designed for targeting a highly conserved region in the HSP70 gene of Trypanosoma cruzi. Backward, forward and loop primers were manually designed across a region of 236 bp. The optimal melting temperature and delta G values were estimated in the OligoAnalyzer tool (IDT). Our LAMP-PCR protocol amplified T. cruzi DNA from discreet typing units (DTUs) I, II, IV, V, and VI. The reaction did not amplify DNA from T. rangeli or Leishmania (L. amazonensis, L. braziliensis) used as controls. The proposed method was able to detect about 28 fg of parasite DNA extracted from infected blood samples at 1X106 epimastigotes/mL, equivalent to less than one parasite. Parasite DNA could be detected in different types of samples including blood coat, anticoagulated blood, and buffy coat. This method is fast, temp stable, and cheap. This portable method can facilitate the screening and monitoring of patients in endemic regions for Chagas disease. Further efforts will be focused on simplifying the DNA extraction protocol, evaluating clinical samples, and scaling the method in endemic regions.

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A SET OF DIAGNOSTIC TESTS USEFUL FOR THE DETECTION AND IDENTIFICATION OF LEISHMNANIA PARASITES CAUSING CUTANEOUS LEISHMANIASIS

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The new WHO roadmap for NTDs 2021-2030 identified diagnostics among top priorities to achieve the 2030 targets for Leishmaniases control. Simple, rapid and accurate diagnostics are essential to control CL. Leishmania (L) species identification is essential for diagnosis, patient's management and an adequate therapeutic strategy. Diagnosis tools applied for the identification of L. parasites depends on laboratory equipment and facilities. The aim of this study was to develop a set of innovative and specific molecular tools for L species detection and identification adapted for well as well as poorly equipped laboratories. Using comparative genomic analyses of L. genomes we selected species specific, distinctive targets and designed a range of PCR primer pairs that we assessed for taxa-specific DNA amplification of L species encountered in MENA region. Four primer pairs were retained. Three of them, showing L. species-specific amplification, were investigated to develop a PCR multiplex-lateral flow chromatography (LF) on a customized microfluidics for DNA-DNA hybridization. This test requires basic equipment such as a thermocycler. Readout for detection and identification is made in 3' on the LF after a 2h PCR. Another pair was designed for generic amplification of a L. DNA fragment containing species-specific SNPs adequate for PCR High Resolution melting analysis (PCR-HRM) as an alternative test in well equipped centers with the advantage of detection and identification made by the software at the endpoint (1h30'). Both approaches reduce time to result delivery and obviate the need for agarose gel electrophoresis. Tested on reference L.strains, the tests were shown to consistently identify the studied L. species and to have an analytical sensitivity of detection of 0.01ng & 0.002ng for the PCR-LF and the PCR-HRM, respectively. Tested on cutaneous samples collected from the Parasitology department-Farhat Hached UH Tunisia, the tests showed promising sensitivity & specificity. The study delivers simple and specific tools for accurate detection & identification of L. parasites in clinical samples that could be used as diagnosis tests

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THE PATHWAY TO SUSTAINABLE ELIMINATION OF HUMAN AFRICAN TRYPANOSOMIASIS IN DEMOCRATIC REPUBLIC OF CONGO

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Gambiense HAT (gHAT) has been targeted for elimination as public health problem (PHP) by 2020 and now for elimination of transmission (EoT) by 2030. The Democratic Republic of the Congo (DRC), the most affected country; is inexorably moving towards gHAT elimination countrywide. As the trend of the disease may vary from one region to another, we aim to analyze the disease current results and trend toward gHAT elimination as well as the quality and coverage of gHAT control activities using data archived in the WHO Atlas of HAT from 2000 to 2016 at country, provincial and health district (HD) levels. We found that the prevalence of gHAT in DRC was substantial decreased. However, provinces, like Maindombe and Kwilu remained most prevalent compared to others like Nord Ubangi and Sud Ubangi. HAT screening coverage, population attendance rate to active screening, the proportion of patients who received treatment, and the therapeutic efficacy rate have been identified as factors associated with disease trend. Around 16.0% of the 257 endemic HDs, that reported at least one case of HAT between 2000 to 2016, had not yet reached the target of HAT elimination as PHP according to Franco et al (2020) in 2016. Although the number of people actively screened annually remained almost stable, active screening was poorly implemented according to the recommended algorithm. Nearly two-thirds of endemic HDs were not covered by a health facility (HF) implementing the full range of HAT activities and approximately 40% of endemic health areas were not covered by a HF capable of screening for HAT. Active screening as implemented and the low coverage of passive screening may hide some cases that could be a source of resurgence in the future and do not appear to be sufficient to ensure surveillance in the post-elimination period and provide sufficient confidence in sustainability towards an EoT. And indeed, one fact that appears to support this conclusion is a relative increasing number of cases in the country between 2020 and 2021 from 395 to 425. There is a need to improve coverage and implementation of active and passive screening strategies and monitor to confirm current achievement in DRC.

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DETECTION OF SALMONELLA TYPHI BACTERIOPHAGES IN SURFACE WATERS AS A SCALABLE APPROACH TO ENVIRONMENTAL SURVEILLANCE

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Environmental surveillance, using detection of Salmonella Typhi DNA, has emerged as a potentially useful tool to identify typhoid-endemic settings; however, it is relatively costly and requires molecular diagnostic capacity. We sought to determine whether S. Typhi bacteriophages are abundant in water sources in a typhoid-endemic setting, using low-cost assays. We collected drinking and surface water samples from urban, peri-urban and rural areas in 4 regions of Nepal. We performed a double agar overlay with S. Typhi to assess the presence of bacteriophages. We isolated and tested phages against multiple strains to assess their host range. We performed whole genome sequencing of isolated phages, and generated phylogenies using conserved genes. S. Typhi-specific bacteriophages were detected in 54.9% (198/361) of river water samples and 6.3% (1/16) drinking water samples from the Kathmandu Valley and Kavrepalanchok. Water samples collected within or downstream of population-dense areas were more likely to be positive (72.6%, 193/266) than those collected upstream from population centers (5.3%, 5/95) (p=0.005). In urban Biratnagar and rural Dolakha, where typhoid incidence is low, only 6.7% (1/15, Biratnagar) and 0% (0/16, Dolakha) samples contained phages. All S. Typhi phages were unable to infect other Salmonella and non-Salmonella strains, nor a Vi-knockout S. Typhi strain. Representative strains from S. Typhi lineages were variably susceptible to the isolated phages. Phylogenetic analysis showed that S. Typhi phages belonged to two different viral families (Autographiviridae and Siphoviridae) and clustered in three distinct groups. S. Typhi bacteriophages were highly abundant in surface waters of typhoid-endemic communities but rarely detected in low typhoid burden communities. Bacteriophages recovered were specific for S. Typhi and required Vi polysaccharide for infection. Screening small volumes of water with simple, low-cost plaque assays enables detection of S. Typhi phages and should be further evaluated as a scalable tool for typhoid environmental surveillance.

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SEROINCIDENCE OF SALMONELLA ENTERICA SEROVARS TYPHI AND PARATYPHI IN CHILDREN IN KENYA

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Salmonella enterica serovars Typhi and Paratyphi can cause variable disease which can range from asymptomatic carriage to significant illness and mortality globally. Diagnosis is often limited by access to microbiologic laboratories in low and middle income countries where there is high prevalence and risk of infection. Surveillance is therefore impacted with no great understanding of the population-level burden of infection. Here we applied a new serologic tool to measure population-level incidence from cross-sectional serosurveys using anti-IgG and IgA responses to a typhoidal pore-forming toxin (Hemolysin E). We tested serum from Kenyan children collected in 2017 in four different communities, two in western Kenya (Kisumu and Chulaimbo) and two in coastal Kenya (Ukunda and Msambweni). We found a substantial difference in typhoidal exposure in western and coastal Kenya, with an approximate 10-fold higher difference in the IgG response in the coastal communities, suggesting a higher burden of these pathogens in the region. We also explored for associated risks, specifically evaluating the role of the water source, population density, and wealth in those communities and found high seroincidence with non-piped water, higher population density, and lower wealth. These insights are of great importance as there is limited serological typhoid data available from Kenya and especially the coastal region. This information can shed more evidence for the importance of surveillance and vaccination implementation for the Kenyan community.

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EFFICACY AND SAFETY OF A TYPHOID CONJUGATE VACCINE: FINAL ANALYSIS OF A FOUR-YEAR, PHASE 3 TRIAL IN MALAWIAN CHILDREN

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A single dose of typhoid conjugate vaccine has been shown to be safe, immunogenic, and efficacious in preventing typhoid fever in Malawian children for 18 months post-vaccination. Here, we present long-term efficacy data after an extended surveillance period of 4-4.61 years post-vaccination in Malawi. We assessed the efficacy and safety of a typhoid Vi polysaccharide tetanus toxoid conjugate vaccine (Vi-TT) in a phase 3, double-blind, randomized controlled clinical trial in Blantyre, Malawi. Participants aged 9 months - 12 years were individually randomized in a 1:1 ratio to receive single dose Vi-TT or control meningococcal capsular group A conjugate vaccine (MenA). Vaccine efficacy was defined as the percentage reduction in the incidence rate ratio for blood-culture confirmed typhoid fever among Vi-TT compared to MenA recipients. We included 28,130 children in the intention-to-treat analysis (14,069 Vi-TT and 14,061 MenA). During passive surveillance, we screened 39,174 febrile study children, 10,777 met suspected typhoid eligibility criteria and 10,136 blood cultures were collected. Typhoid fever occurred in 24 Vi-TT participants and 110 controls, translating to an overall incidence of 39.7 (95% confidence interval (CI): 25.4-59) and 182.7 (95% CI 150.1-220.2) per 100,000 person-years of observation, respectively, and an overall vaccine efficacy of 78.3% (95% CI 66.3%-86.1%). When stratified by sequential one-year time intervals, vaccine efficacy was 83.4% (60.1%-94.3%) between year 0 and 1 after vaccination, 77.0% (42.9%-92.3%) between year 1 and 2, 77.0% (16.4%-95.8%) between year 2 and 3, 68.2% (27.2%-87.6%) between year 3 and 4, and 90.1% (30.5%-99.8%) between year 4 and 4.61. Vaccine efficacy was similar among three age groups (<2 years: 70.6%; 2-5 years: 79.6%; ≥5 years: 79.3%; p=0.85). There were 554 severe adverse events and 34 deaths; none of them were considered related to vaccination. In conclusion, a single dose of Vi-TT is safe, and provides high sustained vaccine efficacy over at least 4 years after administration in all age groups studied, including children who will receive the vaccine during routine immunization.

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CROSS PROTECTION OF HETEROLOGOUS SHIGELLA FLEXNERI 2A AND S. SONNEI CHALLENGE IN HEALTHY ADULTS IN THEUNITED STATES

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Shigella is a major cause of diarrhea in low- and middle-income countries, as well as becoming increasingly antibiotic resistant. Efforts are underway to develop vaccines against Shigella; however, the diverse serotypes of disease-causing strains necessitate a multivalent vaccine. Understanding conserved epitopes and correlates of protection can aid in the design of broadly protective vaccines. This controlled human infection model (CHIM) study sought to assess cross-protection and markers of protection after challenge and heterologous rechallenge with different Shigella serotypes. Cohort 1 was challenged with S. sonnei, followed by a S. flexneri 2a challenge 3 to 4 months later. Cohort 2 was challenged with S. flexneri, followed by a S. sonnei challenge 4 months later. Naïve volunteers were included with each rechallenge to ensure acceptable attack rates. Stools were collected and tested for the challenge organism. Blood and stool samples were saved for immunologic assays. A total of 46 individuals were enrolled; 28 received S. sonnei, of which 19 were rechallenged with S. flexneri. Eighteen subjects received S. flexneri 2a; 10 were rechallenged with S. sonnei. In preliminary analyses, of the naïve volunteers who were challenged with S. sonnei, 18/28 (64%) met the consensus criteria for shigellosis or required early treatment. Of the volunteers challenged initially with S. flexneri 2a, 13/17 (77%) met shigellosis or early treatment criteria. Among volunteers initially challenged with S. sonnei, 4/19 (21%) met shigellosis or early treatment criteria following subsequent challenge with S. flexneri. In contrast, among volunteers initially challenged with S. flexneri, 8/10 (80%) met shigellosis or early treatment criteria following S. sonnei challenge. Stool culture data support the clinical findings. Immunologic analyses are ongoing. In conclusion, prior S. sonnei exposure provides significant protection against S. flexneri 2a. Prior S. flexneri 2a infection provides no clear protection against subsequent S. sonnei infection. These data raise intriguing questions about conserved epitopes and immunological memory.

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DEVELOPMENT OF A SHIGELLA MULTIVALENT BIOCONJUGATE VACCINE: A PHASE I/II RANDOMIZED, CONTROLLED AND AGE DESCENDING STUDY INCLUDING DOSE FINDING IN KENYAN INFANTS

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Shigella is among the most common causes of severe diarrhea and dysentery worldwide, especially among young children from lower resourced countries and travelers. Although several oral Shigella vaccines have been clinically evaluated, risk of reactogenicity and potential reversion back to a pathogenic phenotype have proven challenging. Thus, a new type of vaccine to prevent shigellosis is key. The O-antigen serotype-specific immune response detected in association with convalescence from shigellosis has encouraged development of a new generation of glycoconjugates as an alternative vaccine strategy against Shigella. A Shigella flexneri 2a bioconjugate has shown, in a controlled human infection model, protection from the most severe form of the disease after challenge with S. flexneri 2a strain 2457T. In addition, immune responses post vaccination were associated with a lower disease severity score. The potential of bioconjugation to develop a high fidelity and cost-effective multivalent Shigella vaccine targeting the most common serotypes contributing to global morbidity and mortality has been exploited. The tetravalent Shigella4V bioconjugate, including O-antigens from S. flexneri 2a, 3a, 6 and sonnei, has been evaluated for safety and immunogenicity in the target population of 9 months old infants. The trial was conducted in Kenya starting with a step 1, age descending and dose-escalating cohort, followed by a step 2 dose finding cohort where the target population received a 3 dose schedule of the bioconjugate delivered with and without alum adjuvant. The doses used were 4, 12, 24 and 48 µg which each represents the total polysaccharide across the four Shigella O-antigens. The last patient last visit occurred in Q4 2022 and immunogenicity and safety data (from the target population) from the interim analysis (IA) was made available in Q3 2022, the remaining data will be available in Q4 2023. The IA data has shown good immunogenicity 1 month post 2nd vaccination across all treatment groups and serotypes along with well distributed and mostly mild safety events. Following the positive IA results, we have progressed towards the next steps.

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HUMAN MILK OLIGOSACCHARIDES AND CAMPYLOBACTER JEJUNI INFECTION RISK IN NICARAGUAN CHILDREN

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Campylobacter jejuni infection causes acute gastroenteritis and is associated with malnutrition, stunting, and cognitive delays. C. jejuni uses α-1,2 fucosylated and sialylated oligosaccharides on the intestinal epithelia as binding factors to infect the gut. Human milk oligosaccharides (HMOs) in breastmilk may protect against C. jejuni infection by acting as decoy receptors for C. jejuni and by shaping the gut microbiome. We examined HMOs and C. jejuni infection risk in an observational cohort of non-exclusively breastfed infants in Nicaragua. HMO composition at 2 months (range 1.1-4.8) was measured with fluorescent high-and-ultra-high-pressure liquid chromatography. Children were surveilled weekly for diarrhea, and C. jejuni in stool was detected using qPCR of the 16S rRNA and cadF genes followed by Sanger sequencing. We mapped cumulative risk of C. jejuni infection over 36-months by tertiles of concentrations of the α-1,2 fucosylated HMOs 2'-fucosyllactose (2'FL) and lacto-N-fucopentaose-I (LNFP-I), and the siallylated HMOs 3'-siallylactose (3'SL) and 6'SL. We also assessed the 12 and 36-mo relative hazards (HR) of C. jejuni infection for each HMO stratum, adjusting for total weeks of any breastfeeding at the time of HMO collection. Analyses were stratified by child secretor and Lewis B phenotypes which determine oligosaccharide expression in the gut epithelium. Of 419 mother-child pairs with breastmilk analyzed, 49 (12%) had at least one C. jejuni infection. Surprisingly, in the first 12 months of life, Lewis B and secretor children consuming the top tertile of 3'SL (HR=2.09, 95% CI 1.02, 4.30), had twice the risk of C. jejuni infection compared to children consuming the bottom tertile of both HMOs. This difference attenuated slightly between 12-36 months. As expected, Lewis B children consuming milk in the top tertile for 2'FL (HR=0.5, 95% CI 0.24, 1.03) and LNFP-I (HR=0.49, 95% CI 0.25, 0.99) had half the risk of infection of children consuming milk in the lowest tertile for both HMOs. Our findings support evidence that the α-1,2 fucosylated HMOs 2'FL and LNFP-I may protect against C. jejuni infection in breastfeeding children.

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PREDICTING SEROCONVERSION FAILURE AFTER ORAL POLIO VACCINATION IN CHILDREN IN LOW- AND MIDDLE-INCOME COUNTRIES

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While there has been tremendous progress in the eradication of poliovirus, close to 50 countries are either experiencing or are at high risk of re-emergence of polio. The majority of polio infections are in low and middle income countries (LMICs), where oral vaccine efficacy is lower than in higher-income countries, associated with poorer vaccine immunogenicity. Our goal was to develop a clinical prediction rule to identify children likely to fail to seroconvert after polio vaccination. We used clinical and demographic data from the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) study to build predictive models to identify children who fail to seroconvert following oral polio vaccination (OPV) in eight countries. Failure to seroconvert was defined as a log2 titer <3 for polio-virus serum neutralizing antibody titers measured using WHO-standardized microneutralization assays collected at 7 and 15 months of age. We screened variables using random forests, and assessed predictive performance with random forest regression and logistic regression using cross-validation. Of the 1294 children analyzed who received at least three doses of OPV, 15.1% and 11.5% had failed to seroconvert at 7 and 15 months, respectively. Top predictors were well-aligned with known risk factors of seroconversion failure, including breastfeeding practices, indicators of household crowding, maternal education, and acute diarrhea and respiratory symptoms. Our ability to predict seroconversion failure was poor for serotype 1, serotype 3, and polio of any serotype (AUC)=0.58 (95% CI: 0.55, 0.62) for a model including the top five predictive variables. For serotype 2, we achieved an AUC=0.77 (95% CI: 0.73, 0.81) with five predictive variables. Our findings indicate that use of prediction rules may help identify children at risk of failure to seroconvert after vaccination, which could help target polio eradication efforts. We also demonstrate that predictive ability differs by serotype, and how risk factors may not be the best predictors of vaccine immunogenicity.

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ASSESSING THE CONTRIBUTION OF NUCLEOTIDE VARIATIONS IN THE MAYARO VIRUS GENOME TO ITS ADAPTIVE LANDSCAPE IN AEDES AEGYPTI AND ANOPHELES ALBOPICTUS MOSQUITOES

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Mayaro virus (MAYV) is an arbovirus of the Alphavirus genus and the etiologic agent of Mayaro fever (MAYF). MAYV is maintained in forests by an enzootic cycle, and no urban outbreaks have been confirmed to date. With the expansion of the Aedes (Stegomyia) mosquito distribution, and MAYV continuous circulation, we hypothesized that infection of these mosquitoes by MAYV could result in adaptive mutations that favor transmission. To investigate mutations that could arise in MAYV infection of A. aegypti and A. albopictus from Salvador, Brazil, we fed these mosquitoes a blood meal containing 7 log10 PFU/ml of clonally derived MAYV strain CH (genotype D) which resulted in an 85% infection rate at 14 days post feeding. The salivary glands were dissected and organized into 3 pools of 15 glands each. The RNA was deep sequenced with Illumina (NextSeq 550), and analyzed for single nucleotide polymorphisms using LoFreq software. For A. aegypti and A. albopictus, respectively, we identified 128 and 30 minority variants that were not present in the parental virus. We selected mutations occurring in the genome of at least one MAYV strain on the Pubmed database for study, to reflect those that could be occurring in nature, and applied a Z-score to rank them. We have cloned and rescued four of these naturally occurring mutations in the Mayaro CH background and tested their fitness for infection and transmission using competition assays in mosquitoes and dissected the salivary gland for analysis. Only one of these viruses, with a mutation in nsP3, had increased fitness as assessed using salivary gland samples. For future studies of nucleotide variations in the context of MAYV genotype L, we also described and characterized a novel MAYV clone, strain BeH505465. These results suggest that minority variants that provide a modest fitness advantage for MAYV transmission by Aedes mosquitoes could arise after a single infection round and may contribute to the risk of urban outbreaks. This work underscores the critical importance of surveillance efforts to quickly identify urban emergence and the urgent need to develop effective vaccines and treatments against MAYF.

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USING BARCODED WEST NILE VIRUS TO QUANTIFY THE IMPACT OF TISSUE-ASSOCIATED BOTTLENECKS ON VIRUS POPULATIONS IN ENZOOTIC AND BRIDGE VECTORS OF WEST NILE VIRUS

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Each step during arthropod infection constitutes a physiological barrier to virus transmission. These barriers impose stochastic reductions on arbovirus populations, frequently termed bottlenecks. In vectors of West Nile virus (WNV), the main bottlenecks associated with infection, dissemination, and transmission occur during infection of and escape from the midgut and salivary glands. The severity of these bottlenecks varies by tissue and potentially mosquito species. Arboviruses such as WNV are maintained in nature by multiple mosquito species with varying levels of vector competence (VC, efficiency of pathogen transmission). Importantly, the extent to which population bottlenecks and VC are linked is poorly understood. Additionally, quantitative analyses of mosquito bottlenecks on virus population dynamics are limited. To address these knowledge gaps, we used molecularly barcoded WNV (bcWNV) to quantitatively measure tissue-associated population bottlenecks in Culex tarsalis, Culex quinquefasciatus, and Aedes aegypti - three variably competent WNV vectors. In all species we observed reductions in bcWNV population richness and complexity upon escape from the midgut and entry of the salivary glands. In Aedes mosquitoes, barcode diversity in the midgut was significantly lower compared to Culex species. Importantly, population richness and complexity did not differ significantly between salivary glands and saliva from any species, indicating that bottleneck severity post-midgut infection does not differ between vectors of varying competence. Barcode frequency in the input population was positively correlated with successful transmission in Culex, however, high frequency in the bloodmeal did not guarantee transmission in any species. Cx. tarsalis, had the highest probability of transmitting rare barcodes when compared to lower competence vectors. This work provides insight into stochastic influences on virus population dynamics during mosquito infection in vectors of varying competence and suggests that vector competence may influence the successful transmission of rare virus variants in a population.

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INTRA-HOST DIVERSITY IN VACCINATED COVID-19 PATIENTS INFECTED WITH DIFFERENT SARS-COV-2 VARIANTS

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Virus Intra-Host Genetic Diversity (IHGD) can influence transmission and virulence by evading host immune response and disease severity, especially for SARS-CoV-2 variants. First, to evaluate the IHGD in unvaccinated (Uv, individuals infected with SARS-CoV-2, without any dose of vaccine) and vaccinated (V, individuals vaccinated with two doses of CoronaVac - Butantan/Sinovac) patients, we analyzed 120 COVID-19 samples from São José do Rio Preto and surrounding cities, obtained from April to July 2021. Total RNA was extracted, and the whole-genome sequencing was performed using Illumina CovidSeq. Using Pangolin COVID-19 Lineage Assigner Tool, these genomes were classified into Gamma lineage. The intra-host single nucleotide diversity analysis was carried out using LoFreq, and annotation and prediction of genetic effects was annotated using the SnpEff. The inference of selective pressures was performed using HyPhy to detect codons evolving on diversifying (DS) or purifying selection (PS). Our results evidenced that vaccination with CoronaVac favors negative selection at the intra-host level, in different genome regions, especially in nonstructural protein-coding genes, preventing further SARS-CoV-2 genetic diversity and reinforcing the importance of vaccination to reduce virus transmission. After this, we aim to analyze the influence of booster doses on IHGD of SARS-CoV-2 in COVID-19 patients infected with other variants. So far, total RNA and whole-genome sequencing have been carried out on 762 samples from patients with two or three doses of vaccine, obtained from October 2021 to December 2022. Genomes were classified in the VOCs Delta and Omicron, of which 475 correspond to patients who received two doses of vaccine, and 287 correspond to patients who received three doses. Our next steps are subdividing the samples based on vaccination status, vaccine type (inactivated virus, viral vector, and RNA technologies), and SARS-CoV-2 variant to compare intra-host diversity in different conditions and investigate possible immune-escape mutations among vaccinated individuals.

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VIRAL SEQUENCE DATA FOR EPIDEMIOLOGICAL CHARACTERIZATION OF GLOBAL DENGUE VIRUS OUTBREAKS

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Dengue is a re-emerging arbovirus that poses a significant public health risk. Dengue virus exhibits complex disease dynamics driven by a range of factors including those acting at the evolutionary scale such as clade replacement, ecological scale such as climate change, and demographic scale such as urbanization. These factors influence the emergence and expansion of the virus, resulting in outbreaks in previously naïve areas. Despite the increase in frequency of dengue virus outbreaks in recent years, a detailed characterization of these outbreaks and identification of potential evolutionary, ecological and demographic drivers of dengue introduction and subsequent spread has not been conducted. In this analysis we use publicly available viral sequence data downloaded from online databases to characterize detected outbreaks of dengue virus, and determine the influence of evolutionary, ecological and demographic drivers on dengue outbreaks. Viral sequence data annotated with date and location information corresponding to the envelope gene portion of dengue 2 virus was downloaded from publicly available online databases. Maximum likelihood phylogenetic trees were inferred in RaxML from aligned sequences and used to define sequence clusters corresponding to dengue outbreaks. Outbreaks sequences were defined as genetically similar clusters of sequences collected within a date range from the same location. Birth-death skyline models in BEAST2 were used to infer key epidemiological parameters of each identified outbreak cluster, including time varying effective reproductive number and sampling proportion. Epidemiological parameters derived from phylodynamic models were used to compare global outbreaks of dengue 2 virus and show the potential influence of evolutionary, ecological and demographic drivers on dengue outbreaks. Our analysis utilizes a global sequence dataset to determine the factors influencing dengue virus outbreaks.

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THE IMPACT OF TEMPERATURE ON WEST NILE VIRUS MOSQUITO BOTTLENECKS AND ANTIVIRAL IMMUNITY

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West Nile virus is an arbovirus that is mainly transmitted by Culex mosquitoes. Within a mosquito, viruses encounter four physical barriers during systemic infection: midgut infection barrier, midgut escape barrier, salivary gland infection barrier, and salivary gland escape barrier. The strength of each of these barriers varies by virus, mosquito species, and other factors (e.g., microbiome, coinfection, etc.). Temperature is frequently the strongest abiotic factor impacting the efficiency of WNV transmission by Culex. However, the relationship between temperature and the strength of each bottleneck within the mosquito is poorly understood. Arboviruses exist in nature as genetically complex mutant swarms, with bottlenecks stochastically reducing the size and complexity of these virus populations. To mimic this genetic diversity, we utilized a barcoded West Nile virus (bcWNV) containing ~106 unique genetic markers that are approximately fitness neutral. We infected Cx. tarsalis with bcWNV and held them at 22°C, 26°C and 30°C to determine the role of temperature on the strength of population bottlenecks during arbovirus infection of mosquito vectors. We observed similar infection rates and viral loads in all mosquito tissues regardless of temperature. Using deep sequencing, we will determine the extent to which temperature impacts WNV population diversity and complexity. Additionally, increased temperature is known to alter many aspects of mosquito biology, but its impacts on mosquito antiviral immunity are currently unclear. We will thus characterize how temperature impacts mosquito antiviral responses to determine if altered temperatures change expression of innate immunity (focusing on the JAK-STAT, IMD, Toll, and RNAi pathways). Together, these results will shed light on the relationships between temperature, virus evolutionary dynamics and antiviral immunity.

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GENOMIC SURVEILLANCE DURING THEFIRST-EVER HYPERENDEMIC TRANSMISSION OF ALL FOUR DENGUE VIRUS SEROTYPES IN NICARAGUA IN 2022 REVEALS NEW VIRAL INTRODUCTIONS POST-PANDEMIC

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Nicaragua, as with most Central and South American countries, has been severely impacted over the last decades by major epidemics of dengue. Since dengue virus (DENV) detection in 1985, co-circulation of serotypes has been limited to two or three, with one always predominating. However, for the first time in the country's epidemiological history, we detected the co-circulation of all four serotypes of DENV in Nicaragua in 2022. Here, we describe the molecular and epidemiological characteristics of the 2022 epidemic to better understand the evolutionary histories of DENV currently circulating. Our findings show an introduction of a new clade of DENV-1 into the country more closely related to viruses circulating in Ecuador in

2014 than to prior DENV-1 circulating in Nicaragua in 2016, although both fall within the American/African genotype V. DENV-2 sequences were all members of the same lineage that recently dominated in Nicaragua, in association with the 2016 and 2019 epidemics, falling within the American/Asian genotype II. DENV-3 viruses, last circulating in Nicaragua in 2014, fell within the same genotype III (Indian subcontinent) as before but formed a distinct group more closely related to Southeast Asian strains from as recent as 2019 as well as strains circulating in Florida and Cuba in 2022 than to prior Nicaraguan strains. The sequences of DENV-4, which very rarely causes clinical cases in Nicaragua, all fell within genotype IIB and descended from a widespread South American lineage with strong similarity to recent records from Mexico (2021) and Florida (2022). Our study reveals a shift in the epidemic dynamics in Nicaragua with a rise to co-dominance of DENV-1 and DENV-4 taking over where DENV-2 was formerly most common, and a strong influence of introduction and global exchange shaping the pattern of DENV circulation for three of the four serotypes. With a resurgence of travel following pandemic-related border closure and re-openings, DENV co-circulation of multiple serotypes across much broader regional scales could impact herd immunity and case severity rates and have other public health impacts yet to be determined.

5075

METAGENOMICS IDENTIFIES EMERGING AND RE-EMERGING VIRUSES IN NIGERIAN COHORTS WITH ACUTE FEBRILE ILLNESSES, INCLUDING PATHOGENS OF GLOBAL CONCERN

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Effective infectious disease surveillance is essential for clinical care and pandemic prevention, but few clinical tests are widely available. Additionally, the presence of one pathogen does not always mean the absence of others, and many infections have overlapping, nonspecific symptoms. Lack of diagnostics is challenging in low- and middle-income countries (LMICs), where the disease burden is the largest. As a result, misdiagnoses with common infections or a lack of diagnosis often occur. Metagenomics can identify species in samples, diagnose infections, and track outbreaks. However, metagenomics is typically used in highly resourced environments, with a need for information on its most valuable and practical application. We applied and evaluated metagenomic sequencing in three different contexts: population-level surveillance of cases suspected of Lassa Fever, investigation of three suspected outbreaks, and diagnosis of clinically challenging cases. We characterized viral infections in the plasma of 612 samples collected in Nigeria over four years (2017-2020) to assess the suitability of unbiased metagenomic sequencing for pathogen surveillance and detection. We made sequencing libraries using the Illumina Nextera platform and assigned taxa to reads via the Microsoft Premonition pipeline, followed by de novo assembly of viral genomes. Using this single workflow, we assembled the genomes of 13 viruses, including the first genomes of human blood-associated dicistrovirus and Coxsackievirus-B3 from Nigeria. We also identified the aetiology of two outbreaks – yellow fever virus and Monkeypox virus – and correctly failed to identify an infectious aetiology in a suspected outbreak that was ultimately determined to be caused by pesticide poisoning. We identified plausible etiologies in two of the eight clinically difficult cases. Therefore, a regional, Nigerian-driven metagenomics approach to public health problems can quickly and accurately identify different pathogens. Genomics infrastructure in LMICs provides an opportunity to use infectious disease genomics thoughtfully as we move beyond the SARS-COV2 pandemic.

5076

ASSESSING RISK FACTORS FOR MALARIA AND SCHISTOSOMIASIS AMONG CHILDREN IN MISUNGWI, TANZANIA, AN AREA OF CO-ENDEMICITY: A MIXED METHODS STUDY

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Malaria and schistosomiasis are two major parasitic vector-borne diseases that are a particular threat to young children in rural areas of Sub-Saharan Africa. In the present study, we investigated factors that are associated with malaria, schistosomiasis, and co-infection among school-aged children, using an explanatory sequential mixed-methods approach. A cross-sectional study was conducted in January 2022 in Misungwi, Lake Victoria zone, Tanzania, that sampled 1,300 children aged 5 to 14 years old for malaria and schistosomiasis. Mixed-effect logistic regression models were used to assess the association between infection prevalence and seroprevalence, and environmental determinants that create favorable conditions for vectors and parasites and social determinants that relate to disease exposure. Community mapping combined with direct field observations were conducted in August 2022 in two selected villages from the cross-sectional study to understand specific water use behaviours and to identify potential malaria mosquito larval breeding sites and freshwater snail habitat. The prevalence of malaria, seroprevalence of schistosomiasis, and co-infection in this study were 40.4%, 94.3%, and 38.1%, respectively. Individual-level factors emerged as the primary determinants driving the association with disease infection, with age and sex (boys vs girls) being statistically and positively associated with malaria, schistosomiasis, and co-infection ($P<0.05$ for all). Community maps identified many unimproved water sources in both villages that were used by humans, cattle, or both. We found that children primarily fetched water, and that unprotected wells were dedicated for drinking water whereas ponds were dedicated for other domestic uses and cattle. Although not identified in the community maps, we found hand pumps in both villages that were not in use because of unpleasant taste and cost. This study improves our understanding of social and environmental factors that are associated with malaria, schistosomiasis, and co-infection which can inform potential entry points for integrated disease prevention and control.

5077

ONE HEALTH APPROACH TO NIPAH VIRUS OUTBREAK INVESTIGATION AMIDST OF COVID-19 PANDEMIC IN BANGLADESH, 2021-2022

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Nipah virus (NiV) is an emerging bat-borne virus causing fatal encephalitis outbreaks. Until 2020, Bangladesh reported 319 NiV cases with >70% mortality. Amidst the COVID-19 pandemic, A multidisciplinary team investigated five suspected NiV spillover events in three districts of Bangladesh between 2021 and 2022 to identify the source, behavioral risk practices, and environmental exposures. We collected epidemiological, behavioral, and ecological data from outbreak communities and biological specimens of bats. We captured 60 Pteropus medius bats per outbreak event and environmental pool urine samples (N=314) from seven bat roosts within 10km radius of the outbreak's epicenter. The bat samples were tested for NiV by rRT-PCR and consensus PCR assay targeting rdrp genes of paramyxovirus (PMV) to detect known and novel PMV and to screen serum samples using multiplex Luminex assay for henipavirus panel. We detected two novel henipa-like paramyxoviruses in bats. The seroprevalence of NiV was 15.2% (34, CI: 10.74%-20.56%), and Hendra virus was 1.3% (3/224), Cedar 1.3% (3/224), Mojiang 0.9% (2/224) and Kumasi virus 1.3% (3/224). The behavioral investigation showed that all cases had a history of drinking contaminated raw date palm sap (RDPS) within 14 days prior to the onset of symptoms. In the outbreak communities, the participants have the habit of drinking RDPS 73.1% (CI: 67.04%-78.51%), eating bat bitten fruits 17.96% (CI: 13.36%-23.35%). Moreover, around 47% of the respondents had date palm trees in their household, among 74.78% were nursing. Serological and virological data showed diverse henipavirus circulating in bats. The high density of date palm trees and habits of drinking raw sap and eating half-eaten fruits in the outbreak communities. Drinking bat contaminated RDPS might be the source of NiV infection in humans. We recommend stringent one health surveillance and awareness campaigns in high-risk communities to reduce human-bat interactions and minimize spillover of the bat-borne virus to humans.

5078

DELINEATING THEROLE OF RATS, CLIMATE AND ENVIRONMENT AS DRIVERS OF LEPTOSPIRA SPILLOVER TRANSMISSION USING ECO-EPIDEMIOLOGICAL GEOSTATISTICS IN AN URBAN BRAZILIAN INFORMAL SETTLEMENT

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Rat-borne leptospirosis is an emerging zoonotic disease in marginalised urban settings globally. Spillover transmission is driven by complex interactions between humans, the rat reservoir, rainfall and the microenvironment, but has not been studied through a One Health approach. We conducted a longitudinal eco-epidemiological study in a high-risk community in Brazil, by following a cohort of 2,115 residents during a three-year period (2014-2018) and ascertaining serological evidence for leptospiral infection during biannual serosurveys. A concurrent rat ecology study collected information on the fine-scale spatial distribution of tracking plate measurements of 'rattiness', our proxy for rat abundance and exposure of interest, during each of the six follow-up periods. We developed and applied a novel eco-epidemiological spatiotemporal geostatistical framework to jointly model rattiness and human infection risk. The overall cohort infection rate was 11.9 (95%CI, 11.0, 12.9) infections per 1,000 person-months. We found that residents who were male, with low literacy skills, walked barefoot, had experienced heavy rainfall or household flooding, or who lived in households at low elevations, close to an open sewer or with a soil backyard were at increased risk of infection. Rattiness was associated with infection risk at all elevation levels (OR 1.17 95%CI 1.01, 1.42), but more strongly at high elevations (OR 1.52 95%CI 1.23, 1.87). This relationship was the same in the dry and rainy seasons. These findings provide evidence for two key Leptospira spillover mechanisms. Rat shedding close to the household acts as a source of baseline infections throughout the year, particularly in higher elevation areas where flood-driven pathogen dispersion is limited. Periods of intense rainfall then drive excess infections through large flooding-associated outbreaks. In addition to informing targeted intervention for urban leptospirosis, this study provides a methodological basis to model interactions between reservoirs, environment and human risk behaviours which may be generalisable to other One Health threats with complex epidemiology.

5079

BREAKING TRANSMISSION: A TRANSDISCIPLINARY ONE HEALTH APPROACH TO IMPROVE HOOKWORM CONTROL

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Hookworm disease is a major global public health concern, despite targeted control programs of at-risk populations. The success of these programs has been hindered by the rapid re-infection rates linked to persistent reservoirs and the low sensitivity of conventional coprodiagnostic techniques employed.In study 1, we used standard faecal flotation (SFF) and a multiplex qPCR assay to calculate and compare species-specific cure and egg reduction rates of single dose albendazole (400 mg) against hookworm infections at community level. In study 2, we combined microscopic and molecular typing to unveil infections by hookworm-like parasites in people in rural communities. In study 3, we developed a novel multi-host (dog and human) transmission model of Ancylostoma ceylanicum, the main zoonotic hookworm in Asia, and compare the effectiveness of human-only and "One Health" (human plus dog) MDA strategies under a range of eco-epidemiological assumptions.We revealed a substantial difference in cure rate of hookworm infection(s) following albendazole treatment using the SFF (81.5%) and mqPCR (46.4%) assays, and provide the first data on the efficacy of this drug against the zoonotic hookworm A. ceylanicum. In study 2, we identified infections with Trichostrongylus spp. of livestock origin and spurious passage of Melodoygine eggs in people living in remote communities. Finally, we show that One Health interventions—targeting both dogs and humans—could suppress prevalence in humans to ≤ 1% by the end of 2030, even with only modest coverage (25-50%) of the animal reservoir. With increasing coverage, One Health interventions may even interrupt transmission.These findings show that the adoption of refined a transdisciplinary One Health

approach is central to monitoring hookworm infections and the success of control strategies, which can ultimately aid in reducing associated morbidity in human populations. We provide evidence that One Health MDA strategy could be highly effective against A. ceylanicum hookworm in endemic regions of Southeast Asia and beyond and will be essential for sustained elimination and reaching the WHO 2030 goals.

5080

BARRIERS AND ENABLERS TO THE IMPLEMENTATION OF THE ANTIMICROBIAL RESISTANCE NATIONAL ACTION PLAN IN MALAWI

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Antimicrobial resistance (AMR) is a major threat to global health resulting in over 1 million deaths annually. The WHO Global Action Plan on AMR (2015) was adapted in Malawi, as the National Action Plan (NAP) on AMR, retaining similar objectives. Adaptation of global policies to local contexts often besets by challenges. We therefore conducted a qualitative study to explore barriers and enablers to the implementation of AMR NAP in Malawi. National data collection involved 22 in-depth interviews (IDIs) with policymakers and stakeholders, and 2 series of semi structured interviews with AMR core group members. District data was collected through 15 IDIs with district policymakers within one health sectors in Blantyre and Chikwawa districts. Data was analyzed thematically. Results showed that AMR in Malawi is socially constructed as an issue of one health, development, healthcare policy, health security threat, and innovation. Enablers for the NAP in Malawi include the use of One Health approach; strong Ministry of Health leadership; use of AMR policy champions; political will; and media engagements. Barriers within sectors included lack of priority setting, coordination, relationships, reporting and use of data, capacity, resources, and evidence. Outside MoH, AMR was viewed as a human health issue, there was incomprehension, sectors working and being resourced in silos, lesser engagement in environmental sector, water splits between ministries, duplicated functions among agencies. For improved AMR fight in Malawi, our study recommends updating legislation and enforcement; increasing awareness of communities and politicians; improving data for AMR in humans and animals; linkage and use of "strong" existing programmes e.g., HIV, decentralisation; and increased and reallocation of resources.

5081

A PLANETARY HEALTH INNOVATION FOR DISEASE, SUSTAINABILITY, FOOD, WATER, AND POVERTY CHALLENGES IN WEST AFRICA

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Many communities in low- and middle-income countries globally lack sustainable, cost-effective, mutually beneficial solutions for infectious disease, food, water, and poverty challenges, despite their inherent interdependence. Here, we provide support for the hypothesis that agricultural development and fertilizer use in West Africa increase the burden of the parasitic disease schistosomiasis by fueling the growth of submerged aquatic vegetation that chokes out water access points and serves as habitat for freshwater snails that transmit Schistosoma parasites to >200 million people globally. In a cluster randomized controlled trial where we removed invasive submerged vegetation from water points at 8 of 16 villages (i.e., clusters), control sites had 1.46 times higher intestinal Schistosoma infection rates in schoolchildren and lower open water access than removal sites. Vegetation removal did not have any detectable long-term adverse effects on local water quality or freshwater biodiversity. In feeding trials, the removed vegetation was as effective as traditional livestock feed but 41-179 times cheaper and converting the vegetation to compost provided private crop production and total (public health plus crop production benefits) benefit-to-cost ratios as high as 4.0 and 8.8, respectively. Thus, the approach yielded an economic incentive—with important public health co-benefits—to maintain cleared waterways and return nutrients captured in aquatic plants back to agriculture with promise of breaking poverty-disease traps. To facilitate targeting and scaling of the intervention, we lay the foundation for using remote sensing technology to detect snail habitat. By offering a rare, profitable, win-win approach to addressing food and water access, poverty alleviation, infectious disease control, and environmental sustainability, we hope to inspire the interdisciplinary search for planetary health solutions to the numerous and formidable, co-dependent global grand challenges of the 21st century.

5082

APPLYING A ONE HEALTH DISPARITIES FRAMEWORK TO ADDRESS THE SOCIAL GRADIENT AND HEALTH DISPARITIES OF BLASTOCYSTIS SP. INFECTION IN NORTHEAST MADAGASCAR

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Blastocystis sp. is a globally distributed enteric protozoan parasite that infects humans and a wide range of non-human animals. Its global distribution and wide host range contribute to its high prevalence and strain diversity in humans and other animals, particularly in low-income countries, where it is estimated to infect 30-60% of people. By applying the One Health Disparities framework, our research aims to study exposure disparities by identifying characteristics that expose some community members more than others to Blastocystis sp. We used a mixed-methods approach to investigate the predictors of Blastocystis sp. infection in a population of rural small stakeholder farmers in northeast Madagascar undergoing rapid change in their natural environments. We hypothesized that low socio-economic status, low educational attainment, low health literacy, hygiene practices, and high animal contact would increase the risk of Blastocystis sp. infection. We surveyed and collected fecal samples from 184 adults in one rural village. Fecal samples were screened using DNA metabarcoding, and predictions were tested using generalized linear models (GLM). We found that 64% of participants were infected with Blastocystis sp. representing 114 genetic variants and 4 subtypes. We identified Blastocystis sp. infection risk was higher in individuals who were middle aged (46-60 years old; 18-25 year reference category), lived in a house with wood plank flooring (concrete flooring reference category), washed hands with only water (soap and water reference category), and increased interactions with poultry (rodent reference category). The results suggest that demographic, socio-economic, hand hygiene, and animal interactions influence infection with Blastocystis sp. and highlight health interventions to mitigate zoonotic disease transmission in a low-resource setting. Future research could investigate whether Blastocystis sp. infections are associated with specific disease symptoms, or if they instead represent asymptomatic infections.

5083

EMERGENCE AND SPREAD OF HEARTLAND AND BOURBON VIRUSES IN NEW YORK STATE

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Heartland virus (HRTV, Phenuviridae: Bandavirus) and Bourbon virus (BRBV, Orthomyxoviridae: Thogotovirus) are emerging tickborne viruses in the United States (US). HRTV and BRBV were both identified from human cases in the Midwestern US in 2009 and 2014. Since the discovery of HRTV, more than 60 cases have been recorded in 14 states and at least 4 cases of BRBV in 3 states. Vector surveillance conducted during epidemiological investigations for HRTV and BRBV and results of experimental infection studies led to the incrimination of Amblyomma americanum as the vector for both viruses. While A. americanum are typically found in midwestern and southern regions of the US, this species has experienced a recolonization of former territory and an expanded geographic range now extends as far north as southern coastal Maine. Passive surveillance through commercial laboratory testing first identified HRTV and BRBV in New York State (NYS) in 2018 and 2019, respectively. Enhanced surveillance efforts conducted in Suffolk County since have consistently detected the viruses in A. americanum with high seropositivity rates observed in white-tailed deer. To further our understanding of the emergence and spread of these viruses in NYS and the northeastern US, we conducted full genome sequencing and phenotypic characterization on HRTV and BRBV isolates from 2018-2022. Preliminary sequencing results revealed the existence of distinct clades of both HRTV and BRBV when compared to midwestern isolates. Characterization in cell culture and experimentally infected A. americanum revealed little phenotypic distinction among and between the midwestern and NYS HRTV isolates. NYS BRBV isolates, however, display high levels of both genetic and phenotypic variability compared to each other and representative midwestern BRBV isolates. We also found BRBV but not HRTV NY isolates infect and replicate in Ix. scapularis following virus immersion. Genotypic divergence of both HRTV and BRBV suggest multiple, separate introductions of each virus into NYS with emergence of varying phenotypes potentially due to adaptation to geographically distinct transmission cycles.

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INTERSPECIES CO-FEEDING TRANSMISSION OF HEARTLAND VIRUS BETWEEN A NATIVE TICK SPECIES, AMBLYOMMA AMERICANUM, AND THE INVASIVE EAST ASIAN TICK, HAEMAPHYSALIS LONGICORNIS

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The Asian Longhorned Tick, Haemaphysalis longicornis, is an invasive species from East Asia that has recently established populations in 18 states in the U.S. and continues to expand its geographic range. In its native range, H. longicornis is the main vector of the bandavirus, Severe Fever with Thrombocytopenia Syndrome virus (SFTSV). SFTSV is genetically closely related to Heartland virus (HRTV), an emerging North American tick-borne bandavirus responsible for human disease cases in the midwestern, northeastern, and southern United States. Our laboratory recently demonstrated that H. longicornis ticks can transovarially transmit HRTV, and we also have evidence suggesting horizontal transmission of HRTV from H. longicornis to vertebrate hosts. The main vector species for HRTV is the native Amblyomma americanum tick, which shares overlapping geographic territory with the invasive H. longicornis tick. In recent field studies, all three life stages of invasive H. longicornis have been detected feeding alongside native A. americanum ticks on the same host animals (e.g., deer, raccoons, opossums). Consequently, we hypothesize that invasive H. longicornis ticks co-feeding with native HRTV-infected A. americanum can acquire virus independent of host viremia, and that co-feeding HRTV transmission is dependent on localized skin infection. Using an in vivo tick transmission model, we tested our hypothesis by co-feeding HRTV-infected A. americanum nymphs with uninfected H. longicornis larvae or nymphs and screened the fed H. longicornis ticks for the presence of HRTV at different co-feeding proximities on the host. Using q-RT-PCR, HRTV RNA was detected in fed H. longicornis larvae and nymphs collected from multiple mice, providing evidence of interspecies co-feeding transmission of HRTV. Interestingly, this interspecies co-feeding transmission of HRTV occurs in the absence of host viremia; therefore, it is possible that a localized skin infection facilitates HRTV transmission between co-feeding ticks in the absence of host viremia. Experiments are underway to further examine the role of host skin in co-feeding transmission of HRTV.

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BORRELIA BURGDORFERI ENZOOTIC CYCLE IN CONSTANT FLUX

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The enzootic cycle of Borrelia burgdorferi, the agent of Lyme disease, relies on larval deer ticks feeding upon mammalian hosts to acquire infection. White-footed mice are thought to be the most important reservoir for immature deer ticks, but other hosts can also serve as a source of infection. The relative importance of a host is determined by local habitat conditions that often favor certain species. Identification of the dominant reservoir host at individual sites would greatly facilitate risk reduction measures by allowing targeted efforts. However, very little work has been done to understand the stability of host species' contribution to the enzootic cycle over time. Using our established methods for bloodmeal analysis on questing nymphal ticks, we followed two field sites, Martha's Vineyard and Nantucket Island, for 4 years to determine how bloodmeal hosts of nymphal ticks change over time. In addition, we examined the stability of the enzootic cycle at each site by identifying Borrelia-infected ticks by PCR and determining the host from which they had acquired infection. In 2018, mice were the predominant host on Nantucket having fed 58% overall and 63% of the infected nymphs. Over time, this steadily declined to 13% overall and none of the infected ticks. Borrelia rates fluctuated between 12% and 26%, and the hosts responsible for infected nymphs differed each year. On Martha's Vineyard, shrews were the dominant host for ticks in 2019, feeding 37% overall. However, they fed only 18% of infected ticks. Instead, mice were the predominant reservoir host, having fed 41% of the infected nymphs, despite only having fed 15% overall. Shrews remained the dominant host throughout the study, but the prevalence of infection steadily dropped from 17% to 5%. We conclude that the enzootic cycle of B. burgdoferi is in constant flux; the species contributing Borrelia-infected ticks at a single site can vary greatly from year to year. Furthermore, the species that feeds the most ticks may not be the most important source of infection.

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SPATIOTEMPORAL EVOLUTION OF LYME DISEASE IN NORTH CAROLINA FROM 2010 TO 2020

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Lyme disease is the most common vector-borne disease in the United States with a majority of cases occurring in the Northeast and upper Midwest. While historically a low incidence state, North Carolina (NC) has seen substantial increases in reported Lyme disease cases over the past decade. The aim of this study was to characterize the spatiotemporal evolution of Lyme disease in NC from 2010 to 2020. Confirmed and

probable cases reported to the NC Division of Public Health were included in the analysis. Cases with a documented travel history to high or medium-transmission states were excluded. The study period was divided into four subperiods: 2010-2012, 2013-2015, 2016-2018, and 2019-2020. Data were aggregated by zip code of residence of the identified case. Absolute change in incidence per 100,000 from 2010-2012 to 2019-2020 was mapped to identify zip codes with the largest changes. Global and local spatial autocorrelation analyses were performed to evaluate the overall distribution of cases and identify high incidence zip codes with high incidence neighboring zip codes (i.e., hotspot areas) for each period. Overall, we found the largest absolute changes in incidence, up to 464.7 cases per 100,000 people in zip codes located in Ashe County, in the northwestern part of the state and extending towards Buncombe County. The distribution of cases became increasingly and significantly clustered over the study period, from a Moran's I of 0.012 ($p = 0.126$) in 2010-2012 to a Moran's I of 0.403 ($p < 0.05$) in 2019-2020. Hotspots included 22 high incidence zip codes in the 2019-2020 subperiod in the northwestern part of the state, largely co-located with areas experiencing the largest absolute changes in incidence. The results demonstrate the rapid emergence of Lyme disease in northwestern NC over the past decade. Incidence rates in many of the highest transmission zip codes now approach those reported in high-transmission states such as Maine and Rhode Island. Efforts targeted to these geographic areas are urgently needed to educate local residents, medical providers, and public health officials in order to prevent and ultimately reduce the burden of Lyme disease.

5087

ECO-EPIDEMIOLOGY OF RICKETTSIA SPP. IN RURAL ANDEAN COMMUNITIES: FIRST REPORT OF R. MONACENSIS AND R. RAOULTII-LIKE ORGANISMS IN SOUTH AMERICA AND THEIR POTENTIAL VECTORS

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Tick-borne rickettsioses are emerging zoonoses with public health implications. In the Andean region of Piura, northern Peru, a seroprevalence of Spotted Fever Group rickettsiae of 10-19% was reported in humans. In addition, the vector of Babesia microti has been found infesting domestic animals in this region. The close contact of rural Andean human populations to potential reservoirs of these tick-borne diseases and their vectors highlights the emerging risk of pathogen spread. We conducted a cross-sectional study in five rural Andean communities in Piura, to improve the understanding of the epidemiology and enzootic ecology of Rickettsia spp. and Babesia spp. We collected dried blood samples from febrile human patients, and ectoparasites and tissue samples from wild and peridomestic rodents. We used real time-PCR (qPCR) targeting the rickettsial conserved gltA gene, and conventional PCR targeting the Babesia 18S rRNA gene to screen all samples. Ticks that were positive for Rickettsia spp. were amplified using conventional PCR for the 17 kDa gene followed by Sanger sequencing. Of the 23 ticks collected, 3 (13%) were qPCR-positive for Rickettsia spp. The 17 kDa amplicon derived from one Ixodes boliviensis tick showed a high degree of similarity to R. monacensis (99.3-99.5%), while another from a tick in Amblyomma maculatum species complex was 100% identical to R. raoultii. Of the 130 rodents captured, 2 (1.5%) were qPCR-positive for Rickettsia spp. (Rattus rattus and Akodon mollis). All 32 human samples were qPCR negative for Rickettsia spp. and all samples were PCR negative for Babesia spp. This is the first molecular detection of R. monacensis and R. raoultii-like organisms in South America, expanding their geographic range beyond Europe and Asia. Results indicate that Rickettsia spp. are circulating among peridomestic and wild rodents and their ticks. An evaluation of vector competence and capacity will be crucial to elucidate whether the A. maculatum species complex is among the vectors of R. raoultii-like organisms. Sequencing of all 17kDa positive samples using gltA and sca5 genes is ongoing to confirm rickettsiae circulation.

5088

SCRUB TYPHUS OUTBREAK IN AUSTRALIAN MILITARY PERSONNEL

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Scrub typhus (Orientia tsutsugamushi) is a bacterial disease transmitted following the bite of an infected mite. A recent outbreak involving 24 personnel from two Australian Defence Force (ADF) infantry units occurred following separate training events conducted at Cowley Beach Training Area (CBTA), northern Queensland, during June 2022.Investigation of this outbreak highlighted the potential severity as well as the difficulty in accurate diagnosis of the disease. Seven of the 24 diseased personnel presented to hospital, with five admitted. All hospitalized soldiers responded to doxycycline treatment. Challenges to diagnosis and accurate case classification included initial difficulties in recognising case clustering following geographic dispersion of personnel post-training exercise, large numbers of cross-reactive serological results flagging positivity to unrelated infections, requirements for repeat blood testing to inform serological diagnosis, and the need to specifically request scrub typhus serology, in addition to standard rickettisal diagnostic tests, through the contracted pathology service provider. Investigation findings regarding the use of relevant personal protective measures including doxycycline prophylaxis, and associated barriers, will also be presented. Rickettsial disease is recognised as a likely underdiagnosed cause of pyrexia in people in disease endemic regions, including Northern Queensland. Outbreak occurrence highlights the need for improved understanding regarding the geographic and ecological risk factors for disease. Diagnostics for forces that may be deployed in austere environments in the Western Indo-pacific region also require improvement.

5089

ESTIMATING THE SEROINCIDENCE OF SCRUB TYPHUS USING ANTIBODY DYNAMICS FOLLOWING INFECTION

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Scrub typhus is an acute febrile illness caused by the bacterium Orientia tsutsugamushi. Characterizing the population-level burden of scrub typhus is challenging due to the lack of accessible and accurate diagnostics. We describe a new approach using information about seroresponse after infection to generate population-level scrub typhus seroincidence estimates. We use data from two clinical studies of scrub typhus patients enrolled in Chiang Rai, Thailand, and Vellore, India, and representative population data from two serosurveys in and around the Kathmandu valley, Nepal, and Vellore, India. The samples were tested for IgM and IgG responses to Orientia tsutsugamushi-derived recombinant 56-kDa antigen using commercial ELISA kits. We used Bayesian hierarchical models to fit two-phase models to the antibody responses from scrub typhus cases and used the joint distributions of the peak antibody titers and decay rates to estimate population-level incidence rates in the cross-sectional serosurveys. We compared this new method to a traditional cut-off-based approach for estimating seroincidence. Among 18 to 29-year-olds, the seroincidence of scrub typhus was 886 (95% CI 432-1817) per 100,000 person-years in India and 945 (95% CI: 616-1449) per 100,000 in Nepal. Seroincidence rose with age, reaching a rate of 3231 (95% CI: 2630-3969) per 100,000 among 50 to 89-year-olds in Vellore, India. The seroincidence rates estimated using a cutoff were half the rates we estimated using antibody dynamics. The approach described here can be deployed prospectively,

coupled with existing serosurveys, or leverage banked samples to rapidly characterize scrub typhus burden and generate scrub typhus seroincidence estimates that are comparable across populations, regions, and time.

5091

A CONTENT REVIEW OF COVID-19 RELATED APPS USED IN VIETNAM

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Various digital applications (apps) have been developed to combat the spread of COVID-19. In Vietnam, many COVID-19 apps have been launched by private developers or the Ministry of Health with overlapping features and purposes, which greatly confused Vietnamese residents. This problem has raised a concern about the usefulness and effectiveness of these apps during the pandemic in Vietnam. We aim to evaluate all current Vietnamese COVID-19 apps including features, purposes and functionality, advantages, disadvantages, and ethical issues of each app, to eventually provide reliable resources for the Vietnamese government to develop a unique national COVID-19 app. We conducted a systematic and manual search on 1st October 2022, on PubMed, Scopus, Google, and BBC New's official website to identify all available COVID-19 apps in Vietnam. The relevant apps were discussed to reach a consensus and comply with a list of included apps for further assessment. Thirty Vietnam-based COVID-19 mobile apps were identified in the Apple and Google Play Store, which were evaluated through opinions on these stores, along with an analysis carried out by the research team members. These are duplicated features and functions among apps detected and some apps have lacked important functionality such as vaccination-related features. It is crucial to develop one complete app that fulfills the most useful features, addresses the common errors, and replaces all current apps to facilitate user experience.

5092

COMPREHENSIVE COST-EFFECTIVENESS ANALYSIS OF A NEW COMPARTMENTAL MODEL FOR BACTERIAL MENINGITIS CONSIDERING THE INFLUENCE OF THE MEDIA

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Mathematical epidemiology has paid some attention to the study of bacterial meningitis because of the severity of the disease and the way it spreads through a population. In this paper, we formulated a new compartmental model for meningitis to study the impact of media on reducing the severity of the disease in Ghana. We obtain the control reproduction number and the herd immunity rate in the presence of vaccination. We noticed that the meningitis death rate could be controlled with an increase in publicity of the dynamics of the spread of the disease and the ability to seek immediate medical treatment. We conduct a sensitivity analysis using Latin hypercube sampling. It is noticed that the transmission rate, vaccination, and the media have a negative nonlinear correlation. The effects of media, vaccination and treatment as a function of time are also investigated using an optimal control model. We display the efficiencies of the controls and demonstrate the mean and incremental cost-effectiveness ratios. The cost of controlling meningitis in the presence of media, vaccination, and treatment is discussed, and we hope this study will further educate the public on this topic.

5094

COST-EFFECTIVENESS ANALYSIS OF FOURTH GENERATION RAPID DIAGNOSTIC TESTING FOR HIV AMONG MEN WHO HAVE SEX WITH MEN IN NIGERIA

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Fourth-generation HIV rapid diagnostic tests for HIV include both HIV antibodies and p24 antigen, increasing the ability to detect acute HIV infections. The study compared the costs and health outcomes of using fourth-generation rapid diagnostic tests to third-generation (antibody-only) tests when screening men who have sex with men (MSM) from a health system perspective in Nigeria. A health economic cost-effectiveness model was developed to compare outcomes for different screening options. A decision-tree structure was used for evaluating the screening outcomes based upon the diagnostic accuracy and timing of the test. Health and costs associated with the different screening outcomes were modelled using a Markov-based framework to reflect clinical progression of HIV infection with early and late treatment. The population was modelled throughout a lifetime horizon, and captures costs, quality-adjusted life years (QALYs), disability-adjusted life years (DALYs), and transmission of new cases. Input parameters were derived from local sources where available and adapted from regional estimates where Nigeria-specific estimates were lacking. Given the absence of HTA guidelines in Nigeria, an international reference case for economic evaluation in low-middle income countries was used. Given an assumption that 0.7% of patients are pre-seroconversion at the point of testing, screening MSM who are unaware of HIV status yields an additional cost of US $2,260 per DALY averted, and US $802 per QALY gained, both of which are below Nigeria's GDP per capita. The relative value of fourth-generation tests increases with a higher proportion of cases with asymptomatic and acute infections. The analysis shows that switching to fourth-generation tests may be an effective strategy for improving detection of new cases - especially those who are pre-seroconversion - and prevent further transmission of HIV at a feasible cost.

5096

DIGITIZATION OF THE NATIONAL LONG ACTING INSECTICIDE TREATED MOSQUITO NET MASS DISTRIBUTION CAMPAIGN IN GUINEA: PROCESS, CHALLENGES AND LESSONS LEARNED

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In Guinea, mass distribution of Long-Acting Insecticidal Nets (LLINs) is a key component of malaria prevention strategies and has contributed to a significant decrease in malaria prevalence since 2013. In 2022, the country implemented the first ever digitization of the fourth, tri-annual national LLIN distribution campaign to improve data quality and optimize the different stages of the campaign. The purpose of this study was to analyze the implementation process and document the challenges and lessons learned from this digitization. We conducted a descriptive study to document the planning and implementation of the campaign stages. A mobile application called "MILDA2" integrated with the District Health Information Software 2 (DHIS2) was used to enumerate households, scan QR codes for distribution and manage the flow stock of LLINs in real time. Campaign results, challenges encountered, and lessons learned are described in this work. A total of 17,160,359 individuals were enumerated (< 5.8% of the projection) among 2,746,044 households nationwide, which was 4% more than the

micro-planning projections, corresponding to an average of 6.2 people per household. 8,927,983 LLINs were distributed nationally for a total of 2,511,150 households served (i.e., 91.4% of the households enumerated). 16,473,945 people (96%) were covered by LLINs (1 LLIN for every 1.9 people). With the support of its partners, Guinea successfully conducted its first fully digitized national LLIN campaign in 2022. Despite myriad challenges in the planning and implementation of the campaign, digitization improved data completeness, transparency in LLIN management, and geographic coverage. Maintaining this innovation is essential for future, effective mass campaign implementations for better malaria prevention and control in Guinea.

5097

SYSTEMATIC REVIEW AND META ANALYSIS ON PREVALENCE OF ORAL SUBMUCOUS FIBROSIS

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Systematic Review and Meta analysis on prevalence of Oral SubmucousFibrosis.ABSTRACTOral submucous fibrosis (OSF) is a potentially malignant condition, linked to the causativehabit of chewing areca nut. Since the discovery of this condition in the 1960s, numerousepidemiological studies have been conducted to assess its prevalence. With the proliferationof commercially available areca nut products and its increasing popularity amongst the youth,the prevalence has been on the rise. The present meta analysis was initiated to collate andanalyse the data on the prevalence of the condition in India and different parts of the world.Literature search from databases like Pubmed, PubGet, NLM, Ovid, Medline, Cochrane andElsevier was conducted using specific keywords. The search period ranged from 1960 to2022. After screening the studies based on inclusion and exclusion criteria, data on studydesigns, associated habits, prevalence rates, country of study were extracted. Meta analysisusing random effects model was performed to obtain pooled prevalence rate. Additionally,subgroup analysis, funnel plot and sensitivity analysis were also performed. The pooledprevalence of OSF among the included 61 studies was 9% (95% CI:5% to 35%). Majority ofthe studies were conducted in Asia (95.1%) and 52 studies belonged to India. The prevalenceof OSF varied from least being 0.03% to highest rate of 85.5% in the present study. Thefunnel plot and Egger's test indicated presence of publication bias. The present meta-analysisreview shows that reported prevalence rates of OSF in worldwide vary in wide degreedependent upon the region and sample size. The variation in a large part is also due to skewedand biased study designs and sample selections. Thus, the need for a comprehensiveepidemiological survey spread across many countries to assess the prevalence rate of OSFbecomes even more necessary.

5098

WHO ESPEN COUNTRY HEALTH INFORMATION PLATFORM

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The Country Health Information Platform (CHIP) is a web-based data visualization tool, utilizing cloud hosting, web-APIs, and business intelligence software, that allows anyone to review key NTD data from official annual reporting forms submitted to the World Health Organization (WHO) and the International Trachoma Initiative (ITI). These annual forms are single year forms that report on endemicity for the five PC-NTDs, treatments delivered to eliminate these NTDs, and the impact surveys conducted to determine the future treatment strategy. Because the forms are single year, and elimination of PC-NTDs as a public health problem requires multiple years of intervention, CHIP presents these data overtime to assist national programmes and partners to make informed decisions using these data. Since launching 2021, CHIP as been scaled up to be available to all countries with an active NTD programme in the WHO African region. We will use this poster session to present the tool, highlight the functionality, and present the results from pre-test and post-test training surveys.

5099

HEALTH AND ECONOMIC IMPACTS OF SUBSTANDARD UTEROTONICS IN GHANA AND NIGERIA

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The study is to advance Universal Health Coverage (UHC) by building the evidence base on the threat that substandard uterotonics pose to postpartum hemorrhage (PPH) and maternal mortality. We modeled the use of substandard uterotonics in preventing PPH and assessed the health and economic burden on governments, healthcare providers, payors, and families in Ghana and Nigeria. A decision-tree model was built to simulate vaginal and cesarean section delivery, quality of uterotonics and their use, and risk of PPH. We then compared scenarios results with and without substandard uterotonics. The model simulated women giving birth in different settings based on their characteristics using data from countries' Demographic and Health Survey. Use of uterotonics by delivery setting and subsequent steps of treatment were simulated. Literature and key informants were utilized to generate model inputs and assumptions. Risks of health outcomes were abstracted from a Cochrane review on the effect of uterotonics. Data from the E-MOTIVE trial was used to model health outcomes based on oxytocin quality. Data on quality of the commonly used uterotonics were also utilized. We estimated that millions of mothers in Ghana and Nigeria receive poor-quality uterotonics annually, resulting in hundreds of thousands of preventable PPH cases. Without substandard uterotonics, healthcare providers could reduce uterotonic use and save on blood transfusions, while averting thousands of maternal deaths due to PPH. Substandard uterotonics also led to out-of-pocket and insurance costs for additional treatments, blood transfusions, and longer hospitalizations, placing an avertable economic burden on families and governments. The study demonstrates that use of quality-assured uterotonics would result in economic savings and a reduction in occurrence of PPH. Reducing the health and economic burden of PPH in low-resource settings is essential toward decreasing maternal mortality. This underlines the importance medicines quality assurance systems play for country governments to scale the implementation of UHC.

5100

SPATIOTEMPORAL ANALYSIS OF THE RELATIVE RISK OF POST-INFECTIOUS VERSUS NON-POST-INFECTIOUS HYDROCEPHALUS AND ITS RELATIONSHIP WITH ENVIRONMENTAL FACTORS

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The bacteria, Paenibacillus thiaminolyticus, has recently been identified as contributing to neonatal sepsis and subsequent post-infectious hydrocephalus (PIH) in Ugandan infants. The absence of infection in mothers suggests that the infants must have been exposed to the bacteria in the first days of life. The biogeography of P. thiaminolyticus is currently unknown, however, the spatiotemporal distribution of patients with PIH shows evidence of inhomogeneity. Based on an observed seasonal increase in PIH cases when the rains come in, it is hypothesized that the distribution of the bacteria is related to environmental variables. This work uses data collected over a 20-year period by the CURE Children's Hospital of Uganda (CCHU) in Mbale on infants with hydrocephalus. The data includes cases of PIH and non-post-infectious hydrocephalus (NPIH). By using NPIH as the control population we estimate the relative risk (RR) of PIH. We assume that the point pattern data given by the spatiotemporal coordinates of the PIH and NPIH cases are realizations of two underlying inhomogeneous Poisson point processes. By examining the ratio of their intensities, we are able to fit a logistic model to the data. Our model identifies areas of elevated RR which can be utilized to inform diagnostics and treatment at point-of-care. We demonstrate increased RR i) spatially: in the area north-west of lake Kyoga, throughout the study period and

ii) temporally: for the years 2006-2012, across the whole of Uganda. By incorporating information on environmental variables, including rainfall, temperature, and the Standardized Precipitation Evapotranspiration Index (SPEI), we can explain some of this increased RR. In particular, we find evidence of a significant positive association between RR of PIH and rainfall. By incorporating real-time data, the model can be used to predict times, locations, and environmental conditions with increased risk of PIH, to inform preventative measures, and to direct further studies into the biogeography of P. thiaminolyticus.

5101

IS SUB-SAHARAN AFRICA READY FOR DIGITAL CLINICAL TRIALS?

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Digital Clinical trials, also known as Decentralized Clinical Trials (DCTs), leverage digital technologies to facilitate recruitment/ retention, data collection, and analyses and hence, increase the efficiency of clinical trials in developing interventions against various health problems. DCTs are gaining traction after their iterative implementations during the COVID-19 pandemic. Guidelines and recommendations for implementing DCTs in developed countries are in their formative stage, while applicable recommendations for developing countries are yet to be described. DCTs have several utility features, which make them very attractive for implementation in Sub-Saharan Africa (SSA). Opportunities that enable the implementation of DCTs in the continent, such as an increasing trend in innovative health technologies, are also flourishing in the continent. However, several potential challenges still require a workaround before implementing such trials in SSA. This paper highlights the potential opportunities and challenges surrounding the implementation of DCTs in SSA and puts forward suggestions on how to exploit the opportunities and address the challenges. The paper also highlights the survey's findings on the perceptions of experts with experience conducting DCTs in SSA on the opportunities and challenges of implementing DCTs in the continent.

5102

SPATIO-TEMPORAL OCCURRENCE, BURDEN, RISK FACTORS AND MODELLING METHODS FOR ESTIMATING SCRUB TYPHUS BURDEN FROM GLOBAL TO SUBNATIONAL RESOLUTIONS: A SYSTEMATIC REVIEW

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Scrub typhus, caused by Orientia tsutsugamushi, poses a significant public health threat, especially in the Asia-Pacific region. This systematic review aims to synthesize the spatio-temporal occurrence, burden, risk factors, and modelling methods for estimating scrub typhus burden across various geographical resolutions (PROSPERO #CRD42022315209). We searched PubMed, Scopus, Web of Science, China National Knowledge Infrastructure and other databases for articles published up to May 2022, with no language restrictions, for studies that quantified the occurrence, burden, risk factors, and modelling methods of scrub typhus. Study quality was assessed using a modified version of the Newcastle-Ottawa Scale. Our database search returned 13,272 articles, of which 2,109 were deemed eligible for full-text review. Ultimately, 640 articles were incorporated into our systematic review and meta-analysis, spanning 29 countries from 1957 to 2020. Overall, the global prevalence of scrub typhus varied significantly across different regions and time periods with seroprevalence among healthy populations ranging from 0% to 30% (median 11.5%). Reported incidence was found to be increasing in countries with established surveillance systems, with China reporting the highest incidence (527.7/100,000). The case fatality rate varies widely by region and time, with India reporting the highest case fatality rate (32.8%). Meteorology, landcover, and human activities were identified as key factors of disease acquisition. Boosted regression trees (BRT), ecological niche modelling (ENM) approach and Bayesian hierarchical models were employed to estimate risk. A substantial global burden of scrub typhus exists, with significant variations in occurrence and distribution across different regions and time periods. The meta-analysis will be continued, and we believe that this comprehensive systematic review will result in more attention for this neglected disease and help establish the research agenda for producing new generalizable information to bridge gaps in comprehension of the burden of scrub typhus.

5103

MATHEMATICAL MODELS OF PLASMODIUM VIVAX MALARIA: A SYSTEMATIC REVIEW

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Plasmodium vivax causes significant morbidity and mortality worldwide. With an extensive geographic distribution and specific considerations for its diagnosis and treatment, P. vivax poses unique challenges for malaria control and elimination. Mathematical modeling is a useful tool to aid decision making. As the scientific community's understanding of P. vivax and mixed infections continues to evolve and expand, there is an opportunity to review and learn from existing models to improve future model development and application. We conducted a systematic literature review of mathematical models of P. vivax malaria transmission. Our aim was to investigate the characteristics, key features, parameter values and evolution of these models; to explore common themes and identify knowledge gaps. We searched MEDLINE, Scopus, Web of Science, and Embase, for articles published in English until 8 August 2022. We included population- and individual-based mathematical models of P. vivax or mixed species models incorporating P. vivax. We excluded pharmacokinetic/ pharmacodynamic models, models that had no human component, and models that were within-host only. Two reviewers independently conducted a title-abstract screen, followed by a full text screen. Disagreements between reviewers were resolved through the authors' consensus. The systematic review yielded 1,923 results. After removing duplicates, we screened 842 abstracts. We screened 105 full text publications, of which 58 were included in the final analysis. We present summary characteristics of the included publications (e.g., geographic focus, species included, type of model, interventions). We identify and discuss key model features, exploring the similarities and differences between model structures and approaches. We show a map of the evolution and relationship between the models. We synthesize model parameter values, presenting the distribution and source of values. Finally we critically discuss gaps and challenges for modeling P. vivax and mixed species infections.

5104

STRATIFICATION OF MALARIA BURDEN AND SUBNATIONAL TAILORING OF INTERVENTIONS TOWARDS TO INFORM THE DEVELOPMENT OF THENATIONAL MALARIA ELIMINATION STRATEGIC PLAN IN GHANA

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As part of the pillars of HBHI - use of strategic information for decision making, stratification of malaria burden at subnational level is imperative

to inform appropriate interventions to be deployed. In 2022, the name of the Ghana National Malaria Program was changed from Control to an Elimination Programme. This called for a new strategic plan to be developed to reflect the scope and strategies to be implemented under the elimination agenda. This abstract outlines the processes and methods used in developing risk stratification of malaria at district level and tailoring of interventions towards malaria elimination in Ghana. A subnational level of malaria burden was conducted with guidance from WHO to stratify the country according to its epidemiology and transmission risk factors and inform where strategic interventions will be implemented under the elimination framework. Routine health facility data aggregated at district level was combined with prevalence estimates from Malaria Atlas Project (MAP) and All-cause mortality estimates from the Institute for Health Metrics and Evaluation to categorize the districts into very low, low, moderate, and high epidemiological strata. Appropriate interventions and strategies were developed for each strata and discussed with multi-sectorial stakeholders for buy-in and ownership. The plan is to whip up political commitment and ensure all sectors are involved in the further reduction of malaria in the country.

5105

MOLECULAR BIOMARKER IDENTIFICATION IN SEASONAL CARDIOVASCULAR COMORBID DISEASES (SCCD) USING NETWORK METANALYSIS

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The start of many illnesses is known to be significantly influenced by seasonal variations in the human cardiovascular system. Confounding variables include behavioral and environmental factors; failure to account for such factors makes determining the real temporal effect of certain disorders challenging. Numerous clinical investigations, on the other hand, suggest that only some groups of people are more seasonal sensitive, and that their maladaptation may contribute to a variety of disorders. As a result, evaluating the etiological and seasonal sensitive patterns of cardiovascular diseases (CVD), which affect the majority of the human population, is crucial. The study's premise was that cardiovascular and related disorders have significant links with seasonal and etiological fluctuations. Thus, in the current study, data mining was used to find 852 disease association connections between cardiovascular and related illnesses from a systematic review of 4519 papers. To focus on only the most prevalent CVDs, a disease ontology-based semantic similarity network (DSN) study was carried out. Furthermore, topological analysis was employed that predicted the seven CVDs in three clusters. The seasonal sensitivity and temporal association of these seven CVDs were then investigated using Mann-Kendall and Cox-Stuart models and their temporal connections were validated using LOESS and TBATS. The study provides indirect evidence of a significant etiological relationship between three cardiovascular diseases, including MI, atrial fibrillation, and atherosclerosis, all of which are seasonal in the majority of the world's population. As a result, these three conditions qualify as seasonal cardiovascular comorbidities (SCCD). Following that, secondary network met analysis using GEO data from GSE2240 (atrial fibrillation) and GSE132651 (atherosclerosis) reveals a triad of NRF1-hsa-miR-124-3p-NRF2 is a physiologically and statically significant module, and both NRF-1 and NRF-2 might trigger a cascade that inhibits GSK-3 phosphorylation. This may minimize the risk of myocardial infarction while also improving heart pathology.

5106

THE ROLE OF BELIEFS IN MALARIA PREVENTION AND TREATMENT BEHAVIOR: ANALYSIS OF THE 2021 NIGERIA MALARIA INDICATOR SURVEY

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Malaria remains a major public health problem globally and especially in Sub-Saharan Africa. In 2021, Nigeria accounted for 26.6% of global cases and 38.4% of global deaths among children under the age of five. Underuse of effective tools for prevention and treatment undermines progress against the disease. For example, recent household surveys from Sub-Saharan Africa suggest that only 47% of the population slept under a net, and 33% of children under the age of five did not receive treatment for a fever. We analyzed the 2021 Nigeria Malaria Indicator Survey to examine how people's knowledge and beliefs about malaria were associated with their prevention and treatment behaviors. The survey included 14,476 women respondents as well as data on 3947 children who had a fever in the two weeks prior to the survey. Preliminary analyses suggest that when controlling for age, wealth quintile, education level, region and residence type (urban/rural), women who had heard a message about malaria in the previous six months had significantly higher odds of sleeping under a bed net (OR=1.21, 95% CI [1.07 1.35]), as did women who believed their families were susceptible to malaria (OR=1.30, 95% CI [1.05 1.60]), who believed malaria was a serious disease (OR=1.16, 95%CI [1.02 1.32]) and who perceived widespread community norms around malaria prevention and treatment (OR=1.42, 95% CI [1.23 1.63]). Hearing a message about malaria, perceived susceptibility to malaria, and beliefs about community norms were also significantly positively associated with children under the age of five getting treatment for a fever outside the home. Our results indicate that people's beliefs play an important role in malaria prevention and treatment behavior. Moreover, the findings suggest that sharing information about malaria, particularly regarding the risk of infection and severity of disease, and highlighting the degree to which the community engages in malaria prevention and treatment behaviors, could be effective strategies to increase both use of bed nets and treatment of fevers.

5107

SYSTEMATIC REVIEW: MATHEMATICAL MODELLING PARAMETERS OF THE NINE WORLD HEALTH ORGANIZATION PRIORITY PATHOGENS

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Mathematical modelling of infectious pathogens has been extensively used to understand endemic diseases and respond to outbreaks such as Ebola, measles and COVID-19. Modelling is a useful tool to predict infectious disease dynamics, project the likely future epidemic trajectory and estimate the potential impact of interventions to guide the public health response. In 2019, the World Health Organization updated its list of blueprint priority infectious pathogens that pose the greatest public health risk, due to their epidemic potential and/or lack of suitable interventions or therapeutics. We systematically reviewed parameter values, mathematical models and historical outbreaks for all listed pathogens, excluding disease X: Crimean-Congo haemorrhagic fever, Ebola virus disease, Lassa fever, Marburg virus disease, Middle East respiratory syndrome coronavirus, Nipah and henipaviral diseases, Rift Valley fever, Severe Acute Respiratory Syndrome and Zika virus. We searched OVID Medline and EMBASE and Web of Science until 8th March 2019 and retrieved 95,144 results. After title and abstract screening and full-text review, we found 1,684 papers for data extraction. We collate information required to enable rapid mathematical modelling of these nine pathogens including, but not limited to, fatality ratios, mutation rates, reproduction numbers, risk factors, model structure, seroprevalence and historical outbreaks. Our work highlights areas of uncertainty, especially for pathogens having not yet caused large human epidemics, where it is hard to quantify transmission or severity. By looking

at multiple pathogens simultaneously, we can archetype pathogens into profiles based on their characteristics. This will be useful in future epidemics of these pathogens, to rapidly identify existing parameters, models and outbreak data, enable mapping to these typologies for similar novel pathogens and identify potentially effective interventions. This work will serve as the basis for a dynamic database that could be further enriched by other contributors to ensure this review provides a "live" picture of the current knowledge landscape.

5108

GEOSPATIAL MODELLING OF FEBRILE ILLNESS PREVALENCE AMONG CHILDREN AGED UNDER FIVE YEARS IN UGANDA

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Febrile illness is still one of the major public health problems in Africa. Although it has been recognised as crucial to better understand the spatial distribution, the evidence is still limited. We aim to predict the prevalence of fever cases among children aged under 5 years in Uganda, whilst exploring the association with potential risk factors. We analyse household records from the 2016 Demographic and Health Surveys (DHS) conducted in Uganda. We develop a geostatistical Binomial model to predict the prevalence of fever cases among children aged under 5 years, accounting for environmental, nutritional, and socio-demographic risk factors obtained from publicly available sources. The median crude (empirical) febrile illness prevalence for each cluster was 30.4% (interquartile range:13.6-50.0). There is extensive within-country spatial variation in children's febrile illness prevalence in Uganda and the model indicates the presence of strong spatial correlation, predicting a higher prevalence in the eastern and north-eastern regions. The model indicates the association with some potential risk factors, and the inclusion of them improves the predictive performance of the model. The findings could assist in targeted public health policy-making for fever case management and in hypothesis generation for aetiology.

5109

THE ROLE OF COMMUNITY HEALTH WORKERS IN TREATMENT MONITORING OF RADICAL CURE FOR PLASMODIUM VIVAX MALARIA IN PAPUA, INDONESIA: A MIXED METHODS STUDY

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Adherence to 14-day regimen of radical cure for Plasmodium vivax malaria is improved by supervision. In a highly malaria endemic area in Papua, Indonesia, clinic staff cannot supervise treatment through home visits due to the high number of cases. As part of strengthening malaria case management, a system was developed for clinic staff to refer patients to community health workers (CHWs) for treatment monitoring. The mechanisms and contexts that underlay the effectiveness of this intervention were assessed in a mixed methods study using realist evaluation. Between May 2019 and December 2022, patient referral to CHWs for treatment monitoring was introduced in five public health clinics. Through meetings with malaria program managers, the need to establish communication channels between clinic staff and CHWs was identified as essential for patient referral. CHW treatment monitoring practices were identified by calculating the proportion of referred patients who were monitored, participant observations at the clinic and patients' homes during visits, and interviews with clinic staff and CHWs. CHWs can succeed in finding and visiting patients when they received complete patient information upon referral. Monthly meetings with clinic staff facilitated CHWs acceptance of treatment monitoring as their task. If the CHWs perceived good communication from clinic staff, there is greater incentive to find patients even without complete information. Identifying non-compliance, such as patients who reduced the number of tablets taken per day or stopped taking drugs, increased CHW confidence in treatment monitoring. When an ACT shortage led to prescription of second line drug (quinine), CHWs became more motivated to monitor treatment out of concern over patients not completing antimalarial treatment. The refined referral system was tested with new CHWs recruited later, confirming the importance of regular communication from clinic staff and complete patient information upon referral. In addition, perception of getting direct positive results (e.g. non-compliant patient becomes compliant) directly influenced CHW treatment monitoring practices.

5110

COVID-19 VACCINATION IN GHANA: THE DISCOURSE OF RELIGION, GENDER, PERCEIVED SAFETY OF VACCINE AND GHANAIANS' READINESS TO BE VACCINATED

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Covid -19 was declared a global pandemic in 2020 by the world wealth organization due to its global damage it caused to human life and the negative effect on the global economy. To deal with this pandemic was the global plan to vaccinate globally to achieve a herd immunity. The vaccine exercise was faced with some conspiracy theories ranging from vaccine safety and religious believes. This study examine vaccination in Ghana vis-a-vis the religious and safety paradigm. The cross-sectional survey randomly sampled 2000 participants but 1409 properly completed the questionnaire representing 70% response rate. The study reveals that participants willingness to be vaccinated and be part of the first group of people to be vaccinated was dependent on the religious affiliation of the participants (X2=23.9, p-value =0.02). The study further shows that the Ghanaian perception about the safety of the vaccine was also dependent on the religious belief of the participants (X2=25.9, p-value =0.001).The study however revealed that participants perception about the safety of covid-19 vaccine and the willingness to participates in the vaccination was independent on the gender of the respondent. The study finally revealed that participants wiliness to be vaccinated was independent on the gender of the participant. The study concludes that religious belief significantly influenced participants willingness to be vaccinated. The study recommends to the government of Ghana and the Ministry of Health to be sensitive to the religious leaders in their drive to get the Ghanaian people vaccinated to obtain herd immunity.

5111

PREVALENCE, RISK FACTORS AND CONSEQUENCES OF MICROCEPHALY IN LOW- AND MIDDLE-INCOME COUNTRIES: A CALL TO ACTION FOR THE GLOBAL MATERNAL AND CHILD HEALTH COMMUNITY

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The recent Zika Virus epidemic heightened awareness of the high prevalence of microcephaly in infants in low- and middle-income countries (LMICs). Despite being considered a very rare condition in high-income countries (HICs), the prevalence of microcephaly has been found to be up to 5% in LMICs, irrespective of the presence of Zika Virus circulation, indicating a long-running, underrecognized public health concern. However, microcephaly prevalence estimates in LMICs are still sparse and calculation of microcephaly is not standardized. Furthermore, while risk factors for microcephaly have been identified in HICs, the risk factors for microcephaly may be dramatically different in both type and prevalence in LMICs. The

limited available data suggest that generational malnutrition and related intrauterine growth restriction and low birth weight, frequent infections and malnutrition in infancy, and other poverty-related stressors that are much more common in LMICs may be associated with the high prevalence of microcephaly. Finally, emerging evidence demonstrating the association between microcephaly and poor subsequent neurodevelopment in LMICs highlights the serious consequence of high microcephaly prevalence. Therefore, more in-depth understanding of the prevalence, risk factors and consequences of microcephaly in LMICs is urgently needed. We review existing evidence to identify an appropriate definition of microcephaly for research implementation, and recommend that measurement of head circumference be routinely incorporated in clinical and public health practice in LMIC settings. We then describe the factors that have been associated with microcephaly in LMICs and review the evidence on the association between microcephaly and poor neurodevelopment in LMICs. To encourage and guide advancement of this field, we provide a set of recommendations to improve collection, analysis, and interpretation of the risk factors and consequences of microcephaly in LMICs.

5112

ASSESSMENT OF DIETARY HABITS AND IODINE STATUS AMONG PREGNANT WOMEN IN SOUTHERN GHANA

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Iodine is a micronutrient essential in the production of thyroid hormones for normal neurodevelopment. Based on iodine nutrition global data, nearly two billion (28%) of the world's population, including more than 321 million Africans (39%), are in danger of inadequate iodine intake. The WHO estimates that 60% of pregnant women worldwide do not meet the required intake. Current studies have associated iodine deficiency during pregnancy with a wide range of disorders; stillbirth, spontaneous abortions, hearing defects in infants, and cretinism. The aim of the study was to determine the iodine level and dietary habits in pregnant women. This cross-sectional study was performed among women attending antenatal clinics at Pentecost Hospital, Madina (PHM) in the Greater Accra Region. Dietary information related to iodine was obtained by using a food frequency questionnaire (FFQ). Urine iodine concentration (UIC) was performed on freshly collected urine samples, using the Sandell-Kolthoff reaction method with ammonium persulfate as the digesting agent. Results obtained showed that 50.6% (80/158) of participants had urine iodine levels below the WHO optimum range. Week of gestation had a positive association with the iodine levels in pregnant women. Regarding dietary habits, oats, yogurt, salted fish, and meat intake were significantly associated with urine iodine levels (r ranging from 0.1 - 0.2, p<0.05 in all cases). The study highlights the need for greater advocacy for pregnant women to take in iodine-rich sources of food in order to avoid possible iodine deficiency disorders in themselves and their unborn children.

5113

EFFECT OF PARTICIPANTS AGE AND OCCUPATION ON PERCEIVED SAFETY OF COVID-19 VACCINE AND PARTICIPANTS WILLINGNESS TO BE VACCINATED WITH COVID-19 VACCINE IN GHANA

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The COVID-19 pandemic, declared a global health emergency by the World Health Organization in 2020, had a severe impact on the Ghanaian economy and caused harm to human life globally. This study aimed to provide evidence on the role of age and occupation in determining perceived safety and safety-related information regarding COVID-19 vaccines. The study examined the effect of age on participants' perceived safety of the COVID-19 vaccine, as well as the effect of occupation on their perceived safety and safety-related information. A cross-sectional survey was conducted, randomly sampling 2,000 participants, representing a 70% response rate. The study's results showed that the perceived safety of the COVID-19 vaccine was independent of the participants' occupation (X2=18.14, p-value =0.059). Additionally, the participants' willingness to be vaccinated was independent of their occupation (X2=1.86, p-value =0.86). Finally, the study found that participants willingness to be vaccinated was independent on the age categorization of the participants who participated in the survey. The study concluded that participants perception of the covid-19 vaccine safety was not influenced by the type of occupation and the age categorization of the participants.

5114

EVALUATION OF THE CLINICAL TRIAL OPERATION TRAINING CONDUCTED BY CENTER FOR INNOVATIVE DRUG DEVELOPMENT AND CLINICAL TRIALS FOR AFRICA

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The number of clinical trials conducted in low and middle income countries (LMICs) is not satisfactory. Their quality is also questionable. This might be attributed to shortage of qualified personnel. Competency-based training for trial staff is required to build their capability. To this effect, CDT-Africa has conducted clinical trial operation (ClinOps) training in collaboration with course partners. As alignment of course contents to the local priorities of LMICs is critical for the success of clinical trial training, local tutors who were cognizant of the most common problems faced while conducting clinical trials in LMICs were involved. The training program activities were jointly planned with product development partners. A competency framework with andragogic innovations, jointly set by the Tropical Diseases Research program and The Global Health Network, was used in developing the curriculum. The training used Moodle Learning Management System as its platform for uploading VoiceThread links, learning materials, tasks, forum discussions and other assignments for access to trainees. This paper addresses impact of the training on trainees' confidence in conducting GCP compliant trials. We carried out a survey and used four core competencies: trainees' confidence in i) conducting, ii) managing, iii) designing & maintaining quality system and iv) effectively closing out & reporting results of clinical trials to evaluate the training outcome. Data taken from 69 trainees who took part in both the pre and post training survey were analyzed. Most of the respondents were trial site coordinators. Repeated measure t-test was carried out on four pair of scores in the four core competencies to see the presence of statistically significant difference in the scores of the respondents in confidence measured at the two different times. The test indicated that their confidence in all the four core competencies significantly increased after training compared to what they had before. In conclusion, the ClinOps training helped trainees acquire relevant knowledge & develop confidence in conducting GCP compliant clinical trials.

5115

THE RELATIONSHIP BETWEEN DISTANCE TO PRIMARY HEALTH CENTER, CHILD MORTALITY, AND AZITHROMYCIN MASS DISTRIBUTION IN NIGER: A SUBGROUP ANALYSIS OF THE MORDOR I CLUSTER-RANDOMIZED TRIAL

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Increased distance to health centers has been associated with increased child mortality in several West African settings. Azithromycin mass drug

administration (MDA) has been found to reduce child mortality. Identifying subgroups where mortality reductions are the largest could help target future programs. Our objective was to assess whether distance to primary health center modified the effectiveness of azithromycin MDA to reduce mortality in a subgroup analysis of the MORDOR I-Niger trial. This cluster-randomized trial enrolled 594 rural and peri-urban communities in Dosso and randomized them to biannual oral azithromycin or placebo to children 1-59 months old for 2 years. A population-based census was conducted every 6 months to collect location data, administer treatment, and collect data on mortality and person-time at risk in the target group. Distance from each community center to the nearest primary health center was calculated. Negative binomial regression was used to determine whether the community-level effect of azithromycin on mortality differed by distance to primary health center, controlling for average community age. Median distance from community center to the nearest primary health center was 5 kilometers (km; interquartile range 3.2 to 7.1). For each kilometer increase in distance in the placebo arm, mortality increased by 5% (adjusted incidence rate ratio [aIRR] 1.05, 95% CI 1.03 to 1.07, P-value < 0.001). The effect of azithromycin MDA on mortality was found to vary significantly by distance (P-value for interaction term = 0.02). Overall, we found no difference in mortality by arm in communities closest to primary health centers and an increasing reduction in mortality in the azithromycin arm compared to placebo as distance increased. For example, the reduction in mortality with azithromycin vs placebo was 0% at 0 km from the health center (95% CI -19% to 17%), 4% at 1 km (95% CI -12% to 17%), 16% at 5 km (95 CI 7% to 23%), 28% at 10 km (95% CI 17% to 38%), and 39% at 15 km (20% to 54%). Children who live farthest from existing healthcare facilities may benefit the most from azithromycin MDA.

5116

SPILLOVER EFFECT OF AZITHROMYCIN MASS DRUG ADMINISTRATION ON ANTIMICROBIAL RESISTANCE IN NIGER

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MORDOR was a cluster-randomized mass drug administration (MDA) trial that compared child mortality in communities receiving two years of biannual azithromycin versus placebo. Azithromycin MDA has been shown to increase antimicrobial resistance (AMR) in the target 1-59-month age group. Given the community-based nature of this intervention, AMR may spill over into non-target populations as well. To better characterize the full population-level impact of azithromycin MDA on AMR, this study aimed to evaluate the presence of AMR spillovers in children 7-12 years of age not targeted for MDA. Thirty communities in the MORDOR morbidity trial were randomized to biannual azithromycin or placebo to children 1-59 months old. After 2 years of distributions, nasopharyngeal swabs were collected from a random sample of up to 40 children 7-12 years of age from all communities. Genetic determinants of resistance to macrolides, beta-lactams, tetracyclines, and fluoroquinolones were assessed at the individual level using TaqMan Array card. The presence of resistance determinants for each class was compared by arm using generalized estimating equations to account for clustering by community. Nasopharyngeal swabs were collected from a total of 1,103 children 7-12 years old. Compared to placebo communities, those in azithromycin communities had 1.34 times the odds of macrolide resistance (95% CI: 0.82 - 2.20), 1.06 times the odds of beta-lactam resistance (95% CI: 0.71 - 1.57), 0.99 times the odds of tetracycline resistance (95% CI: 0.45 - 2.20), and 0.45 times the odds of fluoroquinolone resistance (95% CI: 0.20 - 1.01). These findings suggest that there may be an increase in macrolide resistance in untreated children in communities receiving azithromycin versus placebo, although the MORDOR trial was not powered to detect this difference. More research is warranted to further our understanding of such spillover effects as a result of azithromycin distribution in MDA programs.

5117

TAKING BLOOD FROM CHILDREN FOR RESEARCH PURPOSES - WHAT DO PEOPLE THINK ABOUT IT? A QUALITATIVE STUDY TO EXPLORE THEFACILITATORS AND BARRIERS FROM A CLINICAL TRIAL CONDUCTED IN LALITPUR, NEPAL

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Clinical trials are a critical part of evidence-based medicine and blood sample collection is its important component. However, refusal of consent for blood draw is a common challenge associated with it. Literature exploring the perceptions of people regarding blood draw is scarce. We are conducting a qualitative research as a part of a large randomised controlled trial for a typhoid conjugate vaccine in children from Nepal. For the qualitative aspect of the trial, we are seeking to identify the motivators and barriers for blood draw from children for clinical research purposes. We are conducting in-depth interviews (IDIs) with the parents of children less than 18 years and the participants of the vaccine study who are now 18 years or older. There are around 17 study clinics in the community and a tertiary hospital where people with fever can come for check-up and are asked for blood draw if they meet the study fever criteria. So far, 16 in-depth interviews (IDIs) have been conducted with the participants who have consented and denied for blood draw for research purposes. IDI will be conducted until data saturation. We found that most of the participants did not understand the purpose of drawing blood for research purposes and their major motivation to provide consent was the trust towards the health professionals. The perception that it will be painful to draw blood from a sick child, making them weaker, is the major factor for blood draw denial. We also found that people had no problem in drawing out blood from sick adults but they felt the volume of blood drawn from a sick child was excessive, hence their hesitation. We have not heard any social belief related to blood draw so far that could lead towards denial of blood draw. To facilitate research that entails blood draw, health professionals and especially medical officers or nurses should continue to explain in detail about the purpose of blood draw for research purposes. Pain relief ointment can also be considered prior to blood draw. Additionally, engagement activities can be conducted to address the concern of volume and health consequences of blood draw thus improving consent procedures in future studies.

5118

EPIDEMIOLOGY OF LEPROSY IDENTIFIED THROUGH ACTIVE CASE DETECTION IN SIX DISTRICTS OF NEPAL

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Pediatric cases and grade-2 disabilities (G2D) indicate recent transmission and late diagnosis respectively, which necessitate active and early case detection. This operational research was performed to identify approaches best suited for early case detection, determine community-based leprosy epidemiology, and identify hidden leprosy cases early and respond with prompt treatment. Active case detection was performed by: door-to-door visits among vulnerable populations (n=26,469), contact examination and tracing (n=7,608) and screening prison populations (n=4,428) in Siraha, Bardiya, Rautahat, Banke, Lalitpur and Kathmandu districts of Nepal. New case detection rates were highest for contact tracing (250), followed by house-to-house visits (102) and prison screening (45) per 100,000 population screened. However, cost per case identified was cheapest for house-to-house visits (Nepalese rupee (NPR) 76,500/case), then contact tracing (NPR90,286/case) and prison screening (NPR298,300/case). House-to-house and contact tracing case paucibacillary/multibacillary

(PB:MB) ratios were 59:41 and 68:32; female/male ratios 63:37 and 57:43; pediatric cases 11% in both approaches; and G2D 11% and 5% respectively. Developing leprosy was similar among household and neighbor contacts (Odds ratios (OR)=1.4, 95% confidence interval (CI), 0.24-5.85) and for contacts of MB versus PB cases (OR=0.7, 0.26-2.0). Attack rates were similar among household contacts of MB cases (0.32%, 0.07-0.94%) and PB cases (0.13%, 0.03-0.73) and neighbor contacts of MB cases (0.23%, 0.1-0.46) and PB cases (0.48%, 0.19-0.98). BCG vaccination with scar presence had a significant protective effect against leprosy (OR=0.42, 0.22-0.81). In conclusion, the most effective case identification approach here is contact tracing, followed by house-to-house visits in vulnerable populations and screening in prisons, though house-to-house visits were cheaper. The findings suggest hidden cases, recent transmission, and late diagnosis in the community exist and highlight the importance of early case detection.

5119

ADDRESSING PROVIDERS' DISTRUST OF MALARIA RAPID DIAGNOSTIC TESTS THROUGH PEER-TO-PEER ENGAGEMENT

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In Nigeria, 40% of public sector providers prescribe antimalarials without parasitological confirmation. Studies show that provider norms and misconceptions influence adherence to fever case management (FCM) guidelines. From January 2019 to December 2022, Breakthrough ACTION-Nigeria convened quarterly small group discussions with Officers-in-Charge (OICs) from 417 primary health facilities in 5 states to discuss diagnostic norms and misconceptions, exchange experiences, review data, and develop action plans to improve FCM. Selected facilities are designated by the government to provide a minimum package of services within each ward. Before each session, 417 OICs completed self-administered surveys about their own knowledge and attitudes toward FCM. After sessions, OICs conducted similar "step-down" meetings with 712 facility staff. District Health Information System (DHIS) data was analyzed to examine trends in testing and adherence. The testing rate rose from 85% to 94% between Dec 2018 and Dec 2022. The proportion of test-positive cases who received artemisinin-combination therapy (ACT) increased from 82% to over 98%. While the DHIS does not capture test-negative results, clinical diagnosis (proportion of fever cases receiving ACTs without a malaria test) decreased from 20% to 0.8%. Though the number of fever cases seen decreased during the pandemic, testing and adherence rates did not. Average OIC knowledge and attitude scores rose from 44% in 2019 to 80% in 2022, and during meetings, OICs reported improved norms and attitudes toward malaria rapid diagnostic tests (RDTs) among staff. Scores improved after one session, but meeting discussions reflected lingering doubts such as concerns about RDT storage conditions prior to arrival at the facility that diminished with time. Results suggest that a sustained, peer learning approach may address entrenched concerns and contribute to improved FCM adherence. Future research should track attitudinal shifts among facility staff in addition to OICs, use control sites, and compare the peer-to-peer approach to other quality improvement initiatives.

5120

LIVED EXPERIENCES AND COPING STRATEGIES ADOPTED BY ADOLESCENTS IN THE MANAGEMENT OF ONCHOCERCIASIS IN A RESOURCE LIMITED SETTING OF GHANA

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Onchocerciasis is a neglected tropical disease that continue to be a major contributor to disabling skin and eye conditions. Sub-Saharan Africa accounts for 99% of the total global prevalence of the disease, with about 37 million people infected and about 300, 000 permanently blind. This is a cross-sectional study adopting a phenomenological qualitative approach. We conducted in-depth interviews among 16 onchocerciasis adolescent patients between June 2022 – July 2022 in order to explore the lived experiences and coping approaches adopted by adolescents in the management of onchocerciasis. Data was analysed using Interpretative Phenomenological Analysis (IPA) with ATLAS.ti version 7.5.7, and results presented in themes and supported with quotes. Half (50.0%) of the adolescents interviewed were aged 15-17 years old; majority (62%) of them were still in school. Also, 25.0% of them had lived with the condition for over 10 years. The major initial symptoms experienced by adolescents were blurred vision, ball-like moving nodules in the body, and frequent fatigue. Majority of the participants reported that their experience with hospital-based management of their condition in terms of quality of treatment and care they received from the health professionals. Majority of participants preferred hospital management as compared to home-based treatment. The main coping strategies adopted by participants in dealing with their conditions were religious in nature expressed through faith and belief in God by prayer; and recreation by playing football and watching movies. The findings revealed that most participants delayed in seeking healthcare, and only did so after complications had developed. The delay we believe could be due to a lack of access to appropriate information and education about onchocerciasis. Religion and recreation were the main strategies adopted by participants in coping with their conditions. This points to the need for health authorities and policymakers to intensify education and communication campaigns on NTDs in general and onchocerciasis in particular in the last miles settings of developing countries like Ghana.

5121

SPATIAL INEQUALITY IN CHILDHOOD IMMUNIZATION COVERAGE IN NIGERIA: A GEOSTATISTICAL APPROACH

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Routine vaccination for children and mass immunization campaigns are key global public health strategies for reducing morbidity and mortality from infectious diseases. The Expanded Program on Immunization (EPI) aimed at providing routine immunization to all children less than two years of age in Nigeria. Though initial progress towards attaining universal coverage was documented, structural and organizational challenges soon constitute barriers to the ambitious targets of the EPI strategy. Estimates from the 2018 Nigeria Demographic and Health Survey (NDHS) indicate that only 37% of children aged 12-23 months received all basic vaccinations while 21% received all age-appropriate vaccinations. Combining data from 2008, 2013, and 2018 NDHS with ancillary data sources, we adopt a model-based geostatistics approach to characterize and quantify spatial variations in full immunization coverage (defined as children aged 12-23 months who have received one dose of BCG vaccine, three doses of DPT-containing vaccine, three doses of oral polio vaccine, and one dose of measles vaccine) as explained by factors such as women disempowerment, intimate partner violence (IPV), and other child's and mother's characteristics. We also considered the influence of travel time to nearest health facility, fear over personal safety, and local population size on the spatial patterns of immunization coverage. Women disempowerment, IPV and travel time

are among the barriers to uptake of childhood vaccines, exacting varying influence at different locations in Nigeria. Locally tailored intervention would be effective in enhancing coverage in the country.

5122

UNDERSTANDING COVID-19 VACCINE HESITANCY IN THE JOHNSONVILLE, PEPPER WULU TOWN COMMUNITY LIBERIA: A QUALITATIVE STUDY

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The COVID-19 pandemic has had widespread morbidity and mortality, with nearly 6.2 million deaths globally. In Liberia, fewer cases and deaths have been reported than in other countries, but the limited healthcare resources in this low-income country makes the population vulnerable, in the event of more virulent variants. The COVID-19 is no exception. To protect against the COVID-19 virus, vaccines are being distributed; yet coverage targets have not been met. The objectives of this research were to understand COVID-19 vaccine hesitancy among people in the Johnsonville Pepper Wulu Town community, and to gather community feedback on what can be done to encourage the uptake of COVID-19 vaccines. A qualitative study was conducted with purposive sampling identifying 12 community members who were expected to have knowledge and understanding about the COVID-19 vaccine. All participants were aged 18 years or older and had resided in the community for not less than six (6) months. Audio recordings of in-depth interviews were transcribed and manually coded; thematic analysis was undertaken. From the study conducted, three themes were generated to group participants' statements into category which better explained what they know about the COVID-19 vaccine. Out of the 12 participants interviewed, 10 said they have not gotten any dose of the COVID-19 vaccine and were not willing to take the vaccine due to reasons like fear to die in two years after taking the vaccine and lack of trust in Government. Eight indicated that they are not prepared to recommend the vaccine to their child/children, friends or relatives. The results of the study showed that COVID-19 vaccine hesitancy exists in the community and it comes from issues such as misinformation, lack of information, and/or mistrust. Mobilization through prominent individuals and Community based-Organizations along with building emotional support, and increased knowledge to overcome misinformation would help to alleviate the myths of death, and liaising with stakeholders to address concerns around trust could help improve uptake.

5123

AN ETHNOBOTANICAL STUDY ON MEDICINAL PLANTS USED AS ANTIDOTES FOR SNAKEBITE AND AS SNAKE REPELLENTS IN THE HAUTS BASSINS AND SOUTHWEST REGIONS OF BURKINA FASO

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Ophidian envenomation is a public health problem in the tropics and subtropics. Expensivecost of antivenoms forces most of the population to resort to medicinal plants as a first-linetreatment. The use of plant extracts for therapeutic purposes is a common practice intraditional African medicine. The present study aimed to contribute to a better knowledge of medicinal plants used in the treatment of snakebite envenomations and as a snake repellent inthe Hauts-Bassins and Southwest regions of Burkina Faso.In the province of Houet and the South West region, ethnobotanical information was collectedduring six months of the year 2022 from 117 people (traditional health practitioners andherbalists) using a questionnaire. Knowledge was assessed quantitatively using relativecitation frequency. A total of 31 plant families divided into 58 species have been identified by both traditionalpractitioners and herbalists. The distribution of these species by family showed thatPolygalaceae (28.2%), Annonaceae (14.52%), Fabaceae (13.67%) followed by Ebenaceae(3.41%) and Apocynaceae (3.41%) were the most mentioned. Roots were mostly used,68.96% (40/58) in the preparation of remedies. The majority of traditional healers were male(84.61%, 99/117). More than 80% (94/117) of respondents were not literate. Almost all of therespondents, 90% (105/117), had knowledge from their ancestry.The surveys made it possible to inventory a diversity of medicinal species and to collect asmuch information as possible concerning local therapeutic or repellent uses against snakes. Extensive pharmacological and toxicological studies need to be conducted for the reportedmedicinal plants to contribute to the well-being of local communities in tropical andsubtropical regions.

5124

MIXED EFFECTS MODELS IN THE ANALYSIS OF EPSTEIN BARR VIRUS SEROLOGICAL RESPONSES IN CHILDREN FROM CHULAIMBO WESTERN KENYA

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In malaria-endemic regions, infants acquire Epstein Barr virus (EBV) as early as 6-months of age, resulting in poor viral control, which may contribute to endemic Burkitt's lymphoma development. Maternal malaria infection during pregnancy impairs vertical transfer of EBV specific antibodies. The impact of this impairment on the subsequent decay rate of maternally derived anti-EBV specific antibodies in infants remains to be determined. There exist two preferred classes of mixed effects models for analysis of longitudinally collected data; linear (LMMs) and nonlinear NLMMs mixed effects models. Whether LMMs perform sufficiently in scenarios suitable for NLMMs remains unclear. A total of 66 infants from Western Kenya, born to HIV-negative women, with or without malaria during pregnancy were enrolled and followed up from birth through 24 weeks of age. We assessed the performance of mixed effects models in the analysis of EBV serological responses comparing infants born to women with and without malaria infection during pregnancy (MEU and MUU respectively). The levels of anti-VCA and anti-EBNA1 IgG against EBV infection in cord (neonatal) and infant blood samples were quantified using multiplex bead-based assay and analyzed using LMM and NLMM. To evaluate model performance, Pearson correlation test was used to analyze observed versus predicted antibody levels. Decay rates of anti-VCA IgG between MEU and MUU did not differ significantly (P = 0.45). However, the decay rates of anti-EBNA1 IgG were significantly faster in the MUU group compared to MEU (P = 0.03) with a decrease rate of 0.26 and 0.14 per month, respectively. Correlations between observed versus predicted VCA and EBNA1 IgG levels demonstrated the competent performance of LMM in fitting both VCA and EBNA1 IgG responses (r: 0.89 and 0.71, respectively) compared to NLMM (r: 0.95 and 0.89). These findings suggest that in utero malaria exposure does not impact decay rates of maternally derived anti-VCA IgG and EBNA1 IgG. Moreover, both LMM and NLMM performed well with NLMM being slightly more robust in the analysis of EBV serological responses in infants over time.

5125

MOLECULAR CHARACTERIZATION OF THE RHESUS D (RHD) GENE IN BLOOD DONORS WITH THE DEL PHENOTYPE AT THE NATIONAL BLOOD TRANSFUSION CENTER (CNTS) OF BAMAKO, MALI

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The Rh Del phenotype, expressed very weakly on the surface of red blood cells, can only be detected by adsorption/elution. The RhD1227 allele is the most common Rh Del with a grossly intact RhD gene. In Mali, there is very little information on the prevalence of the Del phenotype. The objective of this study was to perform a molecular characterization of the DEL phenotype in blood donors. After confirmation of Rh Del by adsorption/elution on donor blood bags at the CNTS, DNA from the samples was isolated with the QIAamp blood DNA mini kit and amplified by PCR using primers specific to the RhD gene and the RhD1227A allele. Amplicons were visualized on a 1% agarose gel under UV light. 365 serologically negative RhD donors were included in this study. The majority was male with 90.4%. The age range [26-39] represented 52.9% and the mean age was 32.54±33.53 years. The Ccee phenotype accounted for 72.72%. Blood group O was the most represented with 38.6%. The Rh Del phenotype was positive in 7.1% (26/365). All ten exons of the RhD gene were amplified in 69.23% of the Rh Del positives and the RhD 1227A allele was present in the samples. Our study showed the presence of the intact Rh D gene in all samples with the presence of the Rh Del mutation. However, we observed other non-specific amplifications that would be interesting to characterize by sequencing.

5126

ACADEMIC ACHIEVEMENT AMONG CHILDREN WITH SICKLE CELL ANAEMIA IN UGANDA

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Academic achievement among children of school age is crucial in attainment of optimal learning goals. Children with Sickle Cell Anaemia (SCA) are prone to cognitive deterioration which might impact their academic achievement. Limited data exists on the academic achievement of school-going children with SCA in Uganda. We conducted a cross-sectional study among children with SCA aged 6-12 years attending the Sickle Cell Clinic at Mulago National Referral Hospital in 2019. Controls were siblings/immediate relatives without SCA. The Wide Range Achievement Test-4 (WRAT-4), was used to measure cross-sectional spelling, reading, math and sentence comprehension. Age-appropriate items were administered for each age group. The WRAT-4 raw scores were converted to z-scores based on age and gender. T-tests were used to compare the z-scores of the controls with the cases. Linear regressions adjusting for social economic status, home stimulation and environment were used to compare the association between SCA and academic achievement. A p-value <0.05 was considered significant. A total of 68 cases (30 females, 44.1%) and 69 controls (37 females, 53.6%) were enrolled. Mean age was 9.0±2.0 years for both cases and controls. Overall, cases performed poorer than controls (Mean difference: -0.25, 95% CI: -0.02-0.53, p-value=0.03). Results for each subtest demonstrated that cases performed poorer than controls in math, with z-scores of -0.36 vs. 0.02 (p-value= 0.002) and spelling, with z-scores -0.31 vs. 0.03 (p-value=0.02). Cases and controls did not significantly differ in reading, with both groups scoring below the test's mean z-score. In contrast, in sentence comprehension, both cases and controls scored similarly and performed above the mean z-score. No significant differences were found between cases and controls for mother's education, social economic status or home environment. Children with SCA in Uganda have poorer performance in math and spelling compared to their healthy siblings/peers. Additional education support in maths and spelling may be considered to reduce these differences in academic achievement.

5127

HEALTH DETERMINANTS AMONG INDIVIDUALS WORKING AT AMAZONIAN GOLD MINING SITES: A MULTICENTRIC CROSS-SECTIONAL SURVEY

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Many determinants, such as the political, social and economic environment, the physical environment, individual characteristics and behaviors, or access to care, combine to impact the health of individuals and communities. In French Guiana (FG), the people working on the illegal gold mines spread in the heart of the tropical forest are a particularly vulnerable population which lives under the radar of the health system. This study aimed to better understand the individual and collective determinants of health in this specific population. This international multicenter cross-sectional survey included people working on the illegal FG gold mines at the crossing points located at both borders with Suriname and Brazil. After collecting written informed consent, a structured questionnaire was administered. From September to December 2022, 539 gold miners were included in the study. They represented a migrant population (95.8% from Brazil) with little education and low income. They did not have access to drinking water (95.4%) or latrines (95.4%). They were exposed to mercury by inhalation (58.8%) or ingestion (80.5%). They were in close contact with wildlife by hunting (23.8%), eating bushmeat (65.1%) or being bitten by animals or insects (66.8% and 98.3%). Accidents were frequent (13.5%) and access to health care was difficult, mainly because of the distance from health structures. While 11.9% suffered from chronic diseases, treatment interruptions were frequent (26.6%). Women seemed to be less bitten by animals or exposed to mercury but felt less healthy than men. This study shows that the population of gold miners in FG combines different health determinants leading to poor health. Their illegal activity poses ecological, economic and societal problems. But for ethical as well as public health reasons, health promotion actions must be discussed at different levels: individual, environmental or systemic. However, these approaches are worthless without a global societal approach. Public policies around gold mining should take into consideration the individual and collective health dimensions.

5128

DXCONNECT TEST DIRECTORIES: GLOBAL IMPACT THROUGH ACCESSIBLE DATA ON DIAGNOSTIC ASSAYS

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A fundamental lesson from the COVID-19 pandemic is that dissemination of reliable, evidence-based information is essential to confront novel pathogens by enabling robust and reassuring decision-making. The sudden emergence of a vast number of diagnostic tests, without clear guidance on quality, use cases, or routes to procurement, contributed to global instability and panic. FIND established an open-access, centralized directory of COVID-19 diagnostics to track availability, regulatory status and performance of molecular and rapid tests (antibody and antigen). Today, the COVID-19 test directory contains data on 2124 tests, to support countries and other stakeholders with ongoing pandemic response and containment strategies, as well as to bring transparency to the R&D landscape. Test data are gathered via various workstreams, including proactive scouting, review of scientific publications and regulatory databases, and outreach to manufacturers to request direct submission of test data via online forms. Variables collected include product/technology features, performance characteristics, and regulatory status. Interactive dashboards and curated tables are publicly available and updated in real time on the FIND website. In response to positive feedback from stakeholders, new directories were quickly set up in response to the mpox and ebolavirus outbreaks of 2022, which currently contain 119 and 70 tests, respectively. Further, a test directory dedicated to neglected tropical diseases has been set up to bring transparency to the diagnostic pipeline and maximize the impact of scarce resources in that area. Looking to the future, the test directories are being harmonized and consolidated into one single platform, which will facilitate further expansion of test information on other diseases of outbreak potential, vaccine-preventable diseases, tuberculosis, and antimicrobial drug-resistance. By supplying a bird's eye view of the diagnostic landscape, this suite of test directories provides actionable insights that can improve access to diagnostics and global health.

5129

PSYCHOSOCIAL PROBLEMS AFFECTING GIRLS IN SELECTED SCHOOLS IN POST CONFLICT LIBERIA

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In post conflict Liberia, psycho-social problems are those that affect the mental psyche of the individual and therefore affects an individual productive capacity. Girls in secondary schools especially in developing countries endue the burden of psycho-social problems caused by parents, school policy makers; and practitioners recognizes that social, emotional, physical health and other major burden to learning must be addressed if schools are to function satisfactorily and students are to learn and perform effectively. The objectives of the study includes: identify the impact of psychosocial problems affecting girls in secondary schools in post conflict Liberia; identify the challenges of girls in secondary schools in post conflict Liberia; identify the perception of psychosocial problems of girls in secondary schools in post conflict Liberia; identify the problems of poor performance of girls in secondary school; and to identify appropriate suggestions or recommendations that will enhance peaceful co-existence between girls in secondary schools in post conflict Liberia. A cross- sectional mixed method design was used. The sampling method for the research was a random sampling technique. Data was analyzed using Microsoft Office Excel, Frequency tables and SPSS for the quantitative, FGDs and Nvivo was used for the qualitative data. The findings of the study revealed that: the impact of psycho-social problems on girls in secondary schools in post conflict Liberia are: 50% fair, 25% good and 25% bad; the challenges for girls with psycho-social problems in secondary schools in post conflict Liberia are: low average performance (25%), good performance (15%) and poor performance (20%) whereas, the effect of psycho-social problems on girls in secondary schools in post conflict Liberia were found to be: low concentrations and dizziness towards school work. To critically deal with psycho-social problems faced by girls in secondary schools in post conflict Liberia, rehabilitate them by providing good learning atmosphere.

5130

ANTHROPOMETRIC DIFFERENCES IN COMMUNITY- VERSUS CLINIC-RECRUITED INFANTS PARTICIPATING IN A TRIAL OF AZITHROMYCIN FOR PREVENTION OF INFANT MORTALITY

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Community-based distribution of azithromycin to children aged 1-59 months of age has been shown to reduce all-cause childhood mortality. However, studies of clinic-based distribution of azithromycin have generally not shown a difference between children receiving azithromycin and placebo. Clinic-based recruitment strategies may miss the most vulnerable children. Here, we evaluated baseline anthropometric measures in a trial of azithromycin for prevention of infant mortality that recruited infants both directly in the community and in clinics. Infants aged 5-12 weeks were recruited in Nouna District, Burkina Faso via vaccine outreach visits directly in the community or during vaccination visits in primary healthcare facilities. We classified infants as "community-recruited" if they were recruited via these outreach visits, regardless of whether formal enrollment in the trial occurred in the community or clinic. Clinic-recruited infants were recruited and enrolled in the trial during routine EPI vaccination visits. Height, weight, and mid-upper arm circumference measurements were collected at the time of enrollment in the trial. We compared underweight (weight-for-age Z-score < -2), wasting (weight-for-length Z-score < -2), and stunting (length-for-age Z-score < -2) in community versus clinic recruited infants. Among 32,859 infants enrolled in the trial, 65% were recruited in the community and 35% in clinics. Community-recruited infants were a median of 44 days (6.3 weeks) and clinic-recruited infants were a median of 50 days (7.1 weeks) of age. At baseline, 11.5% of infants were underweight, 9.5% were wasted, and 11.4% were stunted. In age- and sex-adjusted models, infants recruited in the community were more often underweight (odds ratio, OR, 1.25, 95% confidence interval, CI, 1.16 to 1.35) and wasted (OR 1.52, 95% CI 1.40 to 1.65). In conclusion, infants recruited in community settings had increased risk of signs of acute malnutrition (wasting and underweight), suggesting that clinic-based recruitment may miss children who would benefit most from interventions meant to improve child health.

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VACCINE MANAGEMENT PRACTICES AMONG HEALTHCARE WORKERS IN NORTHWESTERN STATE, NIGERIA: A COMPARATIVE STUDY

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Effective vaccine stock management is one of the criteria for a functional vaccine supply chain. It helps to maintain quality of vaccines, prevent stockouts and ensure continuous availability of vaccines. The study evaluated vaccine management practices among healthcare workers in equipped and non-equipped public health facilities in Jigawa State, Northwest Nigeria. Jigawa state has 765 functional health facilities providing routine immunization services. A cross sectional comparative study was conducted in November 2022 amongst healthcare workers with sample

size of 400 and multistage sampling technique for selection of respondents. A semi-structured questionnaire was used to obtain information on socio-demographic characteristics, knowledge and attitude on vaccine and cold chain management, and practices of healthcare workers on vaccine stock management. Data was analyzed using the Statistical Package for Social Sciences software version 23. Level of significance set at $p<0.05$. A total of 386 respondents participated in the study with a response rate of 97%. Respondents from equipped and non-equipped health facilities had mean age of 36.8 years ± 8.7 standard deviation and 35.8 years ± 7.1 standard deviation respectively. Two hundred and sixty-five (71.6%) and 105 (28.4%) worked at primary health care centres ($p<0.05$). Increased knowledge ($p>0.05$), years of working experience ($p<0.05$), positive attitude ($p<0.05$), and good practices ($p<0.05$) of vaccines and cold chain management was observed among respondents from equipped health facilities as compared to those from non-equipped health facilities. Barriers to effective vaccine handling include insufficient ice packs and cost of transporting vaccines to the health facility. Drivers of effective vaccine stock management are length of years working in health facilities, good knowledge, and practices on vaccine stock management as evident among healthcare workers from equipped health facilities. The findings from this study should be used to improve effective vaccine stock management at the state, LGA, and health facility levels.

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THE PREVALENCE OF UNDIAGNOSED HYPERTENSION AMONG RESIDENTS OF THE DUPORT ROAD COMMUNITY

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Hypertension is an important public health and medical issue worldwide. It is the largest contributor to global burden of disease, accounting for 7% of global disability adjusted life years. Liberia is a low-income country and as such faces many challenges especially in the health sector. Most time people who visit the hospital for the first time poses serious complication of hypertension thereby placing extra burden on the already challenged healthcare services. Undiagnosed hypertension is a risk factor for mortality and morbidity among Liberians since there is no presenting symptoms, furthermore the idea is regular screening and hospital checkup is not common in Liberia. The study seeks to identify the proportion of older population living with undiagnosed hypertension. A cross sectional study conducted in the Duport Road Community in 2019 with 167 participants' age 30 years and above who has never been diagnosed with hypertension selected for the study. Participants answered a questionnaire through direct interviews and their blood pressures were measured using automated digital blood pressure machine. Individuals who had systolic blood pressure above 139mmHg and or diastolic blood pressure above 89mmHg had two subsequent measurement of their blood pressure. The results of the study revealed that 29% (n = 49) of the participants had Hypertension (systolic blood pressure >139 mmHg and or Diastolic blood pressure of >89mmHg). Furthermore, 70% (n=118) of the study population had not had a blood pressure check in the preceding 5 years or could not remember the last time they check their blood pressure. Out of the 49 participants who were hypertensive, 65% (n = 32) were 50 year old and above. Hypertension is significantly associated with increasing age, while the lack of regular screening regularly health care visit has attributed to the high prevalence of undiagnosed hypertension among the inhabitants of the Duport Road Community.

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INTEGRATED SKIN DISEASE TRAINING IN VANUATU: PEER-SUPPORTED CAPACITY BUILDING TRANSFORMING HEALTH WORKER CONFIDENCE

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Programs targeting Neglected Tropical Diseases (NTDs) are routinely implemented focused on individual diseases. The financial and opportunity costs of single disease activities are substantial, and, as a result, there has been a call to move towards integrated programs targeting multiple NTDs at once. An integral part of a successful NTD program is training health workers (HCWs) on the prevention, diagnosis, treatment, management, and reporting of NTDs in health facilities and communities. As part of a larger implementation project, the Vanuatu Ministry of Health developed and piloted an Integrated Skin Disease (ISD) training targeting yaws, scabies, and leprosy in three Vanuatu provinces between June 2021 and October 2022. The aim was to increase HCWs' confidence and competencies in diagnosing and managing the care of patients with skin diseases, including community low-up. Unlike typical training, which is often didactic and based largely on one-way information delivery from expert to trainee, ISD used principles of adult learning and took a unique participatory, scenario-based, and peer-learning approach. The training improved the capacity and confidence of 97 HCWs to identify, diagnose, treat, and report cases of skin NTDs. ISD introduced new tools and resources to support HCW in managing cases of skin NTDs and new systems to facilitate timely and accurate reporting to the MoH. For example, for scabies, we observed increased knowledge of 30% to diagnose, 32% to treat, and 37% to refer. Participants, supported by the MoH, developed a plan and have continued rolling out the novel training approach. ISD also improved channels of communication. It catalyzed the creation of a self-sustaining network to support continuous learning and peer support. The training methodology increased dialogue between the MoH NTD programs and health facilities, which (i) enriched the learning experience and (ii) highlighted gaps and needs of health clinics. The ISD showed that participatory, peer learning that builds on the direct experience and local contexts of health practitioners and volunteers can strengthen capacity and support local transformation.

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"I BELIEVE BECAUSE THE VACCINE IS NOT COMING TODAY" - AN EXPLORATION OF THE SOCIO-BEHAVIORAL FACTORS INFLUENCING CHILDHOOD VACCINATION UPTAKE IN URBAN POOR SETTLEMENTS IN NAIROBI, KENYA

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Childhood vaccination uptake has been on the decline, with the World Health Organization estimating that approximately 25 million children missed out on one or more vaccination doses in 2021. Often, children residing in marginalized populations are at a higher risk of being unvaccinated. In Kenya, timely immunization coverage in urban poor settlements remains below 50%. Timely vaccination is crucial in maintaining population immunity against vaccine-preventable diseases (VPDs) and in preventing VPD outbreaks. Exploring context specific reasons for missed vaccinations facilitates the development of tailored interventions. This study aimed at exploring the behavioral and social factors that influence timely childhood vaccination uptake in the urban poor settlements of Nairobi, Kenya. Five focus group discussions (FGDs) were conducted with purposively sampled caregivers of children under five years of age residing in two urban slums in Nairobi. Each FGD involved face-to-face discussions with groups of seven to nine caregivers using an open-ended FGD guide. The development of the FGD guide was guided by the Theory of Planned Behavior. The FGDs were audio-recorded, translated and transcribed. Thematic framework

analysis was used to identify emerging themes and patterns. A total of 39 respondents participated in the FGDs. The median age for the participants was 29 years (range 20-52 years). Although vaccination was perceived to be beneficial and effective in preventing disease, uncertainties about the side effects of vaccination, lay theories and cultural beliefs negatively influenced vaccination uptake. The level of spousal support and lack of the mother's autonomy in vaccination decisions greatly influenced access to timely vaccination. There was inadequacy of vaccination information to facilitate caregiver decisions, with male participants expressing marginalization in vaccination messaging and processes. Community derived and context specific approaches such as tailored messaging need to be tested and applied to enhance timely childhood vaccination uptake in these marginalized populations.

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AVAILABILITY AND ACCESSIBILITY OF SUICIDE PREVENTION SERVICES: A GLOBAL INVESTIGATION

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Suicide is a major global public health issue, worlwide. Suicide prevention services, especially helplines, are crucial resources for individuals at risk of suicide, providing immediate crisis counselling, emotional support and information. However, the availability and accessibility of these services vary greatly across countries and regions, and the effectiveness of these services in reducing suicide rates is not well established. We conducted a global, cross-sectional survey of suicide helpline services. A comprehensive directory of helpline services was created by a team of local collaborators to estimate the number of suicide prevention services available in each country. "Find A Helpline," the largest suicide helpline resource, helped disseminate the survey to their network in over 100 countries. In areas with limited outreach, the questionnaire was directly distributed by local collaborators to increase participation. As of writing, we have collected 460 responses from suicide helplines in 104 countries. The results showed that most services (75.7%) were available nationwide, while 15.7% of services were functional at the state/province level, and 4.3% of services were available at the county/district level. Telephone-based services were the most common mode of service delivery (87.8%), with most services (77.6%) operational 24*7. However, 48.5% of the services reported a decrease in funding levels after the onset of the COVID-19 pandemic. Most helplines (82.4%) provided free services, while only 11.5% provided language translation services. Additionally, only 22.2% of the helplines provided annual booster/refresher training for their staff, and lack of funding and low pay for staff were reported as major challenges by many helplines. Youths were regarded as the most difficult groups to consult with. The findings can inform policymakers and stakeholders in developing strategies to improve the availability, quality, and sustainability of suicide helpline services worldwide. The difficulties of consulting with youths also emphasize the need for specialized training and services for this vulnerable group.

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COMPREHENSIBILITY OF THE EBL2007 CLINICAL TRIAL BY PARTICIPANTS FROM THEIR ENROLLMENT UP TO TWO YEARS OF FOLLOW UP

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In Boende, Democratic Republic of Congo (DRC), an Ebola vaccine trial included health care providers and frontliners. A sub-study developed a true/false questionnaire to assess the understanding of trial consent among participants (Test of Understanding, TOU). One of the eligibility criteria for participation in the trial was the ability to successfully answer at least 9/10 questions of the TOU. This substudy assessed whether participants understanding of the consent/EBL2007 vaccine protocol evolved over years after signing consent in a trial that was at least one year in duration. In total, 699 health care providers and frontliners were enrolled (from December to February 2019). Data included all participant scores at day one at baseline, at year one, and at year 2 for their planned follow up visit. We performed a beta regression analysis using the R packages 'betareg' and 'emmeans'. Different models were developed with TOU as dependent variable and year, age, sex and profession as explanatory variables. TOU scores were above 9 at baseline as it was a prerequisite for participation, but dropped in the first year after participation (median TOU = 8, df=2, p-value=<0.0001). The decrease in TOU score over time differed between HCPs occupations (df=12, p-value <0.0001). A significant decrease difference in gender was only observed in the second year for year for women compared to men (median TOU = 8 vs 9, df=6, p-value =0.005) and in for age for the oldest compared to versus youngest categories (median TOU=8 vs 9, df=6, p-value =0.007). The study results suggest though the informed consent is a fact at the start of the study, it may be a concern in clinical studies lasting for at least one year. Once consent is given, it is a distant memory for most participants. One way to address this problem would be to reinstate participants at a well-defined point in the protocol.

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IMPROVED FACILITY BASED INTEGRATED SUPPORTIVE SUPERVISION- GAINS ON HEALTH SYSTEM STRENGTHENING IN OYO STATE

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Nigeria is a high-burden country, which accounts for approximately one in four of the estimated 232 million cases worldwide (World Malaria Report 2022). The US President's Malaria Initiative for States supports Integrated Supportive Supervisory (ISS) visits to health facilities to support health system strengthening in Oyo state. The objectives of the ISS were to measure the quality-of-service delivery at the facilities, assess the functionality of various systems, update and improve the capacity of health workers. Quarterly visits to health facilities were made using an electronic checklist that covers: infrastructure, basic equipment, human resources, essential drugs, and service delivery for the malaria program. A total of 1625 health facilities were visited between September 2020 and December 2022

and 69% were revisited. Stock availability of artemisinin-based combination therapy (ACT)1, ACT4, Sulphadoxine-Pyrimethamine (SP) and rapid diagnostic test (RDT) showed an incremental improvement from 28%, 34%, 59%, 50% in September 2020 to 62%, 68%, 69% and 84% by December of 2021 and 87%, 94 %, 87 % and 96% by December of 2022. Reduction from 25% at baseline to 17% in December 2021 and 8% in December 2022 was noted in the number of patients who were RDT negative and incorrectly treated with ACT. State performance scores for infrastructure, basic equipment, human resource (job presence), essential medicines were noted to improve from 79%, 71%, 60% and 31% in September 2020 to 83%, 78%, 77% and 54% in December 2021 and 81%, 85%, 72% and 64% in December of 2022. Slight decline was noted in performance scores for infrastructure and human resource in 2022. A Pearson correlation coefficient test between number of visits and performance shows a strong positive correlation for infrastructure($r=.94$) ($p<0.01$), basic equipment($r=.91$) ($p<0.01$), essential medicine($r=.81$) ($p<0.01$) and human resource ($r=.93$) ($p<0.01$), thus revealing that the more visits to the facilities the better the improvement in performance. Following up with issues identified to ensure resolutions made during these visits is key to strengthening health systems.

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IMPROVED DATA QUALITY FROM AUTOMATED DHIS2 DATA EXCHANGE BETWEEN THE MALARIA RAPID REPORTING SYSTEM AND HEALTH MANAGEMENT INFORMATION SYSTEMS IN ZAMBIA

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The Zambia National Malaria Elimination Programme relies heavily on robust surveillance systems not only for malaria programming but also to track progress towards elimination and identification of transmission hotspots for targeted responses. However, the Ministry of Health (MOH) collects malaria data through three separate data systems, which makes it difficult to bring these platforms into one main data source for all malaria related indicators. The three platforms are Malaria Rapid Report System (MRRS) managed by National Malaria Elimination Centre (NMEC); Integrated Disease Surveillance and Response (IDSR) managed by the Zambia National Public Health Institute (ZNPHI); and Health Management Information System (HMIS) managed by the MOH.To identify data gaps and harmonize indicators across the three systems, USAID Evidence for Health (E4H) project in collaboration with NMEC conducted a comparative analysis to assess the performance of malaria surveillance systems in Zambia. Data collection was conducted through a review of existing data collection and reporting systems, datasets, data elements, indicators, and organizational units. This was followed by interviews with key stakeholders.The main issues identified across the three systems were: 1) Inconsistencies in the naming conventions of facilities, even where the same unique identifiers were used; 2) Data element and indicator naming conventions were not consistent across all three systems, and; 3) While all the three systems largely adhered to reporting timeliness, about 95% of the data elements and indicators were either named differently or collected with different disaggregation, thus affecting data quality as well as increasing the workload on data collectors. Based on these findings, MOH collaborating with E4H and partners has prioritized the harmonization of all malaria reporting systems through standardization of indicators, data elements and automation of data exchange across platforms to ensure that the overall reporting system functions as one reliable and effective source of information that improves data quality and reduces workload at data sources.

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EXPLORING HEALTHCARE WORKERS' PERCEPTION AND CHALLENGES TO PRACTICING EFFECTIVE INFECTION PREVENTION AND CONTROL IN TERTIARY CARE HOSPITALS: A MULTI-CENTERED STUDY IN BANGLADESH

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Hospital-acquired infections (HAI) are a major public health burden globally. Deficits in infection prevention and control (IPC) knowledge and perceived barriers among healthcare workers (HCWs) put hospital staff, patients, and visitors at greater risk of acquiring infections. This study identified the perceptions and key challenges on IPC including barriers to compliance with IPC measures among HCWs in Bangladesh. Between August 2020 and March 2021, a qualitative exploratory study was conducted at eight tertiary care hospitals across Bangladesh. We conducted 32 in-depth interviews (IDIs) with hospital administrators, senior physicians, nursing matrons, and heads of cleaning staff from each hospital. We also facilitated 24 focus group discussions (FGD) with physicians, nurses, and cleaning staff. IDIs and FGD findings were compared and themes were triangulated across data collection strategies. Responses were analyzed using a thematic framework. The key barriers to effective IPC practices were a lack of dedicated personnel, irregular monitoring and audit, lack of equitable distribution of personal protective equipment, and insufficient supplies of soap and alcohol-based hand rubs. HCWs identified hospitals' physical layout and infrastructure were unsupportive of following IPC best practices. The barriers included the inaccessibility of hand hygiene stations; inadequate space to isolate patients; deficient HCW-to-patient ratios; and a lack of screening for patients with infectious diseases at admission. However, the implementation of basic IPC activities, such as environmental cleaning, was mostly hindered by the overcrowding of patients and visitors. The findings highlighted the critical IPC-related challenges faced by HCWs during their day-to-day service. The IPC practices were mostly hampered due to the insufficient supplies of IPC materials, unsupportive infrastructure, overcrowding of patients and visitors. The findings from this study could aid hospital leadership and policymakers in developing and implementing a tailored intervention to improve the IPC practices among HCWs to reduce the burden of HAIs.

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A PHASE I STUDY TO ASSESS THE SAFETY AND IMMUNOGENICITY OF A RECOMBINANT ADENOVIRUS-BASED VACCINE AGAINST PLAGUE

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Plague, an ancient and lethal zoonosis caused by the bacterium Yersinia pestis, continues to present a threat globally; both to populations in endemic regions, and due to it's potential as a bioweapon. Despite this, there is no current licenced and available vaccine in the Western sphere. The University of Oxford has developed a novel plague vaccine using the replication-deficient simian adenovirus-vector platform (ChAdOx1) and expressing known immunogenic Y.pestis LcrV and F1 antigens (ChAdOx1 Plague). The PlaVac Phase I trial (ISRCTN: 41077863) recruited healthy adult volunteers (18-55years) who received one or two doses of 5 x 1010 VP at intervals of 0 (Group 1), 0 & 56 (Group 2), or 0 & 182 (Group 3) days and were followed-up to day 365. The primary endpoint was safety and tolerability to day 28 post each dose. Secondary endpoints include antibody responses by ELISA at day 28 post each vaccination, and serious

adverse events (SAEs) and haematology and biochemistry parameters (safety bloods) throughout the trial. Forty-five participants were enrolled (33.3% female, 93.3% white ethnicity); 40 completed follow-up to D365. All participants in Groups 1 & 2 completed the vaccination schedule, n=2 in Group 3 did not receive a second dose for reasons unrelated to safety. The majority of solicited local and systemic adverse reactions were mild (Grade 1) in severity, and peaked within 3 days of dosing. Most common were: injection-site pain and tenderness, fatigue, headache, subjective feverishness, malaise and myalgia. The proportion of participants experiencing severe (Grade 3) adverse reactions was reduced after second dose. There were no serious adverse events or vaccine-attributable derangements of safety bloods during follow-up. Analysis of immunology endpoints is underway. These results demonstrate that the ChAdOx1 Plague vaccine is safe in adult humans, with tolerable reactogenicity. Completion of immunogenicity work will support progression to phase II testing.

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SCOPING REVIEW OF ACUTE FEBRILE ILLNESS IN WEST AFRICAN REGION, 2010-2020

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Acute febrile illness (AFI) is a frequent syndrome among persons seeking medical care in West Africa. Determining AFI etiology remains challenging in this region, where laboratory diagnostic capacity is limited. We conducted a scoping literature review to understand the coverage of AFI investigations in West Africa and to identify knowledge gaps regarding AFI etiology in the region. We conducted title and abstract searches of Medline, Embase, Global Health, and OVID databases using the search terms, in both English and French: "undifferentiated fever," "febrile," "non-specific fever," "suspected malaria," "presumed malaria," "presumptive malaria"; and either "West Africa" or the name of any country in ECOWAS (Economic Community of West African States). Using a standardized data collection form, we extracted data from studies that met the following inclusion criteria: published between January 1, 2010, and December 31, 2020; human studies; and AFI etiology determined by laboratory diagnostics. After deduplication, we screened 743 titles and abstracts. We performed full-text screening on 145 publications, and 76 studies were included for data abstraction. Nine of the fifteen (60%) ECOWAS countries were represented in the final publications, of which 57% of studies were in Nigeria. No consistent definition of AFI was utilized. Participant enrollment was most common in health facilities and included urban and rural populations. Studies reported a range in the number of pathogens tested (1-39), with 75% of studies testing for <3 pathogens. The most common laboratory diagnostic methods were microscopy (43%) and polymerase chain reaction (41%); 53% of studies utilized more than one laboratory diagnostic method. Malaria and dengue were the top two pathogens tested for and detected. Knowledge gaps remain about AFI etiologies in West Africa. Published data are helpful but insufficient to fully inform pathogen prioritization and guide the enhancement of surveillance systems in the region.

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ROOT CAUSE ANALYSIS OF HEALTH SECTOR VIOLENCE IN NEPAL: A QUALITATIVE EXPLORATION OF STAKEHOLDERS' VIEWS

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The task force conducted in-depth interviews with key informants, such as healthcare service providers, patient representatives, and other stakeholders, to map out the causes of violence against healthcare professionals and suggest coping mechanisms to create a violence-free environment. The interviews revealed that poor medical services delivery and increased patient awareness of their rights and access to justice are the main reasons for these acts of violence. The trust in medical services has been eroded by unqualified medical professionals, negative media influence, catastrophic out-of-pocket expenses, poor quality of care, commercialization of health services, poor monitoring of medical services, and a lack of professional ethics among some unscrupulous medical professionals. Despite socio-political development, violence against healthcare professionals is still on the rise due to increasing patient awareness and their willingness to seek justice. The healthcare system, healthcare professionals, government, and media all contribute to these disputes, but the poor quality of care, out-of-pocket payments, and negative media influence are the main factors driving the vicious cycle of complexity. To address these issues, the government, healthcare professionals, social actors, and healthcare facilities need to adopt strong policies and mechanisms to manage the problems that arise from these disputes. Trustworthiness and cost-effective treatment approaches by healthcare professionals and facilities are critical to preventing healthcare sector violence in resource-constrained settings. In conclusion, addressing the root causes of healthcare sector violence requires a multi-faceted approach that involves all stakeholders. Improving the quality of care, reducing out-of-pocket expenses, and promoting professional ethics among healthcare professionals are vital to rebuilding patient trust in the healthcare system and reducing violence against healthcare professionals.

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A POPULATION-BASED SEROLOGICAL SURVEY OF VIBRIO CHOLERAE ANTIBODY TITERS PRIOR TO THE 2022 CHOLERA OUTBREAK IN HAITI

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After three years with no confirmed cholera cases in Haiti, an outbreak of Vibrio cholerae O1 emerged in October 2022. Levels of pre-existing antibodies provide an estimate of prior immunologic exposure, reveal potentially relevant immune responses, and set a baseline for future serosurveillance. We analyzed dried blood spots collected in 2021 from a population- weighted representative cross-sectional serosurvey in two communes in the Ouest Department of Haiti. We found lower levels of circulating IgG and IgA antibodies against V. cholerae lipopolysaccharide (LPS, IgG and IgA $p<0.0001$) in those below 5 years of age compared to those five years and older. Among a subset of patients with higher titers of antibodies, we were unable to detect any functional (vibriocidal) antibodies. In conclusion, the lack of detectable functional antibodies, and age-discordant levels of V. cholerae LPS IgG, suggest that populations in Haiti may be highly susceptible to cholera disease, especially among young children.

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ANTIBIOTIC USAGE IN LAYER FARMS: POTENTIAL ROLE IN EMERGENCE OF ANTIBIOTIC RESISTANCE

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Tetracyclines are widely used for preventing diseases in poultry flocks since decades. It has been shown that low and sub-therapeutic doses of tetracyclines can enhance growth and production. However, their non-prudent use is leading to the occurrence of residues contaminated eggs and emergence of antibiotic resistant strains of bacteria. The present study aimed at detection of tetracycline residues in egg samples collected from

100 layer farms located in five different districts of Haryana, India. A total of 100 pooled egg samples were analyzed using High Performance Liquid Chromatography method for the simultaneous detection of residues of four tetracyclines viz., oxytetracycline, tetracycline, chlortetracycline and doxycycline. Out of 100 samples, 13 (13%) were found to be contaminated with residues of tetracyclines at concentration above limit of quantification. Out of these 13 samples, 1 (1%) was positive for tetracycline and 12 (12%) for chlortetracycline. None of the analyzed sample showed residues of oxytetracycline and doxycycline. Out of 13 samples, 5 (38.46%) (1 for tetracycline residues and 4 samples for chlortetracycline residues) exceeded the maximum residue limits established by Food Safety and Standards Authority of India. The presence of chlortetracycline and tetracycline residues above maximum residues limit in eggs is a matter of concern as it indicates non-prudent use of antibiotics in layer birds and possibility of unacceptable health risks to the consumers. The occurrence of these residues is also indicative of poor farm practices such as non-adherence to withdrawal periods. Thus, there is a need to generate awareness among layer farmers regarding the judicious antibiotics usage and sensitization for adherence to withdrawal protocols. Also, there is a need for formulation and implementation of strict legislations for the regulation of non-prudent antibiotic usage in poultry production.

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GLOBAL PUBLIC HEALTH INTELLIGENCE: WORLD HEALTH ORGANIZATION OPERATIONAL PRACTICES

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Early warning is essential for responding to acute public health threats and preventing public health emergencies of international concern. It is one of the most important activities of the World Health Organization (WHO). Therefore, WHO has adopted a robust approach to public health intelligence (PHI). This is underpinned by the International Health Regulations (2005) and focusses on the global detection and verification of acute public health events of potential international public health concern. Here, we describe WHO operational practices and outputs to further transparency and understanding of our operations. Data on signals and acute public health events reported in 2022 were extracted from internal WHO platforms, including the Event Management System (EMS), which is used for tracking health threats globally. Data were assessed, by the WHO Region and over time, using descriptive statistics in R. Globally, 6855 signals of potential public health threats were detected in 2022. After assessment and verification, 457 were considered acute public health events. These occurred in all WHO Regions although the majority of events were reported from African Region (27%, 125) and the Region of the Americas (25%, 112). The main cause of these events were infectious diseases (383, 83%), of which the three most commonly reported were mpox, cholera and, jointly, measles and dengue. In 2022, in response to these and ongoing events, 65 rapid risk assessments were disseminated. These assess the national, regional and global risk and guide response efforts. In addition, 109 bulletins and 88 announcements were posted on the Event Information Site to inform national country governments of acute public health events. Finally, to provide accurate and timely information to the public, 74 Disease Outbreak News (DON) reports were published. In conclusion, PHI is a key feature of global health architecture. Insight from WHO's practices can inform implementation and operations of other actors as well as identify areas of collaboration. Overall, PHI is vital for combatting novel, (re)-emerging and recurring health risk globally.

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EPIDEMIOLOGICAL INVESTIGATION OF GROUPED CASES OF DEATH DUE TO POISONING WITH CLOSTRIDIUM BOTULINUM IN A VILLAGE IN CÔTE D'IVOIRE, AFRICA, DECEMBER 2022 - JANUARY 2023

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Two episodes of death cases occurred in the village of Kpo-Kahankro, in a health area in the Bouaké South health district, in Côte d'Ivoire. The first episode occurred on the night of Friday December 2, 2022, during which 20 children, 6 of whom died, presented with febrile gastroenteritis syndrome, adynamia and convulsions. This situation occurred in the context of funerals, but also of a Vitamin A supplementation campaign in the village. The second episode would have started on January 19, 2023, causing 58 cases including 16 deaths, where a notion of manipulation of an ecological niche was found; a traditional fetish. Epidemiological investigations were carried out respectively for the two episodes, the objectives of which were to: - Describe the phenomenon - Identify the cause - Propose control measures The investigations were carried out by a multidisciplinary team made up of epidemiologists, environmentalists, biologists, clinicians, hygienists and socio-anthropologists. Investigations consisted of questioning parents of patients and villagers, reviewing the medical records of patients and taking biological samples from patients and suspected sources of contamination. A total of 78 cases have been identified, including 22 deaths, i.e. a lethality of 28.2%. Among the cases, 76 children from 0 to 10 years old. The subjects who died were children (20 children) and subjects aged 50 and over (04 subjects). The signs presented were vomiting (71.1%), fever (52.6%), adynamia (39.5%), diarrhea (31.6%), coma (13.2%). Both episodes occurred after manipulation of an ecological niche during rituals. On more than ten blocks in the village, 47.7% of cases live in the block where the ecological niche is located. Clostridium botulinum was found on microbiological examination of the liquid contained in the niche. The destruction of the ecological niche has allowed the phenomenon to stop.

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THE PREVALENCE AND RISK FACTORS OF POST-TRAUMATIC STRESS DISORDER (PTSD): SYMPTOMS AMONG NURSES DURING THE COVID-19 PANDEMIC. A SYSTEMATIC REVIEW AND META-ANALYSIS

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Since the first reported outbreak in Wuhan, China, the Coronavirus disease 2019 (COVID-19) has raised serious concerns globally. The COVID-19 pandemic has caused a severe psychological impact on healthcare workers (HCWs), and especially nurses, who are the most numerous and exposed front-line group. This systematic review and meta-analysis aim to summarize extant literature on the effects of the COVID-19 pandemic on the psychological health of nurses, particularly concerning the prevalence and risk factors for post-traumatic stress disorder (PTSD). A systematic search was conducted on Pubmed, Embase, and PsycInfo from March 2020 to September 2021. Articles were included/excluded

on predetermined eligibility criteria. A random-effects meta-analysis model was performed using proportions to determine the pooled prevalence of PTSD in nurses and evaluate sources of heterogeneity. Relatively high prevalence rates of PTSD were reported in the nurse population during the COVID-19 pandemic in eighteen different countries, globally. Risk factors associated with PTSD include having prior mental health co-morbidities, being a female, having insufficient protective conditions, working in an Intensive Care Unit, and having a young age. The overall pooled prevalence was 32.2% (95% C.I. = 0.239, 0.417) using a random-effects model in synthesizing 30 studies. The regression test of funnel plot asymmetry indicated a significant level of publication bias among studies. The COVID-19 pandemic is associated with significant levels of PTSD among frontline nurses globally. A high level of heterogeneity was observed across studies. Psychological, social, and administrative interventions should be implemented to mitigate heavy psychological distress in nurses.

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PERCEPTIONS OF YELLOW FEVER EMERGENCY MASS VACCINATIONS IN UGANDA: A QUALITATIVE STUDY

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Yellow fever (YF), a mosquito-borne viral hemorrhagic fever, is endemic in South America and Africa. Numerous outbreaks have been reported in Uganda. During emergency mass vaccinations 1.6 million people were immunized against YF in 2011 and 2016. The aim of this study was to explore local perceptions of YF emergency mass immunization to strengthen future vaccination campaigns. In this qualitative study we conducted 43 semi-structured interviews, 10 expert interviews and 4 focus group discussions. All 76 participants were from six affected districts with emergency mass vaccinations. We interviewed pregnant women and elderly people ≥ 65 years, who are excluded from YF vaccination except during mass immunization. For information on YF mass immunization participants relied on community sources. Information was spread door-to-door, during religious gatherings, in communal places, and via radio. Despite awareness campaigns most respondents had no knowledge of the vaccine, and it was unclear to them whether a booster dose was required. A concurrent presidential election during mass immunization led to distrust and rejection of the vaccine by the opposition. Moreover, distrust in YF vaccines was augmented by a lack of reliable and trustful information combined with a politicization of vaccination campaigns. Vaccination campaigns can never be seen completely detached from political systems and power relations. Thus, we recommend improving access to reliable information in remote areas affected by YF outbreaks. We advise to strengthen health education, communication, and engagement via respected and trusted community members.

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ASSESSMENT OF THE AVAILABLE RESOURCES AND MEASURES TO CONTROL COVID-19 AT THE DISTRICT-LEVEL IN LIBERIA

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COVID-19 continues to rapidly spread throughout the world, wreaking havoc on health professionals, health systems, collective mental health, and economies. In low-income countries, COVID-19 challenges frontline workers who may not have access to essential materials and skills for responding to the crisis. This study assessed available resources and measures used by District Surveillance Officers (DSOs) as part of the COVID-19 response in Liberia. A cross-sectional study was conducted between June-November 2021 using a census sampling approach, inviting all 93 DSOs via WhatsApp and email to complete and submit a survey via Google form. Descriptive statistical analysis was conducted. Microsoft Office Excel, frequency tables, and statistical software R studio version 4.2.0 were used appropiately. 75 responses were obtained from a possible 93 participants. DSOs responded that they were trained an average 2.71+1.23 (SD) times in their districts; whereas at the national level, they were trained on average 0.81+0.56 times. DSOs generally reported that measures taken at the district-level were representative of national recommendations, rather than locally developed measures. Respondents took an average 21.95±1.08 hours to investigate a suspected case. The majority of participants had case investigation forms (n=70, 93%) and PPE (n=68, 91%) as physical resources provided by the national level, whereas 8 (11%) of the participants indicated that their districts lacked financial means to conduct effective response efforts. Respondents reported use of similar response measures across districts, which indicates that DSOs were trained consistently about the COVID-19 response. DSOs had enough case investigation forms and PPE, but some took long to investigate cases. Others lacked internet access and electricity to produce reports effectively and efficiently such that there could be delayed reporting or underreporting of actual effort. Therefore, capacity building should support development of both content and physical resource needs for DSOs to ensure more timely reporting and case investigation.

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ANTIBODY RESPONSE TO DIFFERENT COVID-19 VACCINES AMONG THE MIGRANT WORKERS OF BANGLADESH

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Due to the ongoing COVID-19 pandemic, various host countries such as Singapore imposed entry requirements for migrant workers including pre-departure COVID-19 seroconversion proof. To combat COVID-19 worldwide, several vaccines have acquired conditional approval. This study sought to assess antibody levels after immunization with different COVID-19 vaccines among the migrant workers of Bangladesh. Venous blood samples were collected from migrant workers who were vaccinated with different COVID-19 vaccines (n=675). Antibodies to SARS-CoV-2 spike protein (S) and nucleocapsid protein (N) were determined using Roche Elecsys® Anti-SARS-CoV-2 S and N immunoassay, respectively. All participants receiving COVID-19 vaccines showed antibodies to S-protein, while 91.36% were positive for N-specific antibodies. The highest anti-S antibody titers were found among the workers who completed booster doses (13327 U/mL), received mRNA vaccines Moderna/Spikevax (9459 U/mL) or Pfizer-BioNTech/Comirnaty (9181 U/mL), and reported SARS-CoV-2 infection in the last six months (8849 U/mL). The median anti-S antibody titers in the first month since the last vaccination was 8184 U/mL, which declined to 5094 U/mL at the end of six months. A strong correlation of anti-S antibodies was found with past SARS-CoV-2 infection ($p < 0.001$) and the type of vaccines received ($p < 0.001$) in the workers. Bangladeshi migrant workers receiving booster doses of vaccine, vaccinated with mRNA vaccines, and having past SARS-CoV-2 infection, mounted higher antibody responses. However, antibody levels waned with time. These findings suggest a need for further booster doses, preferably with mRNA vaccines for migrant workers before reaching host countries.

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IMPACT OF ARTHROPODS ON THE TRANSMISSION OF DISEASES AND EPIDEMICS IN POPULATIONS WITH POOR HYGIENIC CONDITIONS AND INAPPROPRIATE BEHAVIORAL HABITS IN THEIR HOMES: CASE STUDIES ON POPULATIONS IN THE HEALTH DISTRICTS OF KINYINYA AND GISURU, NOVEMBER 2022 TO FEBRUARY 2023

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Burundi is an East Africa Country with 27,834 km square and a population of 12,574,569 (2022). The country is endemic for malaria, onchocerciasis, schistosomiasis and STH. Some districts have low trachoma rates, but none reach the MDA threshold for azithromycin. Cholera is sporadic every year. The districts of Kinyinya and Gisuru are 2 out of 4 districts in the health province of RUYIGI, they are located in the eastern part of the country and share the common border with Tanzania. The total population of the two districts in 2021 is 176,487. In 2021 Kinyinya district had 18 health centers and 2 district hospitals while GISURU had 14 health centers and 1 hospital. The two districts recorded 2,101 patients placed under observation for malaria with intestinal disorders or severe malaria, severe acute malnutrition. They received new hygienic facilities fitted out (2,473 standpipes, 3,400 hand washing devices, 4,765 garbage pits, 3,004 latrines. Despite all these efforts, the two districts periodically record unusual public health events manifested by skin manifestations with pruritus, followed by lesions and allergies.The investigation of the unusual public health event in these health districts led to the conclusion that the health situation is the consequence of poor hygiene conditions among the affected populations living with the hens. The inappropriate management of these scratch lesions can also be the gateway for pathogenic germs and cause infections of all kinds. The precarious hygiene in the population of these districts increases the risk of persistence of malaria and neglected tropical diseases in this endemic area. In addition, these insects could also be carriers of other transmissible diseases if they are not eliminated effectively. The cohabitation between humans and animals increases the risk of the emergence of zoonosis such as arboviruses which could cause new serious epidemics. Collaboration between the Administration, the Ministry of Public Health and the Ministry of Agriculture, Livestock and the Environment is essential in order to promote the hygiene of the population and healthy breeding without danger to human health.

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RAPID, LOW-COST, AND PORTABLE LAB-IN-A-BOX 'WHITE LOTUS' FOR POINT OF CARE TESTING OF SARS-COV-2 IN LOW MIDDLE INCOME COUNTRIES

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Rapid identification of infectious diseases is critical in controlling their spread. Reverse Transcription Polymerase Chain Reaction (RT-PCR) is the primary approach for detecting large-scale infectious diseases but it is a complex and expensive process that involves several sample preparation and incubation steps at varying temperatures, making it impractical for low- and middle-income countries (LMIC). Reverse Transcription Loop-Mediated Isothermal Amplification (RT-LAMP) offers a simpler alternative to RT-PCR that maintains high sensitivity and the ability to detect variants, however, large-scale implementation of such tests is challenging as it requires sophisticated and expensive equipment, complex sample preparation and specialized storage conditions for assay reagents. Point-of-care tests (POCT) can overcome this challenge by providing low-cost means to perform a rapid diagnosis at the bedside without intricate steps. This study focused on developing a customized portable lab-in-a-box platform for rapid, sensitive, and patient-centered diagnostic approach based on LAMP. The POCT dubbed "White Lotus" was validated for COVID-19 diagnosis by using saliva samples and involved a quicker detection time with a heat inactivation step instead of RNA extraction. The White Lotus combined four essential components to perform the sequence of RT-LAMP steps: a heating block for thermal lysis followed by an isothermal incubator for amplification, a transilluminator module for visual detection, and a controller to provide user interface, control device components and wireless monitoring through a smartphone app. The White Lotus demonstrated excellent positive and negative agreement percentages (PPA 90.91% (30/33); NPA 96.55% (28/29)) compared to the reference RT-PCR, and significantly reduced instrument capital costs. This low-cost POCT will next be coupled with multiplexed diagnosis panels to differentiate between pathogens, species, and variants and could play a critical role in controlling the spread of infectious diseases, particularly in LMIC and resource-limited regions.

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ASSESSMENT OF POINTS OF ENTRY, ISOLATION SITES AND COUNTIES PREPAREDNESS AND RESPONSE TO EBOLA VIRAL DISEASE, OCTOBER 2022, KENYA

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Ebola Virus Disease (EVD) is a rare and deadly disease most commonly affecting people & non-human primates (monkeys, gorillas, & chimpanzees). The Health Department in Uganda confirmed the outbreak of Ebola Virus Disease (EVD) on September 20th,2022 with 130 cases & 43 deaths as of October 31, 2022. There were possibilities of the outbreak spreading to the neighboring 20 high-risk counties in Kenya whose level of preparedness & response was unknown. Therefore, we conducted an assessment to determine the level of preparedness & response in the counties in Kenya. The methodology used was the administration of a standardized questionnaire to determine the level of preparedness & response at the points of entry, ground crossings, & the County Health Management Team between October,20th 2022 to November, 2nd 2022. The surveillance pillars under assessment were; Coordination, Rapid Response Team, Case Management, Laboratory investigation, Infection Prevention & Control, Isolation & Referral system, Training, Risk Communication, Surveillance, & Community Engagement. The eligibility of the counties for assessment was based on the risk of exposure & proximity to the Uganda border which was experiencing an active Ebola virus disease outbreak. Data were analyzed using excel version 2016 to show the level of preparedness & response in percentages for each surveillance pillar. The results after the assessment were as follows; the average score for all nine surveillance pillars was 21%. The performance on individual pillars was as follows; Risk Communication 58%, Infection Prevention & Control 36%, Rapid Response Team 23%, Coordination 22%, Case Management 14%, Referral services 14%, Training 11%, Isolation & Surveillance 6.6% & Laboratory capacity 4% respectively. In conclusion, there was generally very poor performance on Ebola Virus disease preparedness & Response in all the counties under assessment. Therefore, we recommended all the high-risk counties to develop contingency/emergency plans specifically for Ebola Virus Disease and Disease outbreaks in the future.

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SEROPREVALENCE AND RISK FACTORS ASSOCIATED WITH BRUCELLOSIS AMONGST LIVESTOCK AT KITENGULE RANCH IN KAGERA, TANZANIA

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Brucella spp. are highly infectious pathogens causing brucellosis, a significant zoonotic disease affecting livestock, wildlife, and humans. In livestock, brucellosis could cause abortion and reduced milk production. Brucellosis is endemic in Tanzania; however, the prevalence of brucellosis amongst livestock species still needs to be fully established. This study aimed to determine the seroprevalence of brucellosis in cattle, goats, and sheep at Kitengule ranch in Kagera region of Tanzania. A cross-sectional sampling was conducted in early 2023. Blood samples were collected from cattle, goats, and sheep for serological evaluations. Epicollect was used to collect metadata to evaluate the risk factors associated with brucellosis. The presence of serum immunoglobulin against Brucella was tested using Rose Bengal Test and confirmed by cELISA. Descriptive statistics were used to determine the disease's prevalence among livestock species. Serum from 541 cattle and 185 small ruminants (goats/sheep) were tested for Brucella spp. The overall seroprevalence in livestock was 34.2%, comprising 68.1% in small ruminants (n=126, 95% CI= [60.9-74.8]) and 22.6% in cattle (n=122, 95% CI= [19.1-26.3]). Seroprevalence was significantly different between herds (Chi-square p< 0.0001). Multiple logistic regression analysis was run on variables, including animal species, herds, sex, and age. Results indicated that small ruminants are more likely to test positive than cattle (OR=14.0, CI= [6.7-31.4], p< 0.0001). Seropositivity was considerably higher in females than males (OR=3.1, CI= [1.2-4.2], p=0.001). Our results also showed that seropositivity was higher in older animals (> 2 years) compared with younger animals (OR=1.8, CI= [1.2-3.6], p=0.024). Our study suggests a high rate of seroprevalence of brucellosis (34.2%) at the Kitengule ranch compared to the national pooled average (8%). This calls for an urgent unmet need for further investigation of risk factors associated with brucellosis in livestock in other areas of Tanzania to help inform the development of evidence-based control plans benefiting both animal and public sectors.

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STRATEGIES AND POLICIES FOR SUSTAINABLE PATHOGEN GENOMIC SURVEILLANCE IN AFRICA: PRIORITIES, PROGRESS, AND CHALLENGES

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Pathogen genomic surveillance is one of the crucial components of regional and global health security. Africa, with its diverse population and high burden of infectious diseases, has a critical need to integrate genomics into existing systems for outbreak detection and disease surveillance. Here we discuss the priorities, progress, and challenges of developing national strategies and policies for sustainable integration of genomic into existing disease surveillance, preparedness, and response in Africa. The strategies and policies are being developed through a collaborative effort involving Africa CDC, Member States, academia, non-governmental organizations (NGOs), and other stakeholders. The process involves mapping and review of existing policies, a situational analysis of the current state of genomic surveillance, and a stakeholder engagement process to identify priorities and gaps. The strategies and policies prioritize the strengthening of laboratory and bioinformatics infrastructure, the development of human capacity, and the establishment of sustainable funding mechanisms. The strategies also emphasize the importance of collaboration and sharing of data, resources, and expertise among member states and with other global partners. Furthermore, the policies highlight the need for ethical considerations in genomic surveillance, including data privacy, data governance and sharing. Implementation of the strategies and policies will require a multi-sectoral approach and sustained commitment from governments, donors, and other stakeholders. Overall, we highlight the need for sustained investment in genomic surveillance by African Union Member States and underscore the role of international collaborations and partnerships in achieving sustainable disease surveillance and response.

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A STUDY ON KNOWLEDGE, ATTITUDE AND PRACTICE (KAP) ON YELLOW FEVER AMONG COMMUNITY MEMBERS IN FOUR DISTRICTS AFTER AN OUTBREAK IN THE SAVANNAH REGION, GHANA

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In 2021, Yellow Fever (YF) outbreak occurred in, rural and mostly nomadic communities in the Savannah Region of Ghana with over 40 deaths, including children. We determined the knowledge, attitude and practice (KAP) of community members in four districts in the Savannah Region using a questionnaire survey on 869 participants from June to July, 2022. Out of the total inhabitants interviewed, majority 702 (80.8%) indicated they heard about YF through healthcare personnel. 191(22.0%) had knowledge that transmission is through mosquito bites. Two districts; Central Gonja, 171 (86.5%) and Sawla-Tuna-Kalba 172 (86.0%) showed high knowledge on YF, the difference in participant's high-level knowledge on YF between the two districts is statistically not significant (Mann-Whitney test =25706.000 P = 0.262). while North Gonja 58 (21.6%) and West Gonja 52 (26.0%) showed little knowledge on YF. The difference in participant's low-level knowledge on YF between the two districts is statistically not significant (Mann-Whitney test=19900.000 P = 0.886). Among the participants 611 (70.3%) adopted the use of mosquito net, 605 (69.6%) clearing bushes and 636 (73.2%) cleaning of their surroundings as a mosquito preventive measure against the spread of YF. The vaccination of respondents or any household member was likely not influenced by time taken to access health service as explained by the lower correlation coefficient (Spearman Rho correlation coefficient=0.264). The emergency mass YF vaccination carried out by the Ghana Health Service in response to the outbreak in the region could have contributed to the high knowledge of community members on the disease. Regular education on YF in these YF hotspot communities in the Savannah Region and Northern Ghana as a whole will help increase awareness and consequently reduce the risk of transmission of the disease.

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COMMUNITY ENGAGEMENT IN A NEW TRIAL SITE OF THE PARTNERSHIP FOR RESEARCH ON EBOLA VACCINATION IN MALI

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Since the 2014 Ebola virus disease outbreak in West Africa, several clinical trial initiatives have been implemented to accelerate the search for an effective vaccine against the disease. We report on a community engagement process to identify issues related to the understanding and

acceptability of participation in a community-based vaccine trials of the Partnership for Research on Ebola Vaccination (PREVAC) in Mali. To identify a community engagement strategy for a new vaccine against Ebola in Mali. A questionnaire and focus groups (8) involving heads of households, women and community leaders were conducted. 22 community mobilizers were trained on Ebola vaccination and on responsible conduct of research and ethics. “Ice-breakers” meetings with traditional authorities were conducted to establish a participatory framework between the research team and the communities. Study participants expressed a very good knowledge of Ebola, including mode of transmission (32%), prevention (88%) and 97,9% recognized the importance of vaccination. The baseline survey showed that 75,2% were inclined to participate in the vaccine trial. The community engagement strategy, through the series of “Icebreakers” meetings and the interface between the communities and the research team made it possible to dispel the concerns raised for non-participation in clinical trials (lack of confidence in a new vaccine). They made it possible to achieve a retention rate of 94% of the volunteers who made the scheduled 9 visits in the research protocol and more than 4000 home visits. The participatory approach through inclusion of traditional community legitimacy, awareness and information on the vaccine process helped to build trust and acceptability of the vaccine trial. This experience gathered during PREVAC with the NIH can be used to guide future vaccine trials in developing countries.

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COVID-19 ATTITUDES AND VACCINE HESITANCY AMONG AN AGRICULTURAL COMMUNITY IN SOUTHWEST GUATEMALA: A CROSS-SECTIONAL SURVEY

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Despite offering free-of-charge COVID-19 vaccines starting July 2021, Guatemala has one of the lowest vaccination rates in Latin America. During September 28, 2021 to April 11, 2022, we conducted a cross-sectional survey of community members adapting a Center for Disease Control and Prevention (CDC) questionnaire to evaluate COVID-19 vaccine access and hesitancy. Of 233 participants ≥12 years, 127 (55%) received >1 dose of COVID-19 and 4 (2%) reported prior COVID-19 illness. Persons ≥12 years old (eligible for vaccine at the time) who were unvaccinated (n=106) were more likely to be female (73% vs 41%, p<0.001) and homemakers (69% vs 24%, p<0.01) compared with vaccinated participants (n=127). Among those >18 years old, vaccinated individuals were more likely to be moderately or very worried about COVID-19 (n=36, 31%) compared to unvaccinated individuals (n=13, 18%; p=0.04); unvaccinated individuals were more likely to have little no confidence in public health institutions (55% vs 38%, p=0.02). Participants’ primary reported motivations for COVID-19 vaccination were to protect family/friends (68% vaccinated vs 73% unvaccinated, p=0.54), to protect their own health (24% vs 11%, p<0.01), and to protect the health of the community (2.5% vs 3%, p=0.94). Community- and/or home-based vaccination programs, including vaccination of families through the workplace, may better reach female homemakers and reduce inequities and hesitancy, and a such a program is ongoing. In follow-up, beginning March 14, 2023, we began a repeat survey in the same household cohort to assess changing attitudes and access around COVID-19 and COVID-19 vaccines as well as drivers (risk associations) of those changes.

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DESCRIPTION OF AN ACTIVE SURVEILLANCE SYSTEM CONDUCTED IN OUTPATIENT CLINICS FOR PRIORITY ACUTE IN FECTION SYNDROMES IN GUATEMALA

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Due to the high burden of infectious disease and limited diagnostic capabilities in Guatemala, the Vigilancia integrada colaborativa de enfermedades infecciosas agudas prioritarias (VICo-IP) was established to estimate the burden and characterize etiologies for key infectious disease syndromes. VICo-IP operates in Quetzaltenango, a department with a majority urban-dwelling population of nearly 800,000. We examined data from two ambulatory clinics in the San Juan Ostuncalco (SJO) and El Palmar municipalities, which differ in climate, altitude, and ethnic makeup. Patients of all ages who provide consent or assent are screened for signs of acute respiratory (ARI), diarrheal (ADI), or febrile (AFI) syndromes, and epidemiological data and samples (nasopharyngeal and/or oropharyngeal swabs, stool, blood, and urine) are systematically collected. Etiologies are identified by LIAT, FilmArray, and PCR testing. Analysis of surveillance data from a period of continuous enrollment (1 March 2022 to 25 January 2023) reveal differences in disease frequency, notably respiratory and diarrheal, between the two clinics. Overall, of the 644 enrolled participants, mean age was 27.6, and 57.8% were female. 92.2% of patients presented with symptoms of ARI, 16.3% ADI, and 28.9% AFI. 97.2% provided samples for etiological testing. Few cross-syndrome etiologies were seen. SARS-CoV2 (198/409, 48.4%) was the most common respiratory disease etiology found, whereas E. coli strains (12/37, 32.4%) and Leptospira bacteria (7/13, 53.8%) were the most common diarrheal and febrile etiologies identified, respectively. Significantly more laboratory-confirmed diarrheal disease was seen in El Palmar (OR: 14.1, 95% CI: 2.18-283) than SJO. SJO demonstrated significantly greater laboratory-confirmed burden of respiratory disease (OR: 1.80, 95% CI: 1.19-2.75) than El Palmar, indicating local site characteristics should be used to decide on control and mitigation interventions. Examining syndromic data from similar-level facilities can assist public health officials in better understanding population needs and tailoring appropriate interventions.

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STRENGTHENING HEALTH SYSTEMS FUNDAMENTALS CAN PROTECT COUNTRIES FROM COVID-19: A RE-EVALUATION OF THE GLOBAL HEALTH SECURITY INDEX AND ITS SUB-DIMENSIONS

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The Global Health Security Index (GHSI) is a composite index developed in 2019 to assess countries’ preparedness for epidemics and pandemics under the International Health Regulations framework. However, recent research showed that the GHSI was not predictive of countries’ performance during the COVID-19 pandemic, raising questions about its validity as an assessment tool. We empirically explored if and how subcomponents of the GHSI were associated with their ability to safeguard essential health service delivery during the pandemic.Using a difference-in-difference methodology, we assessed the relationship between countries’ ratings pertaining to their overall preparedness and six subcategories and childhood immunization coverage rates during the pandemic. We operationalized the GHSI 2019 and its 6 subcomponents and 34 indicators to assign countries to the treatment (above 80th percentile) and control groups and defined 2020 and 2021 as post-pandemic years. The results were crossed-checked using the World Bank’s governance indicator to ensure the reliability. All analyses were adjusted for potential confounders. While the overall effect of the GHSI on childhood immunization coverage

rates during 2020-2021 was statistically non-significant, countries' commitments to sharing data (coef: 6.0; p =0.017), infrastructure (coef: 3.2; p <0.001), and overall environmental risks (coef: 2.94; p <0.001) were the subcategories most positively associated with preventing declines in childhood immunization coverage. These results were confirmed with the World Bank's governance indicators, which demonstrated that countries' rule of law (coef: 3.58; p <0.000), effective governance (coef: 3.27; p <0.000) and control of corruption (coef: 3.16; p <0.000), were most strongly associated with preventing the declines.Our findings underscore the importance of core health system capacities that shape countries' overall risk landscapes in mitigating the public health consequences of the COVID-19 pandemic and provide prioritization guidance to policymakers to improve countries' preparedness for future epidemics and pandemics.

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THE SYNERGISTIC IMPACT OF UNIVERSAL HEALTH COVERAGE AND GLOBAL HEALTH SECURITY ON HEALTH SERVICE DELIVERY DURING THE COVID-19 PANDEMIC: A DIFFERENCE-IN-DIFFERENCE-IN-DIFFERENCE STUDY OF CHILDHOOD IMMUNIZATION COVERAGE FROM 192 COUNTRIES

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Universal health coverage (UHC) and global health security (GHS) are two high-priority global health agendas that seek to foster health system resilience against health emergencies. Many countries, however, have had to prioritize one agenda over the other due to scarce resources and political pressures. To aid policymakers' decision-making, this study investigated the individual and synergistic effects of countries' UHC and GHS capacity in safeguarding essential health service delivery during the COVID-19 pandemic. We used a quasi-experimental difference-in-difference and difference-in-difference-in-difference methodology to quantify the relationship between 192 countries' progress towards UHC and GHS and those countries' ability to provision 12 essential childhood immunization services between 2010 and 2021. We used the 2019 UHC Service Coverage index to divide countries into a "high UHC group" (above 80th percentile) and the rest, and similarly used the 2019 GHS Index to divide countries into a "high GHS group" and the rest. All analyses were adjusted for potential confounders.Countries with high UHC scores prevented a 3.34% (95% CI: 2.17%, 4.52%; p-value < 0.001) reduction in immunization coverage across 2020 and 2021. Countries with high GHS scores prevented a 2.02% (95% CI: 0.44%, 3.59%; p-value = 0.012) reduction in immunization coverage in 2021 but no statistically significant effect in 2020. The DiDiD model showed that high GHS capacity needed to be augmented with high UHC to prevent a decline in immunization coverage while high UHC alone was able to safeguard immunization coverage during the pandemic.This study found that greater progress towards both UHC and GHS safeguarded essential health service delivery during the pandemic but only progress towards UHC was both a necessary and likely sufficient element for yielding this protective effect. Our results call for strategic investments into both health agendas and future research into possible synergistic effects between the two health frameworks.

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WASTEWATER GENOMIC SURVEILLANCE AS AN APPROACH TO TRACK INFECTIOUS DISEASES PATHOGENS IN THE AGADIR REGION OF MOROCCO

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Wastewater genomic surveillance is a promising approach to monitor pathogens that may constitute a health threat for humans and animals. This approach can be applied as an early warning tool and to enable acting before pathogens spread to the general population. In collaboration with Moroccan health and environmental authorities, we established a platform of experimental and analytical resources to monitor antibiotic resistance genes (ARGs) and SARS-CoV-2 dynamics. The workflow developed comprises sample collection and processing, nucleic acid purification, and downstream genomic pipelines using a real-time quantitative PCR and NGS platforms. Using these resources, first we demonstrate the feasibility of ARGs monitoring by successful profiling of the resistome in 6 wastewater treatment plants (WWTPs) in the Agadir region for the first time in Morocco, providing a better understanding of the status of ARGs and highlights their dissemination potential. Second, we performed genomic surveillance of SARS-CoV-2 during the initial Omicron wave in January 2022. Following automated RNA extraction, SARS-CoV-2 N gene was qPCR amplified and quantified. The results showed that viral load in wastewater influents from these WWTPs ranged from 52.7E+03 to over 75.8E+04 viral N gene copies/L. The evolution of the number of confirmed cases identified by the Ministry of Health, during the same period and in the same geographical area correlates with our viral load findings. NGS sequencing of SARS-CoV-2 genomes recovered from wastewater clearly indicated the predominance of the BA1 variant (99%) with less than 1% for the BA2 variant. Furthermore, the number of infected individuals was predicted by using a SEIR-model and the mass rate of SARS-CoV-2 RNA in wastewater. The results estimated the number of infected persons to be ~25 fold higher than the reported number of cases. This may be due to asymptomatic and undiagnosed cases, and individuals who are positive but do not undergo testing or report to clinics. These results highlight the power of wastewater genomic surveillance as a valuable tool to monitor, better understand and control pathogens.

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THE VIRTUAL BIOREPOSITORY SYSTEM FOR OPEN ACCESS TO SAMPLES: THE ONLINE DELPHI PRIORITIZATION OUTCOME

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An equitable, federated, virtual biorepository system (VBS) with stewardship focused at local sites broadens access to specimens and associated data for outbreak-prone infectious diseases. This would accelerate the development of diagnostics, assessment of vaccine efficacy, and support surveillance and research that is reflective of the populations being served. The VBS is aligned to complement other specimen-sharing efforts as a force multiplier to strengthen global tools for countering epidemics. Our work reveals significant gaps in diversity, equity, and inclusion in accessing specimens/data especially for LMICs. We used an online Delphi process (oDp) as an inclusive approach to engage stakeholders to re-imagine and empower low-resource partners to drive the VBS concept at scale, where they will prioritize the benefits and define sustainable operations in their context. Participants included principal investigators (23), public health/clinical laboratories (9), research institutions (22), commercial diagnostics (3), and biorespository managers (5) working from Africa (15), N. America (10), Europe (9), Latin America (9) and Asia-Pacific (5). We posed 34 questions for participants to rank preferences presented as % in agreement. There was complete consensus (100%) about the need for collecting clinically well characterized specimens and associated data and implementing a cost recovery scheme; followed by serially collected blood and blood-derived samples (95%), access to qualified reference standards (93%), and willingness to share specimens (92%). The VBS is envisaged to combine centralized and federated components (82.9%) with networking and collaboration as the highest ranked benefits. Regulations prohibiting sharing samples out of country (56%) were seen as the greatest challenges. By using the oDp, we were able to successfully use a grassroots effort to

inform us as to our next steps. We suggest that the oDp can be a useful tool to help identify priorities and streamline the work plan for other complex global good products.

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THE VIROME OF PHLEBOTOMINE SAND FLIES FROM SELECT REGIONS OF KENYA

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Sand fly-associated viruses are inadequately researched in Sub-Saharan Africa. Whereas recent surveillance studies in parts of Kenya have revealed a number of arboviruses circulating among sand fly populations, our overall knowledge of the identity of viruses in these vectors remains limited. The present study used metagenomics, viral isolation and Next Generation Sequencing (NGS) to characterize RNA viruses in sand flies. Sand flies were collected between September 2020 and July 2022 in Baringo, West pokot, Nakuru, Kisumu, Kilifi, Kwale and Isiolo counties in Kenya using CDC light traps. The collections were sorted into pools of 10 or less flies and homogenized. Virus isolation was performed in vero cells with CPE positive samples being subjected to NGS. For metagenomic analyses, super-pools were generated based on site of origin. Libraries were prepared and sequenced on the Iseq 100 platform. The unassembled short reads were classified using Kraken 2 metagenomic sequence classifier and mapped to the genomes of isolated viruses. Contigs were generated in Megahit and further taxonomic classification done. Two CPE positive samples resulted in the isolation of the Koutango lineage of West Nile Virus (WNV) and Bogoria virus, a phlebovirus. Read classification led to identification of several viral sequences including Vesicular stomatitis virus, Maraba virus, Carajas virus, Piry virus, Koutango virus (WNV) and Bogoria viruses. From assembled metagenomic sequences, 14 phylogenetically distinct insect specific viruses belonging to Dicistroviridae, Chuviridae, Iflaviridae, Nodaviridae, Tombusviridae, Polycipiviridae families and Negevirus were identified. These results have shown that sandflies from Kenya harbour diverse RNA viruses, some of which are of public health importance.

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SYSTEMATIC REVIEW ON TICKS AND TICK-BORNE DISEASES IN ASIA AND AUSTRALIA

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Globally, tick-borne pathogens of human concern pose a threat to deployed war fighters (DWFs). DWFs pyrethroid treated uniforms are their first line of defense against tick vectors. As climate change shifts vector habitats and affects the value of insecticides for protection, DWFs remain at risk. A systematic literature review was performed to strengthen the knowledge of tick species and their associated pathogens in areas where soldiers may be deployed or stationed.This review focused on the INDOPACOM region including Australia, Bhutan, Guam, Korea, Palau, and the Philippines. Search terms included a variety of ticks and tick-borne diseases in these countries following PRISMA guidelines from 1900 until 2022. The initial search yielded 8,433 articles and 1,184 articles met full review. Full review articles were extracted and uploaded to VectorMap comprising 338 articles from Australia (170), Bhutan (1), Guam (3), Korea (145), Palau (0), and the Philippines (19). Records from these countries included the following hard tick genera: Amblyomma, Aponomma, Dermacentor, Haemaphysalis, Hyalomma, Ixodes and Rhipicephalus, and two soft tick genera: Argas and Ornithodoros. The largest variety of tick species collected were from Australia followed by the Republic of Korea. Numerous pathogens were detected using PCR or IFA including species from the following genera: Anaplasma, Borrelia, Babesia, Coxiella, Ehrlichia, Francisella, Rickettsia, Theileria, and Flavivirus. Ticks were collected from various mammalian and avian hosts including humans.These records contained an abundance of pathogens in ticks from Asia and Australia with the potential to cause human disease. Maps showing the distribution and prevalence of tick species and corresponding pathogens can inform control measures. As vector habitats and behaviors adapt to climate change, continued surveillance will be vital to understanding the risk towards human health. Gaps for future surveillance were noted, especially in Bhutan, Guam, and Palau where few records were found. This valuable knowledge can ensure well informed decisions are made to protect DWFs in these areas.

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MITE-TRANSMITTED INFECTIOUS DISEASES: WIDELY DISTRIBUTED AND NEGLECTED

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Mites are among the smallest arthropod vectors of infectious diseases (IDs) with most species barely visible at less than one µ in length. Bites by house mouse mites can transmit Rickettsia akari, the causative bacterial pathogen of rickettsialpox. Bites by larval trombiculid mites can transmit Orientia tsutsugamuchi, the causative bacterial pathogen of scrub typhus. Rickettsialpox occurs worldwide, and scrub typhus is considered regionally confined to the Tsutsugamuchi Triangle in Asia and Northern Australia. The ecology, epidemiology, clinical manifestations, differential diagnosis, laboratory diagnosis, management, and prevention of mite-transmitted IDs are presented. Internet search engines are queried in order to provide evidence that mite-transmitted IDs are both widely distributed and neglected. Rickettsialpox is widely distributed for several reasons including its animal reservoir, the common house mouse, and its mouse mite vector are ubiquitous; and subclinical and doxycycline-cured cases are often underreported worldwide. Scrub typhus is also widely distributed for several reasons including a global distribution of potential larval mite vectors with new cases of scrub typhus described in the Middle East and South America, far away from the Tsutsugamuchi Triangle. Rickettsialpox and scrub typhus are super-neglected and not included among the WHO listing of neglected diseases. Neglect of these mite-transmitted IDs is evidenced by a lack of research and new drug development as compared to mosquito-borne and tickborne IDs. In addition, there are no vaccines to prevent rickettsialpox and scrub typhus. Targeted research into mite-transmitted IDs, new drug development to counter increasing doxycycline resistance and replace chloramphenicol, and vaccines, especially for scrub typhus, are needed now.

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POPULATIONS STRUCTURE ANALYSIS OF PHLEBOTOMUS PAPATASI POPULATIONS USING TRANSCRIPTOME MICROSATELLITES: POSSIBLE IMPLICATIONS ON GENE EXPRESSION

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Phlebotomus papatasi considered the primary vector of Leishmania major parasites which causes zoonotic cutaneous leishmaniasis (ZCL) in the Middle and far East and in North Africa. P. papatasi populations have been extensively studied and revealed the existence of different genetic populations and subpopulations over its large distribution range. Genetic diversity and population structure analysis using transcriptome microsatellite markers is important to uncover the vector distribution dynamics, an essential for controlling ZCL in endemic areas. In this study, we investigated for the first time the level of genetic variation using expressed sequence

tags EST-SSRs among field and colony P. papatasi samples collected from 25 different locations in 11 countries. The genetic variation reveals the existence of high-level population structures expressed in five distinct populations. These great genetic differences in expressed genes may enable P. papatasi to adapt in different environmental conditions along its distribution range and affects dispersal and control of this species probably by upregulating insecticide resistant genes which is common among vectors of infectious diseases. Moreover, anthropogenic changes can also lead to an increase in the dispersal of sand flies and hence the disease transmission. The investigation of population structuring of P. papatasi may have a great contribution to the L. major containment efforts in these countries. Moreover, the level of genetic variation among these populations may have a great benefit for understanding parasite-vector interaction and contribute to the efforts of vaccine development based on P. papatasi salivary proteins.

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RELATIONSHIP BETWEEN ENVIRONMENTAL FACTORS AND PHYSICO-CHEMICAL PARAMETERS IN THE DISTRIBUTION AND DENSITY OF MOLLUSC INTERMEDIATE HOSTS OF SCHISTOSOMIASIS IN SENEGAL

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A change in the epidemiology of bilharzia has been noted with the appearance of hybrid strains in northern Senegal. The objective of this work is to study the relationship between physico-chemical parameters (water temperature, conductivity, salinity, pH, total dissolved solids), environmental factors (plastic waste, vegetation) and the distribution of molluscs in 14 sites in the Ferlo valley, Lac de Giers and Taouey canal.At each site, prior to any survey, information concerning the habitat was collected, namely the geographical coordinates, pollution, type of vegetation and the presence of animals. To measure the physico-chemical parameters such as water temperature, conductivity, salinity, pH and total dissolved solids we used multiparametric tester with digital probes PC60 (APERA instruments). The technique consisted of immersing the probes in the water to collect these data.The surveys identified 8 species of molluscs, four of which are involved in the transmission of human schistosomes (Biomphalaria pfeifferi, B. globosus, B. truncatus, B. senegalensis) and four other species that are not involved in the transmission of schistosomiasis (B. forskalii, Lymnaea natalensis, Bellamya unicolor and Mellanoides tuberculata). The density of molluscs collected is a function of the nature of the site. This study also shows that environmental parameters (vegetation, pollution) and physicochemical parameters (total dissolved solids, salinity, pH) have effects on the distribution and density of mollusc populations intermediate host of human schistosomes.

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FIRST RECORD OF MOSQUITO BORNE SINDBIS VIRUS <GENOTYPE I> IN BURKINA FASO, WEST AFRICA

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Several mosquito-borne viruses represent a major threat to human health worldwide. Beyond those well-known pathogens, a large diversity of arboviruses transmitted by mosquitoes remains largely unstudied despite an established potential for emergence in some cases. Beyond a high diversity, mosquito arboviruses have also shown an impressive capacity for spread into new regions. Thus, health services require updated characterisations of the arbovirus diversity in a given region to optimize diagnostics. Nevertheless, such updates are rarely carried out, especially in low-income countries. Thus, diagnostics of potential arboviral infections is often limited to high-profile viruses, like dengue virus. This situation probably leads to a large fraction of undiagnosed cases due to arboviruses neglected or recently established in a region. Here, we have characterized the diversity of mosquito-borne viruses in two regions of Burkina Faso. To this end, we have screened a recent and large mosquito collection using untargeted metagenomics. The analysis focused on two mosquito species, Aedes aegypti and Culex quinquefasciatus, considered among the most important vectors of arboviruses worldwide. The screening detected Sindbis virus (SINV, Togaviridae) for the first time in Burkina Faso. This zoonotic arbovirus has spread into Europe from Africa and is the cause of disease outbreaks mainly in Europe. SINV was detected at low prevalence and only in C. quinquefasciatus from one of the regions and at a single year. A phylogenetic analysis placed the nearly-full SINV genome within the cluster of Central African sequences at the origin of the strains that have spread into Europe. Thus, this result extends the region as potential SINV source to Western Africa. Finally, a virus isolate was obtained for future experimental studies. Overall, our results provide insights into the current arbovirus diversity in Burkina Faso and can help to improve diagnosis. Moreover, the approach used here could be applied to other regions in need of a better characterization of the arbovirus diversity in mosquitoes.

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CHANGING EPIDEMIOLOGICAL PATTERN OF VISCERAL LEISHMANIASIS IN NEPAL

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On the Indian subcontinent, visceral leishmaniasis VL is targeted for elimination as a public health problem by 2017. Nepal has achieved the elimination target at district level in 2013 and has been sustained the situation since then. Recently, we conducted a field surveys in non-program hilly districts in Nepal where increasing number of VL cases have been persistently reported since 2000. A house-to-house survey in 14 villages from eight hilly districts documented retrospectively 54 cases of VL, predominantly males, mostly pediatric cases who were reported in the last five years. Anti-Leishmania antibodies were found in 22/23 past-VL cases, in 40/416 9.6% persons without VL and in 12/155 7.7% domestic animals. An age- and sex-matched case-control study showed that exposure to known VL-endemic areas was no risk factor for VL, but having a VL case in the neighborhood was. SSU-rDNA PCR for Leishmania sp. was positive in 24 (5%) of the human, in 18 (12%) of the animal samples and in 16 (14%) bloodfed female Phlebotomus argentipes sand flies. L. donovani was confirmed in two asymptomatic individuals and in one sand fly through hsp70-based sequencing. This study proves that there is indeed ongoing local transmission of Leishmania donovani in areas at an altitude above 600 meters, districts considered higher to non-endemic for VL. This geographical expansion of cases and ongoing local transmission could challenge the aim of the VL elimination program in Nepal. Hence, policy makers should give a high priority in expanding active surveillance and control activities to achieve the realistic goal.

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BEHAVIORAL INTERACTIONS OF BED BUGS WITH LONG-LASTING PYRETHROID-TREATED BED NETS: CHALLENGES FOR VECTOR CONTROL

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Long-lasting insecticide-treated nets (LLINs) have historically been, and remain, one of the most commonly used vector control tools in the campaign against malaria. The emergence of pyrethroid resistant bed bugs in malaria endemic communities and failure to control infestations have been suggested to interfere with the effective use of LLINs. Therefore, the behavioral interactions of bed bugs with commonly used bed nets should be better understood. To investigate the interactions between bed bugs (Cimex lectularius) and LLINs, insecticide-susceptible and pyrethroid-resistant bed bugs were challenged to pass through two

commonly used LLINs in two behavioral assays. We found a significant impact of deltamethrin-treated nets on blood-meal- and aggregation-seeking behaviors of susceptible bed bugs, and no impact of treated nets on resistant bed bugs. Commonly used new LLINs failed to prevent the passage of susceptible and pyrethroid-resistant bed bugs in host-seeking and aggregation-seeking bioassays, resulting in overall low mortality. For the first time, we have shown the strong potential of LLINs to select for resistant non-target pests, and so their potential role in stalling malaria control programs should be further investigated.

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ISOLATION OF MICROSATELLITE LOCI FROM THE GENOME OF PHLEBOTOMUS ARGENTIPES, THE MAJOR VECTOR OF LEISHMANIASIS IN SRI LANKA: A PRELIMINARY STUDY

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The microsatellite markers are promising because of their high polymorphism rate, high abundance, and wide distribution throughout the genome. However, microsatellite markers have not been reported for the sandfly species Phlebotomus argentipes, possibly due to the low abundance in the genome and/or difficulty in isolation. The present study aimed to identify di- or tri-nucleotide microsatellites in P.argentipes. Whole genomic DNA was extracted from a pool of 60 sand flies, then about 9 µg were digested with RsaI restriction enzyme, and adaptors were ligated into the digested DNA. Size selection of the adaptor-ligated DNA was done using running DNA in 1.8% low melting agarose gel, followed by excising the 200-1000 bp range from the smear and recovering the DNA fragments. A PCR evaluated the success of the adaptor ligation to the digested DNA. The DNA fragments were hybridized with 3'-biotin-labeled (GT)12 oligonucleotide and captured using streptavidin-coated magnetic beads. The enriched DNA fragments were recovered by differential stringency washes and amplified by PCR. Cleaned PCR products were ligated into pGEM-T vector, then transformed into Escherichia coli JM109 competent cells and plated onto LB/ampicillin/IPTG/X-gal media. White colonies were used to construct the library which was further screened by PCR amplification. The clones giving two amplified bands were sequenced to confirm the presence of the microsatellite. More than 100 transformants were obtained from the blue/white screening and few of them have been screened by PCR. A total of 12 transformants were shown double bands and one transformant was shown an imperfect (TG) 6 microsatellite loci. In conclusion, the isolation procedure used in this study was successful, but the rest of the transformants should be screened to select a few microsatellite loci. In further studies, polymorphisms have to be evaluated by amplifying the microsatellite sequences using different subsets of P.argentipes with designated primers. This study would expand the knowledge related to the microsatellite markers in P.argentipes and might be helpful in population genetics studies.

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SPECIES COMPOSITION, ACARICIDE RESISTANCE IN AMBLYOMMA VARIEGATUM TICK SPECIES: KNOWLEDGE, ATTITUDE, AND PRACTICES OF LIVESTOCK OWNERS IN DIFFERENT ECOLOGICAL ZONES OF GHANA

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Acaricide failure on cattle has been on the rise globally. In Ghana, acaricides are still used to control ticks although some studies have identified acaricide resistance in ticks and reports the inappropriate use of acaricides. The aim of this study was to determine the distribution of tick species infesting livestock, assess the knowledge, attitude, and practices (KAP) of livestock owners and evaluate the resistance status of larval tick populations to some acaricides used in Ghana. This study was a cross-sectional study and tick populations evaluated in this study were collected from different cattle farms in the guinea savannah, transitional zone, deciduous forest and coastal savannah ecological zones from May to September 2022. Larval packet test was used to evaluate resistance status of Rhipicephalus ticks at discriminating dose (DD), half the discriminating dose (0.5DD) and twice the discriminating dose(2xDD) of three classes of acaricides; cypermethrin, amiraz and chlorpyrifos representing the pyrethroid, amidine and organophosphate groups respectively. The WHO criteria was used for determining the acaricide resistance status of the ticks. Statistical analysis was done using Microsoft Excel 2019 and Stata version 13.0. A total of 1022 ticks of three major genera; Amblyomma (519/1022), Hyalomma sp (136/1022) and Rhipicephalus species (367/1022). Out of the total number of ticks collected, Amblyomma variegatum constituted, 51%, followed by Rhipicephalus boophilus and sanguineus, 36%, Hyalomma rufipes and truncatum, 13%. Amblyomma variegatum was the most dominant species with a representation of 51% and also the most abundant in the different ecological zones, except for the Coastal savanna where Rhipicephalus was the most abundant species with a representation of 71% out of all the ticks collected in that zone. The study showed that Amblyomma variegatum were susceptible to cypermethrin, amiraz and chlorpyrifos acaricides and most farmers employed acaricidal control for treatment of their livestock during tick infestations.

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PHLEBOTOMINE SANDFLY SPECIES FROM OLD AND NEW LEISHMANIASIS FOCI OF COLOMBIA

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Leishmaniasis is a neglected tropical disease endemic in rural as well as urban areas of northern Colombia, which affects mainly the poorest communities; where cutaneous and visceral leishmaniasis are the prevalent clinical forms of the disease. Despite of the above, the sandfly fauna is still poorly known in several leishmaniasis foci of the north of Colombia. Even more important is the appearance of new leishmaniasis transmission foci during the last years. The aim of this work was to identify the sandfly species from old and new leishmaniasis foci of the north of Colombia. Phlebotomines were collected in ten localities of the Departments of Córdoba, Bolívar, Sucre, Cesar, and La Guajira, from 18:00 to 06:00 hours, by using CDC light traps installed in intra, peri and extra-domestic environments. Sandflies were morphologically identified up to the level of species using standard taxonomic keys for New World's sandflies. An epidemiological survey, including the characteristics of the dwellings and their surrounding area, was conducted through a mobile application developed for the study. Seventeen sandfly species were taxonomically identified, including Lutzomyia evansi, L. longipalpis, L. nuneztovari, L. shannoni, L. gomezi, L. panamensis, L. dubitans, L. rangeliana, L. punctigeniculata, L. cayennensis cayennensis, L. micropyga, L. atroclavata, L. carpenteri, L. sp. (series townsendi), L. venezuelensis, Helcocyrtomyia sp., and L. trinidadensis. New locality records are provided for the Colombian sandflies, including recognized vectors of Leishmania spp.

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NATION-WIDE VECTOR SURVEILLANCE OF CHAGAS DISEASE IN EL SALVADOR, 2018-2020

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Chagas disease, caused by the infection of Trypanosoma cruzi, is one of the most serious health issues in Latin American countries. In many endemic countries, infected triatomine bugs are considered majorly responsible for the persistent T. cruzi transmission. However, the up-to-date vector burden has not been evaluated thoroughly due to the cessation of active vector surveillance in the Central American region. Our study focused on updating the risk of vector-borne T. cruzi infection in one of the most Chagas-endemic countries in the region. Nation-wide vector surveillance was performed by conducting house-to-house visits in the domestic environment of El Salvador. Houses were inspected by experienced surveyors for the infestation of vector insects. Infection for T. cruzi was evaluated by microscopic examination of insects' feces, followed by a species confirmation using PCR. As a result, we identified 1529 Triatoma dimidiata from all fourteen departments of El Salvador between the years of 2018 and 2020. No other vector species were captured in this study. Microscopic examination revealed 153 specimens out of 1529 (10.0%) positive for T. cruzi infection, which was confirmed by PCR molecular diagnosis. Geographically, higher infection rates for T. cruzi in T. dimidiata were found in departments sporadically placed across the country. These insights suggested the presence of high-risk areas of Chagas disease transmission in the region.

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EVOLUTION OF INSECTICIDE RESISTANCE OF ANOPHELES GAMBIAE SENSU LATO AND AN. FUNESTUS SENSU LATO IN WESTERN KENYA FROM THE YEARS OF 2019-2022

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Insecticide resistance is a major threat to malaria vector control efforts. Understanding insecticide resistance is crucial for developing effective resistance management strategies and informing the selection and deployment of vector control interventions. The aim of this study was to evaluate the evolution of resistance and mechanisms underlying resistance to pyrethroids, organophosphates and neonicotinoids in malaria mosquito populations in western Kenya. Larvae were collected from Busia, Siaya, and Homa Bay counties in 2019, 2020 and 2022. Susceptibility tube tests, synergist PBO bioassays, and intensity CDC bottle assays were carried out on adult Anopheles gambiae s.l. Five insecticides (deltamethrin, permethrin, alpha-cypermethrin, pirimiphos-methyl, clothianidin) were evaluated. The presence of target site mutation conferring knockdown resistance was investigated using a TaqMan assay. The level of resistance was shown to increase over time for deltamethrin across the 3 sites, with average change in mortality at 46%, 56% and 58% in Busia, Homa Bay and Siaya, respectively. Similar trends were also recorded for permethrin across the sites. Pre-exposure to piperonyl butoxide synergist (PBO) for An. gambiae s.l prior to exposure to pyrethroids significantly increased mortalities but did not fully restore susceptibility. Resistance intensity was low in Homa Bay (>98% mortality at 5X), moderate in Siaya (>98% mortality at 10×) and high in Busia (<98% mortality at 10×). Low to moderate allelic frequencies were detected ranging from as low as 2% to as high as 74% across the sites with 1014S having the highest frequencies of 74% and 61% for An. gambiae s.s. and 8% and 50 % for An. arabiensis in 2021 and 2022 respectively for Busia. Susceptibility to pirimiphos-methyl and clothianidin was recorded across all the sites across all years. The spread of insecticide resistance has significant implications for malaria control in western Kenya. To address this challenge the deployment of new tools including ITNs with dual active ingredients or new class of insecticide is encouraged.

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PHENOTYPIC AND MOLECULAR ASSAYS CONFIRM PUTATIVE PYRETHROID RESISTANCE IN ANOPHELES ALBIMANUS IN MALARIA ELIMINATION SETTINGS IN HONDURAS

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Vector control continues to be the principal strategy for malaria elimination worldwide. In Honduras, control relies on pyrethroid insecticide-treated bednets (ITNs) and indoor residual spraying (IRS) with carbamates. Even with adequate vector control coverage, malaria cases have risen from 330 to 1550 cases per year, between 2019 and 2021. Phenotypic insecticide resistance has been detected previously, and given those findings, we carried out an assessment of key insecticide resistance target-site mechanisms in vector populations from the main endemic areas of the country. Wild-caught adult anophelines were collected in eight localities across six malaria-endemic departments in Honduras, during 2021. Using CDC bottle bioassays, susceptibility to diagnostic doses of deltamethrin, permethrin, and bendiocarb were carried out. PCR and sequencing were used to identify mutations at positions 995 in the VGSC gene and 280 in the Ace-1 gene. Our findings revealed that An. albimanus in three sites were resistant to at least one pyrethroid. Individuals from Gracias a Dios, the main endemic region, were susceptible to deltamethrin. All populations were susceptible to bendiocarb. Populations from Yoro, Comayagua and Olancho reported mortalities ranging from 48 to 89% (permethrin) and 62 to 88% (deltamethrin). Two genotypes (TGT and TTC) equivalent to mutation L995F (16%) and L995C (30%) were detected at the VGSC in 4 of 8 localities. Comayagua showed the highest frequency for L995C (65%), and Santa Rita for L995F (77%). No mutations were found at the Ace-1 gene. A substantial number (44/184) of potential heterozygotes (TNN) for kdr were detected. This is the first report detecting two target-site mutations on the VGSC gene associated with PY resistance in malaria vectors from Honduras, with the L995C allele as the most frequent mutation across the populations screened. Further analysis will clarify the frequency of heterozygotes. The nascent pyrethroid resistance reported here should inform the choice of vector control products from alternative insecticide classes, in order to allow for proactive resistance mitigation and management

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THE GENOMICS BEHIND INSECTICIDE RESISTANCE IN ANOPHELES MOSQUITOES FROM THE BIJAGÓS ARCHIPELAGO

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Evolving insecticide resistance threatens the efficacy of vector control interventions. In turn, this threatens the control of all vector-borne diseases, including malaria. The Bijagós Archipelago is situated off the coast of Guinea-Bissau, West Africa, and is endemic for malaria. The major vectors for malaria in the Bijagós are Anopheles gambiae in the rainy season, and An. melas in the dry season. The mainstay of malaria control in the Bijagós is Long Lasting Insecticide treated Nets. The WHO recommend monitoring insecticide resistance to inform evidence-based vector control interventions. This study investigated the status of insecticide resistance in mosquito vectors across the Bijagós archipelago in 2019 and 2022 using both phenotypic assays and molecular monitoring of resistance markers. WHO bottle bioassays were used to assess phenotypic resistance to deltamethrin, and molecular monitoring was used to investigate the frequency of genomic markers of insecticide resistance to a broad range of insecticides. Molecular monitoring was conducted using high-throughput custom-targeted amplicon sequencing. Collected mosquitoes included a high proportion of An. gambiae/coluzzii hybrids (28%). This study revealed phenotypic resistance to discriminating concentrations of deltamethrin in 50% of the mosquitoes assayed. Whole Genome Sequencing was employed to investigate signatures of directional selection associated with deltamethrin resistance, by comparing genomic diversity in resistant and susceptible mosquitoes. Investigation of molecular markers revealed the presence of mutations associated with pyrethroid resistance in the Voltage Gated Sodium Channel (VGSC) gene (kdr mutations) L995F, N1570Y and A1746S. Mutations in the GSTE2 gene associated with resistance to organophosphates and carbamates were also identified, including F120L and L119V, as well as the RDL A296G mutation associated with resistance to dieldrin and fipronil.

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PROFILING OF INSECTICIDE RESISTANCE, MICROBIOME AND PATHOGEN PREVALENCE IN AEDES AEGYPTI IN PUERTO RICO

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Puerto Rico suffers from the circulation of arboviruses, including dengue, Zika and chikungunya, transmitted by the Aedes aegypti mosquito. The predominant control strategies across the island are breeding habitat removal, larviciding and spatial spraying in response to outbreaks. This study aims to characterise the Ae. aegypti population in Puerto Rico in terms of phenotypic and molecular insecticide resistance, microbiome composition and pathogen prevalence, as well as assessing associations between these factors. Ae. aegypti eggs were collected using ovitraps from 2 sites (Bayamón and San Juan) and reared to adults. These adults were subjected to testing against deltamethrin and malathion at three concentrations. A target amplicon sequencing approach was used to identify genetic variants such as single nucleotide polymorphisms SNPs and insertions/deletions associated with insecticide resistance and identify Wolbachia in the microbiome. We found considerable resistance in both sites to one- and five-times diagnostic dose of deltamethrin and one- and three-times diagnostic dose of malathion. Mortality at one diagnostic dose was under 25% for deltamethrin and under 40% for malathion in mosquitoes from both sites. Molecular assays revealed mutations in insecticide resistance relevant genes including; VGSC, RDL, ACE and GSTE2, including a novel mutation not previously described in Ae. aegypti, but that has been associated with resistance in other insects. Neither Wolbachia nor arboviruses were identified in the samples we screened. Understanding insecticide resistance is vitally important to facilitate the best possible control strategies for arboviral disease. Here we show that this Ae. aegypti population has high levels of resistance to the pyrethroid deltamethrin and the organophosphate, malathion. Insecticide resistance data should be used to inform the future selection of compounds used in larvicides and insecticide spraying for vector control.

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EVALUATION OF THE SUSCEPTIBILITY OF ANOPHELES FUNESTUS POPULATIONS IN THE CENTRE, CENTRE-WEST AND SOUTH-WEST REGIONS OF BURKINA FASO

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In recent years, insecticide resistance in the main malaria vectors has intensified in sub-Saharan Africa. This poses a threat to the effectiveness of insecticide-based vector control interventions. In Burkina Faso the main malaria vectors are members of the gambiae complex and the funestus group. Monitoring the susceptibility level of all vectors is necessary to adapt control strategies. The aim of this study was to update on the insecticide susceptibility profile of Anopheles funestus populations. Indoor resting blood-feed female mosquitoes were collected between September and November 2021 in Naaba-Zana in the Centre, La in the Centre-West and Sibera in the South-West, three villages in Burkina Faso. Female members of the An. funestus s.l. group were oviposited to generate F1. Insecticide tests were performed on the F1 progeny to assess the susceptibility profile of this vector to three classes of insecticides (pyrethroids, carbamates and organophosphates) using the WHO cylindrical-tube test guidelines. The specific composition of the funestus group members, the sporozoite infection rate and the presence of the L119F-GSTe2 gene were investigated. An. funestus s.s. was the only species of the funestus group present in all three localities. The sporozoite infection rate was 6.47%. Anopheles funestus s.s. was resistant to deltamethrin in all the three localities with mortality rates being 21.24%, 35.43% and 65.24% respectively in Naaba-Zana, La and Sibera. However, the population at the La site was resistant to bendiocarb but susceptible to pyrimiphos-methyl. The frequency of the L119F-GSTe2 mutation conferring resistance to DDT and pyrethroids was overall 24.30%. These results suggest that resistance to pyrethroids and carbamates in An. funestus in Burkina Faso could pose a threat to the effectiveness of operational insecticide-based vector control tools.

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MONITORING INSECTICIDE RESISTANCE STATUS OF AEDES AEGYPTI AND AE ALBOPICTUS POPULATIONS IN FIVE LOCAL GOVERNMENT AREAS IN LAGOS STATE, NIGERIA

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Aedes aegypti and Ae. albopictus, the principal vectors of dengue, Zika, and chikungunya viruses, have progressively started to develop resistance against most of the currently used insecticides. This increase in resistant populations makes management crucial to the design of effective disease control. Thus, this study was carried out in Lagos State to determine the insecticide susceptibility status of Aedes species. Bioassays were performed on Aedes species, according to their abundance, in five Local Government Areas (LGAs) between July and September 2022. Aedes larvae and pupae were collected from tires, plastic containers, and abandoned water closets. Ae. aegypti were collected from three LGAs (Ibeju Lekki, Yaba, and Alimoso), while Ae. albopictus were found in the other two LGAs (Ikorodu and Somolu). Immature stages were reared to the adult stage at the insectary of the Nigerian Institute of Medical Research (NIMR). Three to five-day-old sugar-fed females were exposed to four classes of insecticides according to the standard WHO protocol: organochlorines (4% DDT); carbamates (4% bendiocarb); pyrethroids (0.75% permethrin & 0.05% deltamethrin); and organophosphates (5% malathion). Results revealed that the collected populations of Ae. aegypti were susceptible to bendiocarb and malathion (100% mortality to both insecticides), but resistant to permethrin (mortality from Ibeju Lekki was 42%, Yaba was 52%, and Alimoso was 50%), deltamethrin (mortality from Ibeju Lekki 57%, Yaba 59%, and Alimoso 52%) and resistant to DDT (mortality from Ibeju Lekki and Yaba was 100% and Alimoso was 39%). For Aedes albopictus, the Somolu population was 100% susceptible to bendiocarb and malathion but resistant to permethrin and deltamethrin. The Ikorodu population showed 100% susceptibility to malathion and resistance to other insecticides (bendiocarb resulted in 87% mortality, permethrin resulted in 62% mortality, and deltamethrin resulted in 76% mortality). The level of detected resistance in these populations prompts the need to use alternative insecticide classes for the control of Aedes populations in this region.

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INSECTICIDE RESISTANCE SPECTRUM AND PREVALENCE OF L1014F KDR TYPE MUTATION IN ANOPHELES GAMBIAE S.L. IN ABIA STATE, NIGERIA

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Anopheles gambiae s.l. is the primary vector of malaria, a debilitating disease responsible for substantial mortality and morbidity in Sub-Saharan Africa. This study was conducted to evaluate the insecticide resistance status and frequency of L1014F kdr mutation in Anopheles gambiae [Diptera: Culicidae, Giles 1902] within Abia state, Nigeria. Immature stages of An. gambiae (s.l.) were collected from Umudike, Agalaba, and Ebem communities and reared to adulthood. Batches of twenty five sugar fed female mosquitoes, aged 3-5 days, were exposed to four types of WHO insecticide impregnated papers i.e., 4% DDT, 0.75% Permethrin, 0.1% bendiocarb, and 5% Malathion, for one hour and the mortalities were recorded after a recovery period of 24 hours. Mosquitoes were also subjected to molecular diagnosis for speciation, and genotyped for kdr type gene mutation L1014F. Anopheles gambiae (s.l.) was highly resistant to permethrin (Umudike-18.76% mortality, Agalaba-17.51%, Ebem-49.01%) and DDT (0%) in the three locations. Conversely, all the locations recorded complete susceptibility to malathion (100%). Although complete susceptibility to bendiocarb was reported from Umudike (100%) and Ebem (100%), some resistance was reported from Agalaba (87.5%). PCR analyses showed that An. gambiae (s.l.) were predominantly An. gambiae s.s. in Umudike (90%), Agalaba (67.5%)- and Ebem (67.5%), whereas the rest were An. coluzzii. Very high frequencies of the L1014F kdr mutation was observed in all locations [Umudike (1.00), Agalaba (0.98), and Ebem (0.95)]. Interestingly, mosquitoes from Agalaba that survived the 24 hours post-exposure were put in a freezer (-12°C) for about eight hours to die, but it was observed that the mosquitoes which appeared dead in the recovery tubes got resuscitated shortly after they were brought out of the freezer. The worrisome resistance to bendiocarb in Agalaba suggests existence of metabolic resistance that needs to be clarified and calls for urgent implementation of integrated vector control strategies, whereas a study on the possibility of hibernation in An. gambiae s.l. mosquito populations during cold season is suggested.

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EPITHELIAL NITRATION RESPONSE TO PLASMODIUM FALCIPARUM IN INSECTICIDE RESISTANT ANOPHELES COLUZZII MOSQUITOES

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Insecticide-based vector control tools are the most valuable resource to fight malaria infections with insecticide treated bed nets (ITNs) accounting for almost 70% of the reductions in malaria cases between the years 2000 – 2015. Recently, progress in reducing malaria cases has stalled according to the World Malaria Report 2022; this corresponds strongly with the spread of insecticide resistance (IR). The threat is confounded by the use of relatively few insecticides in malaria control programs, highlighted by use of pyrethroids on all bed nets currently distributed. The mosquito harbours the longest-lived life stages of the parasite and offers an attractive target for interrupting the transmission cycle. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) have been shown as effective mediators of the anti-plasmodial immune response in the midgut. In particular in the epithelial nitration reaction, a major barrier for parasite invasion, by attacking ookinetes. Unfortunately, in contrast to rodent malaria this response has been shown mostly ineffective for the human pathogenic parasite Plasmodium falciparum. Transcriptomic analysis of insecticide resistant Anopheles coluzzii mosquitoes from Burkina Faso indicated potential higher levels of metabolic activity, as reported previously. Such high levels may lead to increased RNS/ROS and thus differential vectorial capacity for P. falciparum. The potential for perturbance of the redox state offers exciting new avenues for the development of more effective or additional vector control tools, like attractive targeted sugar baits (ATSBs), for improved integrated vector management directly targeting parasite invasion. This study illustrates the relationship between oxidative stress, insecticide resistance and anti-plasmodial immunity. We demonstrate that the epithelial nitration response and ROS state differs between insecticide resistant and insecticide susceptible mosquitoes of the An. gambiae complex, potentially leading to differential vectorial capacity.

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BREEDING WATER EFFECT ON ANOPHELES GAMBIAE SENSU LATO INSECTICIDE SUSCEPTIBILITY DURING LABORATORY COLONIZATION

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The challenge of insecticide resistance in malaria vector populations has led to the need for laboratory testing of new insecticide formulations using Anopheles gambiae s.l. mosquitoes. This study aimed to investigate how the insecticide resistance profile of laboratory-maintained mosquitoes changes after multiple generations of breeding without the selective pressures found in their natural breeding sites, mainly focusing on the effect of the larval water sources. Anopheles gambiae s.l. larvae from a known insecticide-resistant field population were bred in field, tap, or distilled water for 11 generations under standard laboratory conditions. The adult mosquitoes were then exposed to WHO discriminating insecticide dosage of several insecticides, and the detoxification activity of the population was assessed through a synergist assay with piperonyl butoxide (PBO) and pyrethroids. The enzymatic activity of the various colonies and physicochemical parameters of the different water types were also analyzed. The WHO susceptibility results showed high resistance to all insecticides (mortality ≤ 90%). However, mosquitoes bred in field water showed relatively high mortality upon synergist exposure. The An. gambiae colony bred in field water also showed higher enzymatic activity for α esterase, mixed function oxidases (MFO's), and β esterase compared to the other breeding water types (P≤ 0.05), with insensitive acetylcholinesterase (ACHE) activity remaining constant across all breeding water types. Lastly, the field water was found to be polluted based on the physicochemical parameters measured with reference to WHO guidelines. This study recommends the use of field breeding water to replicate and maintain the observed field levels of phenotype, genotype, and metabolic insecticide resistance in laboratory-reared Anopheles gambiae s.l. mosquitoes, as it outperforms and maintains all three resistant mechanisms.

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NATIONWIDE ASSESSMENT OF MALARIA VECTOR SUSCEPTIBILITY TO CHLORFENAPYR, PYRIPROXYFEN, AND ALPHA-CYPERMETHRIN IN PREPARATION FOR WIDESCALE DEPLOYMENT OF NEW GENERATION NETS (INTERCEPTOR® G2 AND ROYAL GUARD®) IN BENIN

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Pyrethroid resistance is widespread in sub-Saharan Africa, including Benin, and threatens the effectiveness of pyrethroid-treated mosquito nets. To manage this generalized resistance to pyrethroids, new-generation insecticide-treated nets (NG-ITNs) with new active ingredients (AIs) have been developed. Before the deployment of NG-ITNs, it is essential to determine the sensitivity of malaria vectors to new AIs. The objective of this evaluation was to assess malaria vector susceptibility to 3 AIs (chlorfenapyr, pyriproxyfen, and alpha-cypermethrin) before the widescale deployment of Interceptor® G2 and Royal Guard® nets nationwide in Benin. The study was conducted in all 34 health zones throughout Benin. In each health zone, a simple random sample of one commune was selected using the sample function in R. Larval collections, rearing to adults, and susceptibility testing was carried out in all communes between August and December 2022 on Anopheles gambiae s.l. Standard WHO tube test was used for alpha-cypermethrin, and WHO bottle bioassay was used from chlorfenapyr and pyriproxyfen. Mosquitoes were resistant to alpha-cypermethrin with mortality rates ranging from 1% to 69%. Mosquitoes exposed to 100 µg chlorfenapyr died after 24 hours except in 3 communes where mortality rates ranged from 80% and 97%; however, mortality did reach 100% after 48 hours. For pyriproxyfen, all mosquito populations exposed to 100 µg pyriproxyfen were infertile with no eggs reaching the Christopher stage V (the majority were blocked at stage III), whereas most eggs of the same mosquito population exposed to acetone (control) reached the Christopher stages with fertility rates up to 68%. This evaluation provides key data on malaria vector susceptibility to the new AIs on NG-ITNs across Benin, suggesting that the deployment of NG-ITNs should be effective in controlling mosquitoes. However, monitoring of these AIs should continue to detect the emergence of resistance. Although chlorfenapyr was lethal and pyriproxyfen inhibited fertility, operational evaluations will help to better understand the relative efficacy of Interceptor® G2 and Royal Guard® nets.

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ANOPHELES GAMBIAE S.L. KNOCKDOWN RESISTANT MUTANT ALLELES AND SUSCEPTIBILITY TO INSECTICIDES IN THREE SENTINEL SITES OF ZIMBABWE

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Indoor residual spraying and long-lasting insecticidal nets are the mainstay malaria prevention measures in Zimbabwe. However, efficacy of the insecticides is affected by vector resistance mechanisms. Aim of this study is to assess the status of insecticide susceptibility to insecticides sprayed in malaria endemic areas. 1,929 mosquito larvae were collected in Mashonaland East province (Mudzi, Mutoko and Wedza district) from March 2020 to August 2022. The larvae were reared under insectary conditions. WHO tube and bottle bioassays were conducted and mortality rate was assessed after 24 hours. Anopheles arabiensis KGB strain was used as susceptible positive control. An. gambiae s.l specimens morphological identification and confirmatory PCR was determined previously. Further analyse to detect kdr and ACE1R alleles were done in previously reported studies. 5.6% were An. arabiensis, 0.73% An. gambiae ss, 0.47 % An. merus and 93% An. quadriannulatus 100% mortality after 24 hrs exposure was recorded in Wedza. Kdr to clothianidin was recorded 75% in Mutoko and 86.6% mortality rate in Mudzi. PCR showed that 1.44% An. quadriannulatus was resistant to deltamethrin, DDT, pirimiphos-methyl and clothianidin in Mutoko and Mudzi. All An. gambiae ss and An. merus were susceptible whereas 2.04% An. arabiensis species were resistant to deltamethrin in Mutoko. L1014S allele was found in Mudzi 0.01% and Mutoko 0.5%, whereas L1014F allele was 0.4% Mudzi and 0.7% Mutoko. ACE1 resistance was present in Mutoko 1.04% and 0.3% in Mudzi. Deltamethrin insecticide was associated with L1014S mutant allele (p=0.01). DDT and pirimiphos-methyl were associated with L1014F mutant allele (P=0.01). ACE1R was associated with clothianidin and deltamethrin in Mutoko and Mudzi (P=0.01). An. gambiae species were susceptible to alpha-cypermethrin, chlorfenapyr and permethrin insecticides, thus using these insecticides in the study sites is recommended. Furthermore, results have identified the need for new approaches for monitoring insecticide resistance studies since larval collections can be dominated by non-vectors.

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IDENTIFICATION AND INSECTICIDE RESISTANCE PROFILE OF ANOPHELES AZEVEDOI (RIBEIRO, 1969) IN LUANDA PROVINCE, ANGOLA: IMPLICATIONS FOR VECTOR CONTROL

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In collaboration with the National Malaria Control Program, the U.S. President's Malaria Initiative VectorLink project re-established entomological activities in Angola in 2019 through routine assessments of species composition and susceptibility to relevant insecticides of the primary malaria vector species (Anopheles gambiae s.l. and An.funestus s.l). In Luanda Province, the most abundant larval-reared specimens collected for insecticide susceptibility tests were initially morphologically identified as a species of the An. funestus s.l. group. A subset of specimens were analyzed at the CDC Entomology Branch, where morphological and molecular analyses determined they were An. azevedoi. This identification was further confirmed by the US National Museum of Natural History (Smithsonian Institution) where voucher specimens from these collections were indexed. Sequences for the ITS2 and CO1 barcoding genes were produced and reported to GenBank for the first time. Retroactive DNA sequence analysis of archived samples detected An. azevedoi among larval collections in the provinces of Namibe and Benguela, which had been incorrectly reported as An. gambiae s.l.Since 2021, An. azevedoi larvae have been collected in two villages in Luanda Province. WHO insecticide susceptibility assays conducted in 2021 found the species to be resistant to deltamethrin and alpha-cypermethrin (mortality of 56% and 68%, respectively), with pre-exposure to PBO fully restoring susceptibility to both insecticides. Populations were fully susceptible to chlorfenapyr. A sub-sample of adult An. azevedoi collected through indoor CDC light traps underwent blood meal analysis and 9 of 26 had fed on humans. No Plasmodium falciparum sporozoites were detected in this set.These findings show that An. azevedoi is a prevalent species in several regions of Angola. It has been historically incorrectly identified, is resistant to pyrethroids, is present inside houses, and feeds upon humans. Continued entomological monitoring, sporozoite assays, and research on this species is recommended to understand its role in malaria transmission in Angola.

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MONITORING PYRETHROID RESISTANCE INTENSITY IN POPULATIONS OF ANOPHELES GAMBIAE S.L. ACROSS FIVE ECOLOGICAL ZONES IN NIGERIA AND THE IMPLICATIONS FOR VECTOR CONTROL DECISIONS

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Due to widespread pyrethroid resistance, entomological surveillance is an integral part of Nigeria's national insecticide resistance management plan and supports sustainable malaria vector control decisions. We examined the programmatic implications of long-term monitoring of pyrethroid resistance intensity in Nigeria. Intensity assay data from mosquitoes exposed to 5X and 10X permethrin, deltamethrin, and alpha-cypermethrin collected in five ecological zones between 2019-2022 were assessed. Monitoring sites with full resistance intensity data for three out of four years (75%) for all three pyrethroids tested were included in the analysis. An. gambiae s.l. mosquitoes from two sites—Akwa Ibom (mangrove/rainforest ecozone) and Plateau (Guinea savannah ecozone)—reported low resistance intensity (mortality>98% at 5X the diagnostic dose) to alpha-cypermethrin. Low resistance intensity to deltamethrin was reported only in Plateau (Guinea Savannah ecozone). Low permethrin resistance intensity was more widespread (4/5 ecozones), and the proportion of sites reporting increased over time: 44% to 100% in Sahel, 50-100% in Guinea Savannah, 66-100% in Mangrove/Rainforest, and 83-100% in Rainforest/Guinea Savannah. Moderate resistance intensity (mortality>98% at 10X) to permethrin was observed in all ecozones and the proportion of sites reporting this increased from Oyo in the Rainforest/Guinea Savannah (0-16%), Plateau in the Guinea Savannah (0-33%), Kebbi in the Sahel savannah (33.5-55.6%), Akwa Ibom and Cross Rivers in the Mangrove (16.7-100%), and Ebonyi in the Rainforest (50-100%). A high resistance intensity (<98% mortality at 10X) to permethrin was observed in An. gambiae s.l. mosquitoes from 3/5 ecozones and increased from the Plateau in Guinea Savannah (0-16%), Ebonyi in the Rainforest (44-100%) and Akwa Ibom in the Mangrove (83.3-100%). Compared to permethrin, resistance intensity to alpha-cypermethrin and deltamethrin was still low and only established in two ecozones. This assessment provides additional information to Nigeria's National Malaria Elimination Program on the need for new types of ITNs in Nigeria.

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HIGH ENTOMOLOGICAL INOCULATION RATE OF ANOPHELES COUSTANI IN THE MALARIA ELIMINATION SETTINGS OF DEMBIYA DISTRICT, NORTH-WESTERN ETHIOPIA

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Despite the progress in scaling up the intervention tools in Ethiopia, malaria is still a major health problem. Therefore, a continuous monitoring of the local vector behavior & ecology is relevant to design evidence based malaria control strategies. This study investigated the species composition & the biting & resting behaviours of Anopheles mosquitoes in selected localities of Dembiya District. Adult Anopheles mosquitoes were sampled indoors & outdoors from June 2018 to May 2019 by using CDC light traps, pyrethrum spray catches, artificial pit shelters, & mouth aspirators. Anopheles mosquitoes were identified to the species level. Their blood source & Plasmodium sporozoite infections were determined using an Enzyme-linked immunosorbent assay. PCR was used for identification of sibling species of An. gambiae s.l. Anopheles mosquitoes belonging to 11 species were identified from 2,055 collected mosquito specimens. Anopheles pharoensis & An. arabiensis were the dominant species in both Guramba Bata & Arebiya study sites. The CDC light traps caught the highest number of Anopheles mosquitoes in both study sites. The density of outdoor host-seeking & resting Anopheles mosquitoes were higher outdoors than indoors ($P \geq 0.05$). The human blood indexes (HBI) of indoor and outdoor host-seeking An. arabiensis were 17.4% & 15.3%, respectively. The entomological inoculation rate (EIR) of outdoor host-seeking An. arabiensis was 4.7 infective bites/person/year. Additionally, the outdoor EIR of host-seeking An. coustani was 25.7ib/p/year. In conclusion, the indoor & outdoor density of host-seeking & resting Anopheles mosquitoes were comparably high in the Dembiya district. This contrast with the fact

that the area is known for the long-term implementation of vector control strategies. Therefore, re-evaluating vector control strategies considering vector & host behaviour is mandatory to eliminate malaria in the study area. Anopheles pharoensis, An. coustani, and An. squamosus were positive for Plasmodium circum-sporozoite protein, which urges further investigations to substantiate their vectoral role.

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NATURAL INFECTION OF NYSSORHYNCHUS DARLINGI AND NY. BENARROCHI B WITH PLASMODIUM DURING THE DRY SEASON IN THE UNDERSTUDIED LOW TRANSMISSION SETTING OF DATEM DEL MARAÑON PROVINCE, AMAZONIAN PERU

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The persistence of malaria hotspots in Datem del Marañon Province, Peru, prompted vector control units at the Ministry of Health, Loreto Department, to collaborate with the Amazon International Centers of Excellence for Malaria Research to identify the main vectors in several riverine villages that had Annual Parasite Incidences (API) >15 in 2018-2019. Anophelinae were collected indoors and outdoors for two 12-hr nights/community during the dry season in 2019 using Human Landing Catch. We identified four species: Nyssorhynchus benarrochi B, N. darlingi, N. triannulatus and Anopheles mattogrossensis. The most abundant, Ny. benarrochi B, accounted for 96% of the total (7550/7844) of which 62% were captured outdoors (4826/7844). Nine mosquitoes, 4 Ny. benarrochi B and 5 Ny. darlingi, were infected by Plasmodium falciparum, P. vivax or both. Human Biting Rates ranged from 0.5-592.8 bites per person per hour for Ny. benarrochi B and 0.5-32.0 for Ny. darlingi, with EIR values as high as 0.75 infective bites per night for Ny. benarrochi B and 0.50 for Ny. darlingi. These data demonstrate the risk of malaria transmission by both species even during the dry season in villages in multiple watersheds in Datem del Marañon province.

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HOUSES IMPROVING AS A SUPPLEMENTAL INTERVENTION TOOLS FOR REDUCING INDOOR VECTOR DENSITIES AND MALARIA PREVALENCE IN EMANA, CENTER CAMEROON

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Improvement of typical rural houses can effectively reduce indoor vector densities and consequently malaria transmission. We assessed this supplemental control effects in a MILDA low coverage area of center Cameroon. 16 houses were firstly selected based on their indoor density of resting malaria vectors. Half of them randomly chosen for eaves screens (experimental) with fibreglass coated wire mesh and half left unscreened (control). Entomological baseline were collected monthly in both groups. Outdoors and indoors adults mosquitoes were sampling for entomological data collection in each houses using Human Landing Catch (HLC). Malaria prevalence surveys were conducted after mosquitoes sampling in both groups. A total of 300 mosquitoes were collected over six months period using HLC in 16 houses (mean mosquitoes =18.75). Among Anopheles funestus, 63.9% were unfed, 32.9% blood fed, 0.39% gravid and 1.56% half gravid females. 17.7% of An. gambiae were unfed and 82.2% blood fed. More indoor adult mosquitoes were collected in the control (n=74) than experimental houses (n=56). Parasitological surveys results to relatively low malaria parasite prevalence rates in screened houses compared to the control houses. Overall, malaria prevalence was 57.8% (95% CI: 0.32-0.74) n=90, with baseline prevalence rate of 58.5% (95% CI: 0.67-1.13), n=65 and 2nd follow-up survey prevalence of 42.0% (95% CI: 0.52-0.76) n=66. At all the two parasitological follow-up survey points, house screening significantly reduced the malaria prevalence by 43% (p< 0.001). Housing improvement has potential to reduce indoor vector densities and malaria prevalence.

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SPATIO-TEMPORAL DISTRIBUTION OF AEDES SPECIES (DIPTERA: CULICIDAE) IN FOUR LOCAL GOVERNMENT AREAS IN LAGOS STATE, NIGERIA

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The frequency and magnitude of arbovirus outbreaks that are transmitted by Aedes mosquitoes are increasing globally, driven by ecologic, economic, and social factors. Therefore, it is imperative that more detailed monitoring be conducted to enhance the distribution and abundance predictions of the Aedes species to update the risk assessment of arbovirus transmission and improve the planning capabilities of public health decision-makers. Here we aimed at developing a Geographic Information System-based overlay on the spatio-temporal distribution of Aedes species collected from four local government areas (LGAs) in Lagos State (urban; Yaba and Somolu, and rural; Ikorodu and Badagry). Adult trapping was conducted for three consecutive nights on a monthly basis from October 2021 through August 2022, using BioGents lure baited traps. A total of 2,204 mosquitoes were collected and identified revealing 2,148 Aedes mosquitoes belonging to two species: Aedes albopictus (94.7% of specimens) and Aedes aegypti (5.3% of specimens). Results indicated dominant occurrence of Aedes albopictus in the four LGAs in comparison to Aedes aegypti. The highest number of Aedes albopictus was collected from Somolu (accounting for 80.5% of collection records), followed by Badagry (8.1%), Ikorodu (6.2%) and Yaba (5.2%). Of the 114 collected Aedes aegypti, 72% were collected from Somolu compared to other LGAs (22.8% Ikorodu, 5.2% Yaba and 0% Badagry). Both Aedes species were most prevalent during the rainy seasons (accounting for 67% of total) compared to the dry seasons.

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RESIDUAL OF ANOPHELES ARABIENSIS AND A. MELAS IN CENTRAL SENEGAL

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Understanding the behavior and ecology of local malaria vectors is essential for the effectiveness of the commonly used vector-targeted malaria control tools in areas of low malaria transmission. This study was conducted to

determine species composition, biting behavior and infectivity of the major Anopheles vectors of Plasmodium falciparum in low transmission settings in central Senegal. Adult mosquitoes were collected using human landing catches during 2 consecutive nights and Pyrethrum Spray Catches in 30–40 randomly selected rooms, from July 2017 to December 2018 in 3 villages. Anopheline mosquitoes were morphologically identified using conventional keys; their reproductive status assessed by ovary dissections, and a sub-sample of An. gambiae s.l. were identified to species level using polymerase chain reaction (PCR). Plasmodium sporozoite infections were detected using real-time quantitative PCR. During this study 3684 An. were collected of which 97% were An. gambiae s.l., 0.6% were Anopheles funestus, and 2.4% were An. pharoensis. Molecular identification of 1,877 An. gambiae s.l. revealed a predominance of An. arabiensis (68.7%), followed by An. melas (28.8%), and An. coluzzii (2.1%). The overall human-biting rate of An. gambiae s.l. was highest in the inland site of Keur Martin with 4.92 bites per person per night, while it was similar in the deltaic site, Diofior (0.51) and the coastal site, Mbine Coly (0.67). Parity rates were similar in An. arabiensis (45%) and An. melas (42%). Sporozoite infections were detected in both An. arabiensis and An. melas with the respective infection rates of 1.39% (N = 8) and 0.41% (N = 1). Results suggest that low residual malaria in central Senegal is transmitted by An. arabiensis and An. melas. Consequently, both vectors will need to be targeted as part of malaria elimination efforts in this area of Senegal.

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TOWARDS ENVIRONMENTAL SURVEILLANCE OF THE INVASIVE VECTOR SPECIES ANOPHELES STEPHENSI IN SUB-SAHARAN AFRICA

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Anopheles stephensi is a highly competent malaria vector whose historical distribution encompassed the Indian subcontinent, parts of South-East Asia and the Arabian Peninsula. Recently it has become an invasive vector species in the Horn of Africa, where it was first reported in Djibouti in 2012 and since then has spread to Ethiopia, the Republic of Sudan, Somalia, Yemen and most recently Nigeria and Kenya. Unlike An. arabiensis, the main regional malaria vector species, An. stephensi breeds in man-made water containers, buckets, discarded tyres, and water storage tanks for domestic use and construction. These are sites that may not be under routine surveillance by the National Malaria Control Program; such larval habitats are often used by arbovirus-transmitting Aedes species. To inform prospective control strategies, novel surveillance methods for tracking An. stephensi dispersal dynamics and insecticide resistance mechanisms are urgently required, which are both agnostic to mosquito larval morphology and simple to implement at the sampling stage. Using new multiplex TaqMan assays, specifically targeting An. stephensi and Ae. aegypti, we validated the use of environmental DNA (eDNA) for simultaneous vector detection in shared artificial breeding sites. Study findings demonstrated that An. stephensi and Ae. aegypti eDNA deposited by as few as one second instar larva in 1L of water was detectable. Characterization of molecular insecticide resistance mechanisms, using amplicon-sequencing panels (targeting genetic fragments of the voltage-gated sodium channel, acetylcholinesterase and glutathione-s-transferase epsilon 2) for both vector species, was possible from eDNA shed by as few as 16-32 s instar larvae in 50ml of water. An. stephensi eDNA, derived from emergent pupae for 24h, was remarkably stable, and still detectable 2 weeks later. eDNA surveillance has the potential to be implemented in local endemic communities and at points of country entry, to monitor the spread of invasive vector species. Ongoing community studies are validating the feasibility of this technique under field conditions.

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DIFFERENTIAL RISK OF EXPOSURE TO ANOPHELES GAMBIAE S.L. AND AN. FUNESTUS S.L. BITING ESTIMATED FROM HUMAN BEHAVIOR OBSERVATION ADJUSTED ANALYSIS IN MALAWI

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Human behavior plays a vital role in determining the effectiveness of malaria vector control interventions. Human behavior observations (HBO) help in the identification of human-vector exposure points and periods, thereby determining gaps in protection. This information can be used to target malaria vectors with supplementary control interventions. In Malawi, Anopheles funestus s.l. and An. gambiae s.l. are the main malaria vectors and indoor residual spraying and insecticide treated nets (ITNs) are the main vector control interventions. To assess the intersection between mosquito bites and human behavior, we collected HBO data, alongside human landing catches (5pm to 11am) from July 2021 to June 2022 in six high malaria risk districts of Nkhata Bay, Nkhotakota, Mangochi, Balaka, Kasungu and Salima. During each quarterly visit, a supervisor recorded the time household members went inside their houses, went to sleep, woke up, exited the house and net usage. Weighted estimates of mosquito biting rates according to human behavior were generated. Overall, by 10 pm, 95.0% of people were inside their houses and 60.0% sleeping under net. Eighty-six percent of An. funestus s.l. and 62.0% of An. gambiae s.l. bites occurred when people were indoors and asleep. The HBO adjusted proportion of bites prevented by sleeping under net was higher for An. funestus s.l. (56.2%) than An. gambiae s.l. (40.5%). The proportion of bites occurring outdoors for unprotected individuals was higher for An. gambiae s.l. (35.1%) than An. funestus s.l. (10.7%). The proportion of outdoor bites early in the night (5-11pm) was higher for An. gambiae s.l. (69.8%) than An. funestus s.l. (54.3%). The proportion of indoor biting occurring between 11pm and 6am was similar for both An. gambiae s.l. and An. funestus s.l. (87.0%). However, overall indoor bites from An. funestus s.l. were more than three times higher that of An. gambiae s.l. (25.2 vs 7.3 bites/person/ night). ITNs are appropriate intervention since most of the human-vector contact occur indoors while people are asleep. An increase in ITN usage above the current 60% would substantially reduce transmission in these districts.

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ENTOMOLOGICAL AND MOLECULAR SURVEILLANCE OF MALARIA VECTORS IN A RURAL COMMUNITY IN BENGUELA, ANGOLA: IMPLICATIONS FOR LONG-LASTING INSECTICIDE TREATED NET (LLIN) DISTRIBUTION AND VECTOR CONTROL STRATEGIES

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The use of Long-Lasting Insecticide Treated Net (LLIN) remains the primary method for malaria vector control in Angola. In preparation for a mass distribution of LLINs, a malaria entomological survey was conducted in the Benguela province to determine the abundance and behaviors of key malaria vectors in the area. The study focused on Alto Catumbela, a rural community with a history of malaria transmission. Female mosquitoes

were sampled using indoor CDC light traps from February to July 2022. Morphological and molecular identification techniques were used to identify the species and Plasmodium falciparum (Pf) infection status of collected Anopheles mosquitoes. The presence of knockdown resistance mutations (kdr) in An. gambiae complex was also investigated.Of the 715 female An. sp. mosquitoes collected indoors, 60.3% were identified as An. funestus sl, 11.7% as An. gambiae sl, and 28% as other Anopheles species. Molecular identification revealed that An. gambiae sl comprised of 59.5% An. gambiae ss and 31% An. arabiensis. An. funestus group consisted of 83.3% An. funestus ss and 0.5% An. vaneedeni. The overall Pf infection rate was 5.3% in An. funestus ss and 2.3% in An. gambiae ss. The Human Blood Index for An. funestus ss and An. gambiae ss was 100%. Notably, the 1014S (kdr-east), an allele associated with pyrethroid insecticide resistance, was identified for the first time in An. gambiae ss but only in heterozygotes. An. gambiae ss also exhibited a high frequency of the 1014F (kdr-west) kdr mutation. An. arabiensis were found to be wild type.The study highlights An. funestus as the primary malaria vector in the Alto Catumbela during the collection period. The low number of An. gambiae sl captured indoors may indicate a possible behavioral adaptation to previous indoor vector control methods. The presence of kdr mutations in An. gambiae ss is concerning and warrants attention regarding potential pyrethroid insecticide resistance. Overall, this study provides valuable information on the abundance, species composition, and infection status of malaria vectors in the Benguela province, which can inform effective malaria control strategies in the region.

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COMPOSITION AND SEASONALITY OF ANOPHELES GAMBIAE S.L. AND AN. FUNESTUS S.L. IN LIBERIA

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Vector monitoring is critical in understanding the potential dynamics of malaria transmission and making informed decisions in the selection of control interventions and evaluating their impact. To better understand malaria vector composition and seasonality in Liberia, we collected mosquitoes monthly from eight sites in seven counties from September 2021 to October 2022. Three adult mosquito collection methods were used: pyrethrum spray catch (PSC), human landing catch (HLC) and CDC light traps (CDC-LTs). A total of 7748 Anopheles gambiae s.l. (76%), 2417 An. funestus s.l. (24%) and 21 other Anopheles species (0.2%) were collected. More than 98% of mosquitoes collected were An. gambiae s.l. at Jackson Farm, Madina, Saint John and Gbedin Camp3. The population started to increase in March and reached peak from May to July, coinciding with the beginning of the rainy season. After July, the vector population start to decrease gradually. Anopheles funestus s.l. was dominant in Zeansue (89%), where the population started to increase in January and peaked in March-May, which is during the dry season. During the collection period, the average number of An. gambiae s.l collected by method were: 0.87/house/day by PSC, 1.6/trap/night by CDC-LT and 5.8 bites/person/night by HLC; with a similar pattern observed for An. funestus s.l. Of the three collection methods, HLC was the most efficient in mosquito trapping. Twenty one percent (2138/10165) of the combined An. gambiae s.l. and An. funestus s.l. were collected from Zeansue, 19% (1882/10165) were from Saint John and the lowest was from Fissebu, 2% (250/10165). Malaria vector density and composition varied by site with a combined high peak over five months per year. Sites with higher density of malaria vectors, An. gambiae s.l. and An. funestus s.l., could indicate a higher risk of exposure for malaria transmission. Further molecular analysis for of An. gambiae complex and the An. funestus group will help to identify the species composition, parasite infection rate and host blood meal analysis to better understand trends in malaria transmission risk by space and time.

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THE IMPACT OF FOUR YEARS OF INDOOR RESIDUAL SPRAYING WITH PIRIMIPHOS METHYL AND CLOTHIANIDIN ON ENTOMOLOGICAL DRIVERS OF MALARIA TRANSMISSION IN BURKINA FASO, WEST AFRICA

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Since 2018, indoor residual spraying (IRS) has been performed by the National Malaria Control Program in the high-burden districts of Kampti and Solenzo using SumiShield® 50 WG (clothianidin: neonicotinoid), Actellic® 300CS (pirimiphos-methyl: organophosphate) and Fludora Fusion® WP-SB (clothianidin + deltamethrin: pyrethroid) in Burkina Faso. Routine entomological surveillance was conducted to measure the impact of IRS on entomological drivers of malaria transmission. Anopheles gambiae s.l. were sampled monthly from June to December by human landing and pyrethrum spray catches in two sprayed and two unsprayed sentinel sites to measure entomological inoculation rates (EIRs). The residual activity of insecticides was also assessed using the WHO cone test. After the first round of IRS in 2018, there was a significant decrease in malaria transmission in all sprayed districts compared with unsprayed districts as shown by reduced EIR (RR=19.75, CI95%= [8.71-33.45], P<0.001). From 2019 to 2021, the EIR was significantly lower in Kampti compared to Gaoua (unsprayed district) (RR=13.12, CI95%= [4.35.71-21.18] P<0.001). In Solenzo, the EIR varied from one year to the next, but the reduction was not significant. SumiShield® 50 WG and Fludora Fusion® WP-SB lasted more than 7 months covering the malaria transmission period, compared to Actellic® 300CS, which lasted 5 months. These findings highlight varying entomological impact of the IRS at the two sites, in an effort to reduce malaria transmission.

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CIRCUMSPOROZOITE POSITIVE ANOPHELES LONGIPALPIS C MOSQUITO IDENTIFIED IN ZIMBABWE

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Surveillance of malaria vectors in Zimbabwe has historically focused on the two major vectors Anopheles gambiae s.l and An. funestus s.l., both morphologically indistinguishable species groups that require molecular tools for species identification. During routine malaria vector surveillance in rainy and fertile Burma Valley, 174 samples that were identified morphologically as An. funestus s.l., but failed to amplify when processed using the standardized An. funestus s.l. species ID multiplex PCR assay, were sequenced for follow-up and 35 were identified as Anopheles longipalpis C. The finding prompted the Africa University laboratory to investigate the distribution and behavior of An. longipalpis C in Zimbabwe.

Of 1841 An. funestus samples, 529 that had previously amplified the double band pattern matching An. longipalpis C in the An. funestus PCR assay were revisited and analyzed for distribution, biting behaviour, and sporozoite parasite detection. The findings indicate that An. longipalpis C was first collected in 2016 in Burma Valley and through 2022 in Beitbridge, Chakohwa, Burma Valley, Zindi, Acturus, Vumba, Mubairakuenda, Kawere, Makarara, Dendera, and Chiyadzwa. Of 180 blood fed samples, 74.4% were cattle-fed, 11.6% exhibited multiple host meals with a combination of human and animal blood, and 13.8% fed on other animals. Circumsporozoite ELISA testing found one Makarara sample from 2021 to be positive for Plasmodium falciparum (0.5% infectivity). Data in this study revealed An. longipalpis C to be widely distributed in Zimbabwe and supports that An. longipalpis C is still predominantly zoophagic, preferring cattle blood. However, the number of samples positive for combined animal and human blood and the single positive sample suggest An. longipalpis C, its distribution, and behaviour should be closely monitored by national malaria programs. This study highlights the importance of investigating PCR species identification results that don't amplify, to characterize Anopheles species composition and detect previously unidentified Anopheles species and their potential contributions to the spread of malaria.

5200

RESURGENCE OF MALARIA IN UGANDA COINCIDES WITH AN INCREASE IN ABUNDANCE OF ANOPHELES FUNESTUS WITH EVIDENCE OF VARIATION IN SUSCEPTIBILITY TO CLOTHIANIDIN

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Historically, Anopheles gambiae mosquitoes are responsible for the majority of malaria transmissions in Uganda where vector control is reliant upon indoor residual spraying (IRS) or long-lasting insecticidal nets (LLINs). After 5 years of using Bendiocarb followed by Actellic® for IRS, in 2020 Uganda switched to clothianidin-based formulations (Fludora® and Sumishiled®). Following this switch, there has been an apparent resurgence in malaria cases, prompting an investigation. From 2022-23, a 12-month longitudinal survey was conducted in Tororo, one of the IRS districts, utilizing 60 households enrolled in a prospective cohort study. Vector abundance was estimated using CDC-light traps, and assessment of the effectiveness of the IRS used wall cone bioassays and HPLC analysis of samples from sprayed surfaces. Resistance phenotyping was also performed using CDC bottle assays. The data showed a significant change in the abundance and composition of malaria vectors with An. funestus proportion increasing from 10.4% (8.9 - 12.1; 95% CI) of total collections before IRS with clothianidin to 65.2% (61.8 - 68.5; 95% CI) afterwards. Wall cone assays showed that the average mortality in An. gambiae mosquitoes was high (90% - 98%) up to 12 months post spraying. When tests were performed in the same houses, An. funestus had a significantly lower knockdown (7.3%) (F=12.49, df=20, P=0.00083) and 48h mortality (76.1%) (F=3.34, df=20, P=0.0048) compared to An. gambiae (knockdown = 50.9%, 48h mortality = 98.2%). In CDC bottle assays, mortality of wild-caught An. gambiae was 100% at 48h post exposure. HPLC analysis revealed that there was a marked variation in the amount of insecticide on walls ranging from <5 mg/m2 to >200 mg/m2. All houses in all rounds of sampling had less than the recommended dosage of 0.5g/m2 . Overall, these investigations suggest that the malaria resurgence may be driven by An. funestus that is more tolerant to clothianidin-based formulations than An. gambiae. Further investigations including full resistance characterization and examination of behavioural response to clothianidin treated surfaces is currently ongoing.

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IMPACT OF ENVIRONMENTAL MODIFICATION ON THE DYNAMICS, BEHAVIOR, TRANSMISSION RISK AND INSECTICIDE RESISTANCE OF MALARIA VECTORS: THE CASE OF ARJO-DIDESSA SUGARCANE IRRIGATION SCHEME, SOUTHWESTERN ETHIOPIA

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Ethiopia is expanding extensive irrigation developments to meet food demands and alleviate poverty in the country. However, the effect of such water development projects on malaria transmission risk is not well investigated. Moreover, agrochemicals used in irrigation activities are blamed to drive resistance selection in malaria vectors. Studies evaluating the impact of these agrochemicals on malaria vector's resistance are lacking. This study investigated impact of sugarcane irrigation on vector dynamics, behavior, transmission risk and insecticide resistance of malaria vectors in Southwestern Ethiopia. Adult Anopheles mosquitoes were collected using CDC light traps and human landing catches from irrigated and non-irrigated clusters of Arjo-Didessa sugarcane irrigation scheme in wet and dry seasons, between 2018 to 2021. Mosquito species composition, abundance, seasonality, behavior (biting & blood feeding) and Plasmodium infection rates were compared. Mosquitoes were identified to species morphologically and using molecular techniques. Mosquito host blood meal sources were determined by polymerase chain reaction (PCR). Plasmodium sporozoite infections were analyzed using CSP ELISA. Adult Anopheles gambiae s.l. were tested for their susceptibility to insecticides using WHO tube test. Among 6,058 female Anopheles mosquitoes collected, 72.3% (n= 4379) were from irrigated and 27.7% (n= 1679) from non-irrigated clusters. Mosquito composition, abundance and density was significantly higher in the irrigated than non-irrigated clusters during the wet and dry seasons. Anophelines in the irrigated clusters were more anthropophagic and showed overnight as well as outdoor biting activity. A 2-fold higher Plasmodium infection rates were recorded in the irrigated than non-irrigated areas. Anopheles gambiae s.l. was resistant to deltamethrin and alphacypermethrin insecticides. Thus, malaria vector interventions should be strengthened in Arjo-Didessa sugarcane irrigation scheme to reduce malaria transmission risk during wet and dry seasons. Integrated resistance management strategies should also be implemented.

5202

DISTRIBUTION OF ANOPHELES MOSQUITOES AND THEIR ROLE IN MALARIA TRANSMISSION IN SOUTHWESTERN ETHIOPIA

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The species distribution of malaria mosquitoes and their role in disease transmission varies from place to place. Hence, updating the species distribution and identifying their role is essential to design appropriate interventions. This study aimed to assess the Anopheles mosquito species and their infection rate in Southwest Ethiopia. A cross-sectional multistage sampling technique of adult malaria mosquitoes was done from June 2018 to July 2019. With a purposeful selection process, four malaria-endemic zones in the region, two malaria-endemic districts in each zone, and two malarious villages in each district were chosen. Ten per cent of households in each village were visited once to collect adult mosquitoes using Center

for Disease Control and Prevention (CDC) light traps. The head and thorax of adult Anopheles mosquitoes were evaluated for circum-sporozoite proteins (CSPs). At the same time, legs and wings were used to identify sibling species using a polymerase chain reaction (PCR). A total of 1445 Anopheles mosquitoes were examined, comprising eight species, An. arabiensis (84.9%), An. parensis (9.1%), An. pharoensis (4.8%), An. pretoriensis (0.6%), An. demeilloni (0.2%), An. kingi (0.1%), An. sergentii (0.1%), and An. tenebrosus (0.1%). Of 813 An. gambiae complex evaluated by PCR, 97% (785/813) were An. arabiensis and 3% (28/1445) were not amplified. There were 133 An. funestus complex tested for speciation, 88% (117/133) were positive for An. parensis, and 11% (15/133), were not amplified. A single specimen (1%) amplified for An. funestus complex primers was not among the complex species and was later confirmed as An. sergentii by DNA sequencing. Among the 1399 Anopheles tested for CSPs by ELISA, Plasmodium falciparum CSP rate was 0.4% (95% CI: 0.1-0.8), and it was 0.1% (95% CI: 0.002-0.4) for P. vivax. An. arabiensis and An. pharoensis were widely distributed species in the region, but only An. arabiensis was found to be positive for CSPs. Anopheles arabiensis is the primary vector of malaria in the region.

5203

UPDATED ASSESSMENT OF ANOPHELES STEPHENSI PRESENCE IN SOUTHERN YEMEN

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The invasive malaria vector Anopheles stephensi has currently been the focus of attention in the horn of Africa and adjacent countries, since its 2013 introduction to East Africa. Although malaria is endemic in Yemen, the introduction of this vector to the country may drive urban malaria transmission, adding to the current malaria burden, traditionally transmitted by the native vector An. arabiensis in rural areas. Vector surveillance was conducted in nine Governorates covering all southern areas, including Socotra Island, with sites specifically selected from Aden, Lahij and Hadramout based on malaria cases and human populations' records. Larval collection and spray catch methods were conducted to collect mosquitoes An. stephensi larvae were found either alone or coexisting with other species in artificial and natural containers in urban settings. Geospatial and prediction maps were generated to show vector distribution. Species composition, diversity, spatio-temporal distribution, and population dynamic of both An. stephensi and An. arabiensis were observed. The current invasive vector's population dynamic, establishment, the associated sociocultural factors, and the optimization of control measures will be discussed.

5204

CHANGES IN THE BITING BEHAVIOR OF ANOPHELES GAMBIAE S.L. FOLLOWING THE COMBINATION OF MASS-DISTRIBUTION CAMPAIGNS OF INSECTICIDE-TREATED NETS AND INDOOR RESIDUAL SPRAYING OVER FIVE YEARS IN KIREMBA, NORTHERN BURUNDI

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In Burundi, malaria remains a major public health problem, and was responsible for 46% of outpatient consultations and 59 % of hospital deaths in 2021. Anopheles gambiae s.l. is the major malaria vector, and insecticide treated nets (ITNs) and indoor residual spraying (IRS) are the core vector control interventions in the country. Unlike the other entomological monitoring sites in the country, Kiremba health district in northern Burundi received both ITNs, distributed during the 2017 and 2019 mass- campaigns, and yearly IRS implemented from 2017 to 2021. Pyrethroid-treated nets were distributed in 2017 and 2019 whereas, for IRS a carbamate insecticide (bendiocarb) was sprayed in 2017 and 2019 followed by Fludora Fusion (a mixture of neonicotinoid and pyrethroid insecticides) up to 2021. As part of the regular monitoring on the impact of interventions, monthly entomological surveys were conducted using human landing catches to assess malaria vectors feeding behavior. Mosquitoes were collected both indoors and outdoors with four collectors for two consecutive nights in four selected houses. The indoor and outdoor human biting rates (HBRs) of the An. gambiae s.l. compared using the Kruskal-Wallis test. The mean HBR (bites/person/night) of An. gambiae s.l. was similar indoors and outdoors in 2017 (p= 0.27); in 2018 (p=0.46), and in 2019 (p=0.16). Contrary to the previous years, the biting activity was higher outdoors than indoor in 2020 (p= 0.04) and 2021 (p= 0.001). The results indicated the shift in biting behaviors of An. gambiae s.l., from equally feeding indoor and outdoor to predominantly outdoor feeding in Kiremba might be associated with continuous indoor based vector control interventions in the area.

5205

SURVEILLANCE OF AEDES-BORNE ARBOVIRUSES IN SELECTED SITES IN THE SAVANNA REGION OF GHANA

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Aedes-borne arboviruses such as yellow fever (YFV), dengue (DENV), chikungunya (CHIKV), and zika (ZIKV) have increasingly become a critical public health concern worldwide. Many countries all over the world including Africa have experienced emergence and re-emergence of these arboviruses in the past and in recent times. In October 2021, Ghana experienced yellow fever outbreak in the Savanna region. Recent studies showed antibodies to Dengue virus serotype-2 among febrile illness patients in some areas of the Greater Accra region although the virus has not been detected in vectors. Therefore, this study assessed the prevalence of Aedes mosquitoes in Sawla, Larabanga and the Mole National Park, as well as the arboviruses (YFV, DENV, CHIKV, and ZIKV) they may be harboring, as a follow up to the yellow fever outbreaks in these areas. A cross-sectional study was conducted in three study sites (Sawla, Larabanga and Mole National Park). Adult Aedes mosquitoes were collected using the Biogent sentinel traps and immature stages (eggs, larvae, and pupae) were sampled using ovitraps and dippers. The immature stages were raised to adults for identification using morphological keys/features and viral analyses using RT-PCR. Data analysis was performed using two-way ANOVA in excel. A significantly higher number of eggs were collected in Sawla as compared to Larabanga and the Mole National Park ($P < 0.05$). The positive ovitrap index (POI) was high (>10) in all three sites; Sawla: POI = 50%; Larabanga: POI = 50%; Mole National Park: POI = 60%. All the Aedes mosquitoes identified from the three sites were Ae. aegypti, specifically of the subspecies Ae. aegypti formosus. No arbovirus (YFV, DENV, CHIKV, and ZIKV) was detected from the mosquitoes collected after analysis by RT-PCR. The study found that there is a high-risk of Aedes-borne arboviruses in the study areas and regular surveillance is needed to prevent and contain outbreaks.

5206

PILOTING THE USE OF TRANSFLUTHRIN-TREATED EAVE RIBBONS AS A SUPPORTING VECTOR CONTROL TOOL IN A HIGH TRANSMISSION SETTING IN ZAMBIA

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Nchelenge District, Zambia still experiences holoendemic malaria transmission despite over ten years of annual indoor residual spray (IRS)

and intermittent insecticide treated net (ITN) distribution. High levels of resistance to pyrethroids have been demonstrated among the most prominent vector, Anopheles funestus, which may contribute to the lack of effect of these indoor interventions. We examined the insecticidal activity, protective effect, longevity, and acceptance of transfluthrin-treated eave ribbons in Nchelenge District, Zambia. Two household clusters were identified, and transfluthrin-treated eave ribbons were distributed to every household in cluster 1, while cluster 2 received no additional intervention beyond their existing ITNs and annual IRS. Anophelines were collected monthly from 40 households using indoor and outdoor CDC light traps and Prokopak aspirations indoors. Anophelines were morphologically identified and tested for the presence of Plasmodium falciparum sporozoites. Household-level surveys identified key human behaviors that may play a role in the success or failure of the intervention, including evening outdoor activities, outdoor sleeping, and overall acceptance of the spatial repellant. We hypothesize that these ribbons will reduce overall indoor and peri-domestic abundance in treated households, leading to reduced contact with humans and reduced pathogen transmission.

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TREATED EAVE SCREENS IN COMBINATION WITH SCREENED DOORS AND WINDOWS, ARE MORE EFFECTIVE THAN UNTREATED EAVE SCREENS IN A SIMILAR COMBINATION IN REDUCING INDOOR AND OUTDOOR ANOPHELES POPULATIONS UNDER SEMI-FILED CONDITIONS IN WESTERN KENYA

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Human dwellings remain the main point of human-mosquito interaction leading to malaria transmission despite sustained use of insecticide-treated nets (ITNs) and indoor residual spraying (IRS). Simple structural modifications have great potential to prevent mosquito entry into houses and reduce malaria transmission. The study utilized four huts, each constructed inside a separate semi-field structure (SFS) for the experimental release of mosquitoes. Two huts had screened eaves, doors, and air cavities in place of windows while the other two were unscreened. In experiment 1, the eave screened was untreated while in Experiment 2, the eave screen was treated with Actellic® insecticide. The modification cost was less than 250usd/structure. First filial (F1) generation of Anopheles funestus from Siaya, F0 reared from An. arabiensis larvae collected from Ahero and An. arabiensis Dongola strain from the insectary were raised to 3-day-old adults and used in experiments. Two hundred, 3-day old adults of each species were released in each semi-field structure at dusk and recaptured the following morning, counted and recorded by the collection location of each hut. A single volunteer slept in each hut under an untreated bed net each night. Significantly fewer An. arabiensis from Ahero RR=0.10; (95%CI: 0.02-0.63), An. arabiensis Dongola strain RR=0.11; (95%CI: 0.06 - 0.19) and An. funestus from Siaya RR=0.10; (95%CI: 0.06-0.17) were observed inside modified huts compared to unmodified ones. Treating of eave screen material significantly reduced the numbers An. arabiensis from Ahero RR=0.05; (95%CI: 0.00-0.77) and An. arabiensis Dongola strain RR=0.34; (95%CI: 0.18-0.64) indoors of huts with treated eave screen compared to huts with untreated eave screens, while eliminating the An. funestus indoors. Modification of eaves, doors and windows are cheap and effective ways of reducing mosquito entry into houses. Treatment of eave screen material with an effective insecticide further reduced the Anopheles population in and around the screened huts under semi-field conditions and could greatly complement existing vector control efforts.

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IMPACT OF LIVESTOCK MANAGEMENT ON MALARIA TRANSMISSION RISKS IN RURAL TANZANIA

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Livestock keeping is one of potential factors associated with malaria transmission. To date, the impact of livestock keeping on malaria transmission is contradicting with some studies reporting a zooprophylaxis effect while others reporting zoopotentiation effect. This study aimed to assess the impact of livestock management on malaria transmission risks in a malaria endemic region in south-eastern Tanzania. A longitudinal study was done in Minepa village. Forty randomly selected houses were sampled, 20 had livestock and others had no livestock. Daily mosquito collection was done in 8 houses each day, to ensure each house was visited once per week from January to March 2023. Indoor collections used CDC-Light traps and prokopack aspirators. Outdoor collections used human-baited double net traps and resting buckets. Poisson GLMM was used to assess the influence of livestock on mosquito density. A total of 18,620 female Anopheles mosquitoes were collected. Out of these, 98% were An. gambiae s.l. while others were An. funestus, An. pharoensis, An. coustani and An. squamosus. The presence of at least one cow (RR = 2.682, 95% CI: 1.492 - 4.320, p = 0.001), dog (RR=1.895, 95% CI: 1.531-2.346, p < 0.001) and chicken (RR=8.387, 95% CI: 4.667-15.073, p < 0.001) near houses was related to increased catches of An. gambiae mosquitoes indoors. The indoor catches of An. gambiae mosquitoes were negatively associated to the presence of at least one sheep (RR=0.345, 95% CI: 0.125-0.953, p=0.04). The outdoor catches, An. gambiae mosquitoes were associated with the presence of at least one goat (RR=7.079, 95% CI: 4.278-11.715, p<0.001) and chicken (RR=0.383, 95%CI:0.185-0.631, p<0.001). The number of An. funestus indoors was higher in houses with chicken (RR=11.627, 95% CI: 2.111-64.032, p=0.005) than those with no chicken. The study shows that the association between livestock keeping and malaria transmission is controversial as there are livestock which increase malaria vectors while others decrease them indoors and outdoors. Thus, zooprophylaxis and other livestock-based malaria interventions should be used with other interventions for malaria control.

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WOLBACHIA-INFECTED AEDES AEGYPTI TO CONTROL DENGUE IN DHAKA, BANGLADESH

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Arboviral diseases like dengue remain a significant health concern in Bangladesh. The primary approach to controlling dengue is through insecticides, with the vector, Aedes aegypti mosquito, being the main target. However, we confirmed that this strategy is likely to be substantially compromised due to high-intensity insecticide resistance in the Dhaka Ae. aegypti population. Our study revealed high frequencies (~90%) of a homozygous kdr mutation (V1016G) coupled with substantial metabolic resistance. In an experimental free-flight room, domestic and public health aerosols against free-flying and resting Ae. aegypti were mostly ineffective, resulting in up to 74% (±8.21, 95% CI) recovery in 24 hours. Realizing the need for a more sustainable, non-insecticidal approach for dengue control, we then focused on the potential for developing Wolbachia-infected, disease-refractory mosquitoes for release in Dhaka. We created and characterized a wAlbB infected Ae. aegypti with Dhaka genetic background and then compared its fitness to the parental Wolbachia-free Dhaka colony. Complete cytoplasmic incompatibility and maternal transmission were demonstrated, with minimal apparent fitness costs. Similar to the parental Dhaka strain, high-intensity resistance (41 - 54% mortality) to the 10 times diagnostic dose of permethrin was recorded in the wAlbB-Dhaka strain.

Fertility, lifespan, fecundity, and egg viability were comparable with the local Dhaka mosquitoes, and wAlbB-infected males were competitive with local males in mating experiments. Given the lack of substantial fitness cost to host mosquitoes, the insecticide resistance profile of its infected mosquito strain, and the potential for virus blocking, the Wolbachia wAlbB strain is likely to offer a viable alternative to dengue control in Bangladesh.

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3D-SCREENS FOR SUSTAINABLE MALARIA CONTROL: OUTCOMES OF PHASE II SEMI-FIELD EVALUATION AND STUDY DESIGN OF A LARGE-SCALE PHASE III EVALUATION IN NORTHEASTERN TANZANIA

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The increasing prevalence of insecticide-resistant malaria vectors has created a need for sustainable vector control alternatives that are non-reliant on insecticides. A novel insecticide-free window screen, called the 3D-Screen, has been developed to exploit mosquitoes' innate attraction to humans. The screen is composed of 3D conical structures with a perforated tip of 5mm and fully open base of 5 cm diameter that are fitted on a traditional screen (100 cones/m2). When installed as a double screen setup in window openings, forming the 3D-Window Double Screen Trap (3D-WDST), its unidirectional function allows mosquitoes to pass from outside only, trapping them between the double screens. In phase I laboratory studies (2015), the 3D-Screens demonstrated a remarkable efficacy, capturing 92% of the host-seeking mosquitoes in a double screen setup. In phase II semi-field studies, we installed 3D-WDST in window openings of experimental huts and found that the 3D-Screens installed on both sides of the window openings (outside and inside) in huts with open eaves were more effective in trapping female Anophelines (FA) than other conditions (efficacy; 33.11%, CI: 7.399 - 58.81). The introduction of baffles in the huts with 3D-WDST resulted in higher trapping efficacy of 70.32% (CI: 56.87 - 83.77) for FA. Comparison of 3D-Screen with machine-made (MM) and handmade (HM) cones showed no significant difference in the weekly mean catch (P=0.1887), however the integral superiority of MM over HM made it the preferred choice for further testing. To elucidate the efficacy of 3D-Screens in community settings, we conducted a large-scale phase III studies in Muheza, Tanzania, enrolling 892 houses from 14 hamlets, 7 of which received the 3D-WDST and insecticidal nets (LLINs) as intervention and 7 received LLINs only as control in a two-arm cluster randomized controlled trial. Follow up studies on malaria infection, entomological parameters, ancillary social aspects, and cost-effectiveness were conducted during the 52 weeks follow up. Trial findings is expected to be released this year addressing the research gap on sustainable vector control approaches.

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EVIDENCE OF TRANSMISSION OF PLASMODIUM VIVAX 210AND P. VIVAX 247 BY ANOPHELES GAMBIAE AND AN. COLUZZII MAJOR MALARIA VECTORS IN BENIN

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Historically, malaria in sub-Saharan Africa has been almost exclusively attributed to Plasmodium falciparum (Pf). Current diagnostic and surveillance systems in Benin are not designed to accurately identify or report non-Pf human malaria infections, resulting in a dearth of routine epidemiological data on their significance. This study aims to assess and compare the prevalence of circumsporozoite protein (CSP) antibodies of P.f, P. vivax (P.v) 210 and P.v 247 in An .gambiae s.l. in 24 communes of Benin. For that, mosquito collections were performed through human landing catches(HLC) and pyrethrum spray catches (PSC). For HLC, 384 collectors were used overnight while 240 bedrooms were used for PSC. Collected mosquitoes were morphologically identified, and P.f, P.v210 and 247 CSP antibodies were sought in An. gambiae s.l through the ELISA and polymerase chain reaction (PCR) . Of the 32773 collected mosquitoes, 20.9% (n=6857) were An. gambiae s.l, 3.9% (n=1292) An. funestus gr., and 0.6% (n=189) An. nili gr. Molecular species identification performed in An. gambiae s.l. revealed that, An. gambiae (53.68%) was the predominant species, followed by An. coluzzii (45.88%), and An. arabiensis (0.44%). In An. gambiae s.l., the sporozoite rate (SR) was 2.6% (95% CI: 2.1-3.1) for P.f, against 0.30% (95% CI: 0.1-0.5) and 0.2% (95% CI: 0.1-0.4) respectively for P.v 210 and P.v 247. P.f sporozoite positive mosquitoes were mostly An. gambiae (64.35%), followed by An. coluzzii (34.78%) and An. arabiensis (0.86%). At the opposite, for the P.v 210 sporozoite positive mosquitoes, An. coluzzii and An. gambiae accounted respectively for 76.92% (10/13) and 23.08% (3/13). Only An. coluzzii was found infected to P.v247. Overall, the present study shows that P. f is not the sole Plasmodium species involved in malaria cases in Benin. In addition, An. gambiae and An. coluzzii have different ability to get infected to the different identified Plasmodium species. These results will help the National Malaria Control Program to better plan the therapeutic management strategy of malaria cases to move towards the pre-elimination of the disease.

5212

MOSQUITOCIDAL ACTIVITY OF IVERMECTIN-TREATED NETTINGS AND SPRAYED WALLS ON ANOPHELES GAMBIAE

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Ivermectin (IVM) has been proposed as a new tool for malaria control due to its mosquitocidal effect on malaria vectors when they blood feed on treated humans or cattle. Nevertheless, IVM may have a direct insecticidal effect on vectors when applied on bed nets or sprayed walls. We conducted a pilot study to measure the direct mosquitocidal effect of IVM on Anopheles gambiae. Laboratory-reared mosquitoes (Kisumu) were exposed to IVM on impregnated netting materials and sprayed walls (plastered and mud) at a determined discriminating dose using cone bioassays. Mosquito survival was assessed at 24, 48 and 72 hour post-exposure and compared with positive (deltamethrin (DM) and pirimiphos methyl) and negative (no insecticide) controls. Mosquitoes were also blood-fed either 12 hours pre- or post-exposure and monitored for oviposition. Hazard rates for IVM mortality was modeled using Cox proportional hazards model. Over 800 mosquitoes exposed to IVM discriminating concentration of 28mg/ml (2.8% w/v) died within 6 hours when exposed to IVM-treated nettings, within 18 hours for sprayed walls. Mosquito survival on the IVM-treated nettings was similar to that of DM-treated nettings. However, mosquitoes survived significantly longer on the IVM-sprayed walls (100% mortality at 18 hr) compared to positive control walls (100% mortality at 6 hr) (Log rank $X2 = 14.03$, $p<0.001$). The adjusted Cox model predicted a hazard rate of 0.24 (95% CI: 0.19-0.30; $p<0.001$) with IVM compared to DM or pirimiphos methyl. Moreover, a significant interaction was found between treatment and surface predicting a three-fold higher hazard with IVM-treated nettings [HR=3.1 (95% CI: 2.21-4.23); $p<0.001$] but not with IVM-treated plastered walls [HR=1.1 (95% CI: 0.7-1.7); $p=.077$]. IVM also inhibited mosquito blood feeding and oviposition regardless of exposure being pre-or post-feeding. Our findings confirm the direct mosquitocidal effect of IVM on An.

gambiae and suggest that IVM could be deployed as a new insecticide against malaria vectors together with the other currently used insecticides for long-lasting insecticidal nets and indoor residual spraying.

5213

IN SILICO ANALYSIS AND DESIGN OF A MOLECULAR CONSTRUCT TO TARGET THE BETA TUBULIN2 GENE IN ANOPHELES GAMBIAE

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The increasing expansion of vector resistance to insecticides requires finding alternative control methods to achieve malaria elimination. Genetic control is one of the promising approaches to control malaria vectors. In the context of genetic control of malaria vectors, genes involved in reproduction are of crucial importance to replace or suppress a vector population. The search for male-specific transcripts and proteins could lead to a better understanding of testicular specificity signals, whether at the promoter level, at splicing, or during translation. The regulatory sequences of these genes can also be used in genetic control strategies to engineer gene drive systems to disseminate desired traits including pathogen resistance or sex distortion. Beta tubulin2, is one of the genes involved in gamete formation which could be further exploited to optimize the efficiency of genetic control methods under development. Here, we developed in silico, a molecular construct to target beta tubulin2 gene in Anopheles gambiae to interfere with mosquito fertility, basing on Drosophila beta tubulin2 gene which has three putative orthologs in An. gambiae (AGAP010929, AGAP008622 and AGAP008623). Specifically, this is to identify the ortholog of the beta tubulin2 gene in An. gambiae, and to design knockdown and knockout strategies of the beta tubulin2 gene with RNA interference and CRISPR Cas9 technology respectively. A double-stranded RNA of 154 nucleotides was generated for the knockdown and a guide RNA was designed to knockout AGAP008622 gene via the CRISPR/Cas9 strategy. All these designs will be introduced into the mosquito for an in vivo experimental study to characterize the beta tubulin2 gene function in Anopheles

5214

IDENTIFICATION OF ODORANT CO-RECEPTOR GENE IN ANOPHELES GAMBIAE AND IN SILICO DESIGN OF STRATEGIES TO STUDY ITS FUNCTION IN A VECTOR CONTROL PERSPECTIVE

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The most effective strategies to control malaria aimed to prevent the mosquito from biting. The African malaria mosquito shows an incredible preference for humans over other sources of blood, a behaviour that is driven by olfaction and could be exploited for vector control. The odorant receptor co-receptor (ORCO) gene is an essential component in the insect olfactory system and may help drive human-specific odour preferences. To investigate the role of ORCO in host seeking behaviour, we carried out an in silico study with the objective to design strategies to study the function of gene coding for the olfactory co-receptor involved in Anopheles gambiae reception of smell. FlayBase database was used to identify the ortholog of orco gene in Anopheles gambiae. NCBI/BLAST, NCBI/CD-Search and FlayAtlas/MozAtlas databases were used respectively for sequences alignment, conserved domain search and genes expression profile search in order to confirm the orthology. To study the function of the gene, E-RNAi database was used to design a RNA interfering system and CHOPCHOP and Benchling databases were used to design a CRISPR/Cas9 strategy. Our study finds strong evidence to suggest that the ortholog of orco in Anopheles gambiae is Agam/or7, also known as AGAP002560. We designed two experimental approaches to further investigate the function of AGAP002560 based on RNAi knockdown or CRISPR/Cas9 knock-out using custom double string RNA or guide RNAs, respectively. To facilitate the experimental investigation of AGAP002560 knockout, we designed a donor plasmid for homology-directed repair to allow integration of a GFP expression cassette into the AGAP002560 gene. These results constitute an important step in the study of the function of Agam\or7 gene and may yield new approaches for mosquito population control.

5215

MARK RELEASE RECAPTURE EXPERIMENT IN BURKINA FASO DEMONSTRATES REDUCED FITNESS AND DISPERSAL OF GENETICALLY-MODIFIED STERILE MALARIA MOSQUITOES

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Every year, malaria kills approximately 405,000 people in Sub-Saharan Africa, most of them children under the age of five years. In many countries, progress in malaria control has been threatened by the rapid spread of resistance to antimalarial drugs and insecticides. Target Malaria, is a research consortium that aims to develop and share new genetic mosquito control tools for integrated malaria control strategies. In July 2019, in Burkina Faso (BF), the consortium proceeded with the first release of a genetically modified (GM) strain of Anopheles coluzzii called Ac(DSM)2. The Ac(DSM)2, was created through backcrossing Ag(DSM)2 transgenic females from a previously-established early dominant embryo lethality-inducing strain. In June 2019, a large cohort of the strain was produced, sexed, and males dusted with fluorescent powder. A single release of 6,428 hemizygous Ac(DSM)2 males and 8,422 non-transgenic male siblings was conducted in the village of Bana (BF). After 17 days, 527 dusted males were collected from swarms and houses and Polymerase Chain Reaction analysis revealed 145 of these to be Ac(DSM)2 males. GM males were recaptured 50.8 - 497m and siblings 50.8 – 1,678m from the release point. A Bayesian approach showed, that GM males were found to have significantly shorter daily survival rates than their wild type siblings (0.55 - 0.63 vs 0.73-0.77 survival day-1) and were also less mobile (diffusion rates 11,200 - 20,100 m2day-1 vs 28,800 - 75,700 m2day-1). The male population size at the time of the release was estimated to be in the range 28,000-37,000. These results provide information about the fitness and behaviour of GM males released at the start of the rainy season. The first release of genetically modified mosquitoes in Sub-Saharan Africa is an important milestone towards future releases of more effective strains targeting the sibling species of the A. gambiae complex

5216

DENGUE VECTOR HABITAT CREATION IN PUBLIC PLACES: AN UNINTENDED CONSEQUENCE OF THE INSTALLATION OF PUBLIC HANDWASHING STATIONS FOR COVID-19 PREVENTION IN OUAGADOUGOU, BURKINA FASO 2020

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Public places can be an important source of breeding habitats of Aedes aegypti, the main dengue vector, but data to support this evidence are missing in Africa. This study conducted to fill this gap for Ouagadougou, coincided with the COVID-19 pandemic and the consequent installation of handwashing stations (HWS). We investigated the abundance and diversity of water holding containers in some public places of Ouagadougou, including HWS, and assessed their contribution to Ae. aegypti immature stages proliferation. Between September and October 2020, water-holding containers were systematically inspected for Aedes mosquito immature stages in 61 public places of Ouagadougou. All collected immature mosquitoes were counted, identified to genus. Breeding containers abundance and preference were estimated and generalised mixed models were fitted to larval and pupal densities. A total of 924 containers that were considered suitable for Ae. aegypti breeding habitat were identified, of which HWS and tires had the highest proportions of positive containers (37.42% and 37.27% respectively), followed by small containers (SC) (13.03%). At its peak, 44.73% and 41.02% of the total production (produced by all type of containers encountered in public places) of Ae. aegypti larvae and pupae, respectively were produced by HWS. Tires, bucket/can/pot (BCP) and SC followed in terms of larval and pupae productivity. Additionally, some containers were hosting immatures of non-Ae. aegypti mosquito species, including Anopheles gambiae s.l. and Culex species. In conclusion, containers in public places contribute to increase Ae. aegypti immatures densities in Ouagadougou and should be taken into account for dengue control. The major role of newly introduced HWS in Ae. aegypti immatures productivity recommends risk assessment prior to introduction of new tool in the public areas.

5217

RETHINKING INSECTICIDE TREATED NET (ITN) DISTRIBUTION: A REVIEW OF CURRENT DISTRIBUTIONS SYSTEMS, COSTINGS AND CHALLENGES

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While malaria cases and deaths reduced steadily between 2000 and 2009, continued progress has stalled in parallel with annual funding gaps. To optimize the impact of continued limited resources, there is an even greater need to maximize the efficient, effective, and equitable targeting and use of malaria vector control strategies. Countries where malaria is endemic must be able to identify and deploy an optimal mix of vector control interventions suited to their local context, established priorities, and available resources. Insecticide Treated Net distribution through mass campaigns have been the mainstay of vector control interventions for over 20 years. Mass campaigns and continuous distribution channels have delivered over 2.2 billion nets in Sub-Saharan Africa and have been largely responsible for the impressive declines in malaria morbidity and mortality since 2000. However, many factors require new thinking and flexible approaches to ITN distribution including inadequate and inequitable targeting resulting in many households receiving nets they may not need or use while others remain without access, increasing insecticide resistance requiring more expensive nets with dual actives, challenges with durability with nets not lasting as long as expected, decreasing compliance with use particularly in urban areas and increasing fatigue from some partners for mass campaigns. These factors, combined with funding gaps and human resource constraints, necessitate a rethinking of ITN distribution through mass campaigns with a renewed focus on the alternative distribution mechanisms. Findings from a modelling study of continuous distribution versus mass distribution in Tanzania, costings studies of cost per net delivered (mean USD 6.29) from continuous distribution activities in four countries, durability monitoring data showing the period between net receipt and use, and findings from scaling up from pilots to national scale school-based distribution will be presented in order to highlight some of the factors to be considered in order to optimize ITN coverage, increase use, and maximize the impact of available funds.

5218

ASSESSING INSECTICIDE RESISTANCE IN TWO MALE-BIASED ANOPHELES GAMBIAE S.L. TRANSGENIC STRAINS

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The transgenic (TG) mosquito insecticide susceptibility must be determined, in comparison to that of the wild-type (WT), as part of the risk analysis performed prior to their release into the natural environment. Increased resistance could make the TG mosquitoes more difficult to control or could introduce novel resistance levels or mechanisms into the wild mosquitoes. A strain of Anopheles coluzzii, BF_Ac(PMB)1, and one of Anopheles gambiae, UG_Ag(PMB)1, contain a transgene that biases the sex ratio of progeny from TG fathers to > 95% males. These strains were previously developed by repeatedly backcrossing the transgene from Ag(PMB)1 into a WT strain of A. coluzzii from Burkina Faso (BF_Ac(WT)) or a WT strain of A. gambiae from Uganda (UG_Ag(WT)). This study compared TG mosquitoes to their WT counterparts for each introgressed strain. The insecticide susceptibility of females was determined using the standard World Health Organization (WHO) adult insecticide exposure kits and discriminating doses recommended by the WHO. The panel of insecticides included four pyrethroids (alpha-cypermethrin, lambda-cyhalothrin, permethrin, and deltamethrin), a carbamate (bendiocarb), an organophosphate (fenitrothion), and an organochlorine (DDT). Exposures were for 1 h except for fenitrothion which was for 2 h, as recommended by WHO. Mortality was determined 24 h later. Larvae were also exposed to a larvicide that is widely used in Africa, temephos, to determine susceptibility to that insecticide. TG females showed no increases in resistance to eight different insecticides representing four different classes when compared with their WT controls for either strain. When any resistance to insecticides was observed, it was detected in both TG and WT individuals for either strain. Overall, our data demonstrate the transgene has no effect on insecticide resistance for the two transgenic strains tested under the study conditions tested. Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

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ASSESSING VECTOR COMPETENCE FOR PLASMODIUM FALCIPARUM AND O'NYONG-NYONG VIRUS IN A MALE-BIASED ANOPHELES COLUZZII TRANSGENIC STRAIN

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Anopheles mosquitoes vector the etiological agents of important diseases including malaria and O'nyong-nyong virus (ONNV) fever. Because insecticide resistance levels are rising in vector populations, alternative control tools are urgently needed. A promising approach is the use of transgenic (TG) mosquitoes to suppress or modify wild populations. Before such TG mosquitoes can be considered for testing in the field, potential risks to the environment or health caused by their release must first be assessed. As part of a wider vector control development program,

we assessed the impact of a male-biasing transgene introgressed into an Anopheles coluzzii strain from Burkina Faso on vector competence for Plasmodium falciparum and ONNV. Previously, we have shown no significant difference in P. falciparum vector competence in TG females compared to their wild-type (WT) counterparts. In the current study, we determined if a potential reduction in egg production, a phenotype previously observed in females that mate with TG males, affects the P. falciparum infection rates by comparing infection rates in females from two crosses: 1) WT females x TG males, and 2) WT females x WT males. No significant differences were observed between groups (P > 0.05), in terms of oocyst counts 7 days post-infectious blood meal (d pIBM) (median WT: 21, TG: 25), with a slight significant reduction in prevalence in cross 1 (1= 91.3%, 2=97.5%, P: 0.047). Also, no significant increase in sporozoite intensity or prevalence at 11 and 15 d pIBM was seen in either group. For ONNV, the infection, dissemination, and transmission potential rates of TG females were compared to that of WT females. No significant difference was found in the three parameters measured between the two groups. Overall, our data suggest no effect of the transgene, the genetic background or the reduced fecundity on P. falciparum infection rates or ONNV infections for any of the parameters analyzed. Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

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MOLECULAR AND BIOINFORMATIC CHARACTERIZATION OF THE INTROGRESSION OF A MALE-BIASED TRANSGENE INTO A UGANDAN LOCAL WILD-TYPE STRAIN

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To ensure that a transgenic mosquito strain that may eventually be released into the field reflects that of the wild population, a transgene from a founding transgenic strain generated in a laboratory line, is then introgressed into genetic backgrounds of colonies recently established from the field?. However, alleles potentially associated with adaptations to laboratory rearing conditions and to the transgene flanking regions may be inherited with the selected locus to[LAE(1] [BGA(2] the introgressed strain, even when they are separable by recombination. Ag(PMB)1 is a transgenic Anopheles gambiae strain that during male spermatogenesis expresses the I-PpoI variant W124L fused to eGFP, leading to approximately 95% male offspring. The subsequent introgression of the PMB1 transgene into an A. gambiae s.s wild-type (WT) strain from Uganda (UG_Ag(WT)) led to the generation of the UG_Ag(PMB)1 strain. This study describes the introgression process and the molecular characterization of the introgression after six repeated backcrosses of Ag(PMB)1 transgenic females with UG_Ag(WT) males. Life-history traits (i.e. egg yield, hatching rates, etc.), SNP genotyping analysis via KASP assays, and 2La inversion analysis via PCR were conducted. The recorded life-history traits revealed that the newly introgressed strain UG_Ag(PMB)1 is robust and demonstrated sufficient rates in terms of egg yield, hatching, and pupal eclosion to maintain and amplify the colony under lab conditions. Preliminary SNP analyses suggest that the introgressed strain has a similar genotype profile to the UG_Ag(WT) strain for the X and 3L chromosomes, while chromosome 2L carries allelic forms from both parentals. Finally, the 2La genotyping showed that both arrangements of the 2La inversion are present in the WT parental and the introgressed strain. Overall, this study presents a phenotypic and molecular characterization of the PMB1 transgene introgression process into the genetic background of a Ugandan WT strain after six backcrosses.

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MARK, RELEASE AND RECAPTURE EXPERIMENT OF A LABORATORY STRAIN OF ANOPHELES COLUZZII IN TWO VILLAGES IN MALI

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Regular surveys are usually carried out to understand the composition, structure, and abundance of vectors. However, these surveys do not make it possible to estimate the size of the vector population of the locality because the fraction of the people collected is not known. One of the most widely used methods of estimating population size is the “mark-release and recapture” method. Tagging, release, and recapture experiments were carried out in the villages of Tieneguebougou and Ouassorola in Mali for two consecutive years (August 2016, July 2017, and November 2017). For each experiment, approximately 5,000 adult male mosquitoes (Anopheles coluzzii) were released. Swarm sampling was the most productive method for collecting male mosquitoes in the field. The size of the population was estimated in Tiénéguebougou in August 2016 (106,103) greater than that observed in July 2017 (11,546) and November 2017 (29,227), this same phenomenon was observed in Ouassorola, the size of the population observed in August 2016 (90,674) is higher than that observed in July 2017 (19,046) and in November 2017 (19,559). The results of the three mark, release, and recapture experiments show a statistically significant difference between the recapture rates obtained in August 2016 (0.52%), July 2017 (2.07%), and November 2017 (1.09 %), this difference was also observed in the village of Ouassorola during August 2016 (1.78%), July 2017 (1.60%) and November 2017 (0.75%). The daily survival rate for Tieneguebougou is 0.26 in August 2016; 0.35 in July 2017 and 0.22 in November 2017 and that of Ouassorola: 0.35 in August 2016; 0.38 in July 2017, and 0.29 in November 2017. The average distance covered by males varied from 40 m to 100 m.

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MOLECULAR STRATEGIES TO DEPLOY SINGLET OXYGEN AS AN UNASSAILABLE BIOCIDE FOR DISEASE PREVENTION AND VECTOR CONTROL

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Singlet oxygen (1O2) is a potent biocide potentially deployable for integrated control of tropical diseases and their insect vectors. This is a very short-lived oxidative radial, but is highly destructive of cellular molecules when generated intracellularly. Parasites and insects are defenseless against 1O2. Only plants have evolved specific mechanism to detoxify 1O2 by necessity, as it is produced abundantly during photosynthesis. In the presence of atmospheric O2, exposure of certain dyes, e.g. porphyrins and phthalocyanines (PC) to light produces 1O2. Its half-life is only in the order of μs, necessitating its intracellular generation to feasibly harness its biocidal activity effectively. One example is genetic engineering of Leishmania to complement its inherent defects in porphyrin biosynthesis, resulting in cytosolic accumulation of abundant uroporphyrin 1 (URO). Another example is chemical engineering of PC for hydrophilicity and cationicity, facilitating its endocytosis by cells. Leishmania doubly loaded with cytosolic URO

and endosomal PC are inactivated by dim light to completion. These inactivated Leishmania preserved their natural vaccines and adjuvants with prophylactic activities against experimental leishmaniasis. Preliminary data further show the potential of 1O2 -inactivated Leishmania as a platform for safe and effective delivery of transgenically add-on vaccines against malignant and viral diseases in mouse models. Hydrophilic and cationic PC were also shown experimentally to represent a new type of light-activated insecticides, i.e. their mosquito larvicidal activities, featuring the requirement of dim light with <µM LD50 values. Similar results have been obtained by studying PC in additional laboratory insect models. A significant advantage has long been attributed to this type of insecticides, i.e. their aversion to selection of genetic variants for resistance. An additional advantage of PC is their excitability to produce insecticidal 1O2 by deep-penetrating red/IR light invisible to insects, thereby potentially increasing considerably the range and scope of targetable insect vectors.

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DISCOVERING NATURAL PRODUCT CHEMISTRIES FOR VECTOR CONTROL

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Natural products (NPs) represent diverse chemical structures and, potentially, modes of action of vector control importance. NPs have inspired the development of multiple synthetic insecticides, suggesting the discovery of novel NPs for the development of highly effective insecticides needed to control insecticide-resistant vector populations. Here, we report two interdependent studies performed to identify novel mosquito-active insecticide leads with modes of action distinct from existing insecticides used in mosquito control programs. In the first study, we performed a high-content larval phenotypic screen using first instar larvae of Aedes aegypti against 3,680 compounds from the AnalytiCon MEGx Natural Product Libraries and a screening platform developed, as reported previously. Screening revealed five chemistries that caused larval mortality, including rotenone, the detection of which confirmed the ability of the screen to detect mosquito-active NP chemistries. 140 chemistries that caused atypical larval phenotypes, including cuticular pigmentation and morphometric changes relative to negative controls, were also identified by the screen. Some of these chemistries may act via disruption of pathways regulating mosquito melanization, growth and development, including potentially unique targets in the insect nervous systems, thus representing important opportunities for novel insecticide development. In the second study, we performed electrophysiological recordings using the suction electrode technique and ganglia of Blattella germanica to investigate the mode of action and impact on the insect nervous systems of metergoline and NP-1, two chemistries identified by HTP screening. Results suggested metergoline and NP-1 may act via serotonergic pathways and one or more conserved targets in the insect nervous systems, respectively, making them potential leads for the development of new insecticides that could be used to control insecticide-resistant populations. Results will be reviewed and future lines of research proposed in the context of new insecticide development.

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IMPACT OF USING DIFFERENT TYPES OF MOSQUITO TRAPS TO ASSESS ENTOMOLOGICAL EFFICACY OF DUAL-ACTIVE INGREDIENT LONG-LASTING INSECTICIDAL NETS (LLINS) IN BENIN

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Selection of mosquito sampling traps is of crucial importance to evaluate impact of vector control tools on entomological outcomes. During a cluster randomised control trial evaluating the relative efficacy of two dual-active ingredient (a.i.) nets compared to pyrethroid only nets, we assessed performance of different mosquito trap types: Human Landing Catch (HLC), CDC light traps, and Pyrethrum Spray Catch (PSC). Anopheles mosquitoes were collected with the three trap types in 4 houses in each of the 60 trial clusters at baseline and every quarter for 24 months using PSC and HLC, while CDC light traps were performed during two quarters only. The density of An. gambiae s.l and its Plasmodium falciparum sporozoite infection were assessed. Mean density of vectors collected per trap per night was the highest with HLC (15.9), followed by CDC light trap (6.8), with the PSC (1.1) collecting 10 times less mosquitoes than HLC. All three trap types showed that the lowest mosquitoes density was collected in the Interceptor G2® dual a.i. arm compared to the other arms, although only HLC and PSC demonstrated strong evidence of this due to a greater number of collection rounds than CDC light traps. Furthermore, CDC light traps and PSC measured similar reductions in SR and EIR* (*CDC light trap only) as compared to HLC between study arms. The broadly similar results between trap types suggest that the more ethically acceptable, cheaper and logistically simpler methods such as CDC light traps could be prioritised for use in large community trials for measuring efficacy of vector control tools.

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EFFICACY OF PYRETHROID-PYRIPROXYFEN AND PYRETHROID-CHLORFENAPYR LONG-LASTING IMPREGNATED NETS (LLINS) FOR THE CONTROL OF NON-ANOPHELES MOSQUITOES: SECONDARY ANALYSIS FROM A CLUSTER RANDOMIZED CONTROLLED TRIAL

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Failure to control nuisance of mosquitoes may potentially affect adherence to vector control tools. The present study compares the vector density of Culex spp and Mansonia spp across the two dual a.i. LLINs and the standard pyrethroid-only LLIN arms, and assessing the seasonality of these mosquito species. 85,723 Culex spp and 144,025 Mansonia spp were caught over the study period. The density of Culex and Mansonia reduced in all three arms over the study period. There was no evidence of a significant reduction of the indoor or outdoor density of Culex spp in either dual a.i. long lasting net arms as compared to the standard pyrethroid only net arm [(indoor DR=0.9 (95% CI: 0.4-2.4), p=0.8817 for the alphacypermethrin-pyriproxyfen LLIN, indoor DR=0.6 (95% CI: 0.2-1.5) p=0.2793 for the alphacypermethrin-chlorfenapyr LLIN]. No evidence for differential reductions between arms was observed for Mansonia spp. A high density of Culex spp was found both in rainy and dry seasons, while for Mansonia spp this was mainly observed during the rainy season. These results suggest that the novel insecticides on the dual a.i. LLIN did not have additional impact on these species, and that pyrethroids might still be effective on them. Further work is required to determine whether these species of mosquitoes have resistance to the insecticides tested in this trial.

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EFFICACY OF PIRIKOOL® 300 CS USED FOR INDOOR RESIDUAL SPRAYING ON THREE DIFFERENT SUBSTRATES IN SEMI-FIELD EXPERIMENTAL CONDITIONS

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Vector control using insecticides is a key prevention strategy against malaria. Unfortunately, insecticide resistance in mosquitoes threatens all progress in malaria control. In the perspective of managing this resistance, new insecticide formulations are being urged to improve the effectiveness of vector control tools. The efficacy and residual activity of Pirikool® 300CS was evaluated in comparison with Actellic® 300CS in experimental huts at the Tiassalé experimental station on three substrates including cement wood and mud. The mortality, blood-feeding inhibition, exiting behaviour and deterrency of free-flying wild mosquitoes was evaluated. Bioassay cone assays with susceptible and resistant mosquito strains were conducted in the huts to determine residual efficacy. A total of 20505 mosquitoes of which 10979 (53.5%) wild female Anopheles gambiae were collected for 112 nights. Residual efficacy obtained from monthly cone bioassay was higher than 80% with the susceptible, laboratory-maintained Anopheles gambiae Kisumu strain from the first to the tenth study period on all three types of treated substrate for both Actellic® 300CS and Pirikool® 300CS. This residual efficacy on the wild Tiassalé strain was over 80% until the 4th month of study on all Pirikool® 300CS and Actellic® 300CS treated substrates. Overall 24-hour mortalities of wild free-flying An. gambiae s.l. which entered the experimental huts over the 8-months trial on Pirikool® 300CS treatment was 50.5%, 75.9% and 52.7% respectively on cement wall, wood wall and mud wall. The positive reference product Actellic® 300CS treatment induced mortalities of 42.0%, 51.8% and 41.8% on cement wall, wood wall and mud wall. Pirikool® 300CS has performed against resistant strains of An. gambiae s.l. using indoor residual spraying in experimental huts. It could be an alternative product for indoor residual spraying in response to the vectors' resistance to insecticides.

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MEASUREMENT OF OOCYST AND SPOROZOITE INFECTION RATES IN ANOPHELES GAMBIAE S.L. UNDER NATURAL CONDITIONS IN BANCOUMANA, MALI

The dynamics of mosquito infections play a central role in Plasmodium falciparum transmission and human infection rates, and can be considered as an endpoint in trials of transmission-interruption interventions like vaccines. Here we measured natural oocyst and sporozoite infection rates in wild-caught Anopheles gambiae s.l. Every month (Mar 2018-Jul 2019), a team collected mosquitoes in 63 households comprising 503 rooms, for 7,435 collections total (372-494 collections per month). Live mosquito collections using mouth aspiration were followed by pyrethrum spray collections of killed mosquitoes. Live Anopheles mosquitoes with recent bloodmeal were separated from unfed mosquitoes and kept seven days; midguts were dissected and oocyst infections were counted. Killed Anopheles mosquitoes were preserved in 80% ethanol and retained for ELISA-CSP (sporozoite infection rates) and PCR (Anopheles speciations). Collections yielded 4,089 live female Anopheles with an average density of 0.55 (SD = 0.84) per hut; 3,164 (77.4%) mosquitoes survived to dissection, oof which 84 (2.7%) were infected (2.7%) with mean of 2.1 oocysts [range 0-15]. Among 3,143 killed mosquitoes identified morphologically as An. gambiae s.l (mean 0.42 mosquitoes per hut), 25 (0.79%) were positive for CSP infection by ELISA. As expected, the highest number of infected mosquitoes (n=21) were collected during peak transmission season (Aug-Oct). A subset of mosquitoes underwent PCR analysis that identified two predominant species, An. coluzzii and An. arabiensis, at frequencies of 61.5% and 8.6% respectively. These large-scale collections provide an estimate of the incidence of malaria infection in circulating mosquito populations and can be a valuable tool to measure the impact of any malaria control measures tested or implemented in communities.

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EVALUATING MOSQUITO BEHAVIOR DURING EXPOSURE TO DIFFERENT INSECTICIDE-TREATED NETS (ITNS) USING VIDEO CONE TEST

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The increasing resistance of mosquitoes to the active ingredients in Insecticide treated Nets (ITNs) has created a need for the development of effective vector control methods and testing protocols. The Video Cone Test (VCT) builds on the World Health Organization (WHO) cone bioassay by incorporating a behavioural record of mosquito interactions with ITNs. The objective of this study is to assess the behavoioural traits of mosquitoes when exposed to various types of ITNs. To achieve this objective, the study involved exposing 2-5 day old Anopheles gambiae mosquitoes to different ITNs (PermaNet® 2.0, PermaNet® 3.0, and Olyset®) for varying lengths of time (1, 2, 3, 4, 5, and 6-minutes) using the WHO cone bioassay. During the process, mosquito behaviour was recorded using a smartphone, and the activities or movements of mosquitoes in different regions of the cone (Region-0, Region-1, Region-2 and Region-3) were depicted. After exposure, the mosquitoes were given a 10% sugar solution, and mortality was recorded 24 hours later. The study found significant differences in the number of activities observed in each cone region between the two mosquito strains ($p<0.05$), with Region-1 recording the highest activity in both strains. Olyset® did not exhibit any variation between the two strains in any of the regions ($p>0.05$), while PermaNet® 2.0 and PermaNet® 3.0 showed variations between the strains in Regions 1, 2 and 3 ($p<0.05$). Mortality was strongly associated with all regions of the cone ($p<0.00$), with Regions 2 and 3 showing the strongest associations (coefficients = 1.661457 and 1.35458, respectively). These results indicate that different types of ITNs have varying effects on mosquito behaviour. Furthermore, the WHO cone bioassay, with the addition of a camera component can provide valuable insights into mosquito behaviour.

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KEY ENTOMOLOGICAL AND MALARIA INDICATORS DURING THE PERIODS OF INDOOR RESIDUAL SPRAYING WITH PIRIMIPHOS-METHYL AND CLOTHIANIDIN-BASED PRODUCTS IN ZAMBIA

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Zambia deployed pirimiphos-methyl for IRS from 2013 -2018, before switching to clothianidin products from 2019 -2022, given its duration of efficacy was found to be >10 months compared to 4 -5 months for pirimiphos-methyl. The trends in entomological and malaria indicators were reviewed from 2015 -2018 and from 2019 -2022. This analysis investigates whether pirimiphos-methyl should be reintroduced for IRS in Zambia. We analyzed two available and complete entomological indicators—indoor density (ID) and human biting rate (HBR)—collected in 10 sentinel sites from 2015 -2022, as well as annual malaria incidence rates in 116 districts from 2013 -2022. Only one out of the 10 sites had entomological monitoring

data covering the deployment periods of both insecticides; the rest of the sites covered only one of the periods. Mixed effect models were used with random intercept per site and insecticide as fixed effect controlling for the month of collection and rainfall. We found no significant differences in ID and HBR between the pirimiphos-methyl versus clothianidin periods for either An. gambiae s.l. (ID 0.45 vs 0.53, p=0.8141, HBR indoor 1.31 vs 3.81 p=0.8686, HBR outdoor 1.71 vs 3.37 p=0.1612) or An. funestus s.l. (ID 2.70 vs 2.84 p=0.9817, HBR indoor 11.29 vs 19.09 p=0.7912, HBR Outdoor 8.37 vs 9.93 p=0.9664). The malaria incidence rate was significantly lower for pirimiphos-methyl (496.6 per 1,000) compared to clothianidin (613.2 per 1,000) (p<0.0001). This preliminary investigation indicates that the change from pirimiphos-methyl to clothianidin products did not result in a reduction in vector numbers despite the difference in duration of efficacy while malaria incidence rates increased during the period of clothianidin deployment. While these results suggest that pirimiphos-methyl could be safely reintroduced into the IRS insecticide rotation with no significant adverse effect on program outcomes, more analyses controlling for other confounders are still needed.

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MOSQUITO TRAPPING BEDNET (T-NET) FOR INSECTICIDE RESISTANCE MANAGEMENT AND MALARIA CONTROL

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Malaria burden is increasing. An estimated 241 million de cases and 627 000 deaths occurred worldwide in 2020. About 228 million cases were recorded in 2018 while in 2017, the WHO reported 219 million cases and 435,000 related deaths comparing to 216 million cases reported in 2016, which had already increased about 5 million cases over 2015. This situation is problematic and highlights the urgent need to develop new malaria control strategies. The widespread insecticide resistance in malaria vectors is considered as the principal reason why the LLINs along with IRS which have been critical to malaria prevention, are now failing to control the disease. To overcome this problem, we have developed a mosquito trapping bednet, the so-called T-Net which has the particularity to trap and kill mosquitoes regardless of their insecticide resistance status. Field testing in WHO-recommended experimental huts in Africa showed a 4.3-fold greater trap-kill rate of insecticide-free T-Net compared to Permanet 2.0, the most common bednet in Africa. A T-Net population model developed from field data to predict community-level mosquito control showed that the insecticide-free T-Net under field conditions against pyrethroid resistant mosquitoes was 12.7-fold more efficacious than single chemical, pyrethroid-treated nets. The current presentation covers recent findings (currently ongoing studies) in experimental huts comparing the efficacy of treated and untreated T-Nets versus PBO bednets considered by the WHO as reference for vector control and the prevention of malaria in insecticide-resistant areas.

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VALIDATION OF A METHOD FOR DRY PRESERVATION AND REHYDRATION OF ANOPHELES GAMBIAE SENSE LATO FOR PARITY ANALYSIS TO ASSESS IMPACT OF VECTOR CONTROL MEASURES IN THE FIELD

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The control of malaria is still heavily dependent on mosquito control interventions. With progress in malaria control stalling in recent years, it is essential to understand the impact of interventions on vector populations. Age grading is a valuable method for determining whether interventions alter the age structure of target mosquito populations, but current methodologies are logistically challenging to incorporate into clinical trials and routine surveillance. We validated a method for dry preserving mosquitoes using silica gel and rehydrating prior to parity assessment using the ovarian tracheation method. Lab-reared Anopheles coluzzii mosquitoes with known parity-status were dry-preserved in silica gel for 1, 2, 6, 9 and 12 weeks, and rehydrated prior to parity assessment. Results were compared to parity results from freshly-killed mosquitoes from the same colony. Following lab validation, field-caught An. gambiae s.l. from the Bijagós Archipelago, Guinea-Bissau, were assessed by three different assessors who were blinded to each other's scores. Inter-rater reliability (IRR) was calculated for all assessor-pairings, and an overall index of agreement was calculated using the arithmetic mean of these IRRs. The impact of time preserved was investigated using a one-way ANOVA to look for differences in assessor agreement over three timeframes; (1) 16-70 days (2) 71-90 days and (3) 91-110 days. When dry-preserved and rehydrated, the parity status of 90.1% of insectary-reared An. coluzzii were correctly identified compared to 97.8% in freshly-killed mosquitoes. IRR of freshly-killed An. coluzzii was highest (0.94). Results at all time points showed excellent strength of agreement between assessors. For field-caught An. gambiae s.l., the overall index of agreement between all three assessors was 0.86 (95% CIs 0.78-0.93) indicating an almost perfect agreement. Dry preserving and rehydrating Anopheles mosquitoes to assess the efficacy of a control intervention provides an excellent and feasible alternative to using freshly-killed mosquitoes in remote settings where standard methodologies are logistically infeasible.

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IN SILICO DESIGN OF MOLECULAR MODEL TO STUDY THE SIFAMIDE GENE FUNCTION IN ANOPHELES GAMBIAE OLFACTORY SYSTEM, IN A PERSPECTIVE OF GENETIC CONTROL OF THE VECTOR

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Despite decades of control effort, malaria still cause a public health problem. Fortunately, the main vector of the disease Anopheles gambiae has a weakness: it uses its sense of olfaction to target the human host on which feed. Several genes including SIFamide regulate this behaviour in the vector. The overall objective of this study is to develop in silico strategies to access the function of the SIFamide in An. gambiae. For this purpose, the EnsemblMetazoa database was used to identify the orthologue in the mosquito. Then, tools such as BLAST-NCBI, CD-Search, FlyAtlas2 and MozAtlas was used to confirmed this orthologue using Drosophila melanogaster as reference. Also, a knockout model was generated in silico for the orthologue by using CRISPR-Cas9 technology with the CHOPCHOP and Benchling tools. The orthologue identified is AGAP007056. The similarity and identity percentages between the protein and nucleotide sequences, demonstrate the conservation of the gene in insects. Similar expression pattern of the gene was found in An. gambiae and Drosophila melanogaster tissues but appears to be more expressed in the male than female. This could be explained by the fact that the male feeds exclusively on nectar and needs a regular supply of sugar for its survival. Otherwise, the absence of a protein domain could be due to a lack of annotation or that the gene really doesn't have a domain that has remained conserved through evolution. For the knockout technology, the gRNA has 20 bp in size and an efficiency score of 66.62%. It targets a conserved region of exon 2 and [%GC] = 65. The plasmid used for homology repair contains basis features such as a green fluorescent protein flanked by homology arms (1500 bp) immediately upstream and downstream of the Cas 9 cleavage site. Our constructions shown a good efficiency as demonstrate by the e-values less than 0.05. Better understand the phenotype associated to SIFamide expression will allow us to select this trait in a gene drive approach or other strategies targeting the same process in the vector.

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A SEMI-FIELD EVALUATION OF THE USE OF HUMAN LANDING CATCHES VS HUMAN-BAITED DOUBLE NET TRAPS FOR ASSESSING THE IMPACT OF A VOLATILE PYRETHROID SPATIAL REPELLENT AND PYRETHROID-TREATED CLOTHING ON ANOPHELES MINIMUS LANDING

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The mosquito landing rate measured by human landing catches (HLC) is the conventional endpoint used to evaluate the impact of vector control interventions on human-vector exposure. Non-exposure based alternatives to the HLC are desirable to minimize the risk of accidental mosquito bites during evaluations. One such alternative is the human-baited double net trap (HDN), but the estimated personal protection of interventions using the HDN has not been compared to the efficacy estimated using HLC. This study evaluates the performance of the HLC and the HDN for estimating the effect on mosquito landing rates of two intervention types characterized by contrasting modes of action, a volatile pyrethroid spatial repellent (VSPR) and insecticide-treated clothing (ITC). Experiments were performed to estimate the impact of both interventions on mosquito landing using the two methods. A block randomized cross-over design was carried out over 32 nights with both the HLC and HDN. Eight replicates per combination of collection method and intervention or control arm were conducted. For each replicate, 100 Anopheles minimus were released and were collected for 6 hours. For the VPSR, the estimated effect was similar for both methods; when measured by HLC (OR 0.007 95% CI (0.005, 0.01) p<0.001) and by HDN (OR 8.72e14 (0, Inf) p = 0.99), and no mosquitoes were recaptured by HDN. For the ITC, the protective efficacy was measured by HLC (OR 0.30 (0.23, 0.40) p<0.001), but there was no evidence of protection when measured by HDN (OR 1.04 (0.85, 1.27) p=0.69). Interplay between mosquitoes, bite prevention tools, and the sampling method result in vector behaviour changes which may impact the estimated protective efficacy. Consequently, sampling method must be considered when evaluating these interventions. The HDN is a valid alternative trapping method (relative to the HLC) for evaluating the impact of bite prevention methods that affect mosquito behaviour at a distance (e.g., VPSR), but not for interventions that operate through tarsal contact (e.g., ITC).

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FIRST EVIDENCE OF THE PRESENCE OF THE WOLBACHIA AND MICROSPORIDIES MBITA IN NATURALS POPULATIONS OF ANOPHELES GAMBIAE IN SOUTH OF BENIN

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The Wolbachia endosymbiont can have major effects on the reproductive capacity and vectorial capacity of host insects and can be tools to control mosquito-borne pathogens. Anopheles gambiae sl is the main vector of malaria in Africa, but the use of Wolbachia in this species has been limited by difficulties in establishing stable transinfected lines and uncertainty surrounding native infections. The presence of Wolbachia and microsporidia have never been reported in An. gambiae sl in Benin. For this study, we searched for the presence of Wolbachia and Mbita(MB) microsporidia in natural samples of An. gambiae sl. infected or not with plasmodium falciparum collected in southern Benin (Cotonou, Porto-Novo, Calavi) over a period of 6 years. Our results showed that Wolbachia is present at a low prevalence in the natural population of An. gambiae sl. Of 8435 samples analyzed, only 29 were positive for Wolbachia by nested PCR representing 0.34% prevalence. No positive samples were found with regular PCR. However, MB microsporidia were present at a high proportion of 20.62% or 1740 positives out of 8435. The results also showed a very low prevalence of Wolbachia and microsporidia on samples positive for Plasmodium falciparum, respectively 0.33% (1/296) and 1.68% (5/296). The absence of a positive sample with regular PCR is encouraging for applications using Wolbachia-transinfected mosquitoes for malaria control. These results will also enable the National Malaria Control Program to diversify the methods of combating malaria.

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LABORATORY AND SEMI-FIELD EVALUATION OF BIO-EFFICACY AND PHYSICAL INTEGRITY OF OLYSET PLUS AND INTERCEPTOR G2 NETS AFTER THREE YEARS OF FIELD USE IN TANZANIA

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Long-lasting insecticidal nets (LLINs) provide protection against malaria vectors by its residual insecticidal activity even when its fabric is torn. Usage and washes during the LLIN's lifetime could result into loss of insecticidal component to an extent where users can be subjected to high risk of malaria transmission. To sustain gains in malaria control, LLINs should maintain high bio-efficacy and fabric strength for at least 3 years post distribution. Mortality and blood feeding inhibition (BFI) induced by 3 years old used Interceptor G2 (IG2) and Olyset plus (OP) LLINs were assessed following WHO guidelines at both laboratory and semi-field experimental hut trial. Both IG2 and OP LLINs were able to induce significant mortality and BFI to mosquitoes compared to the untreated LLIN (negative control). In cone bioassay, mortality induced by OP nets decreased significantly (50%, 46.3%) with washes and community usage respectively against susceptible Kisumu strain, compared to IG2 (10%, 11.25%). Higher mortality and BFI were induced by IG2 LLIN than OP LLIN in laboratory tunnel tests (against Kisumu strain and pyrethroid resistant Anopheles gambiae Muleba-Kis), and semi-field experimental hut trial against pyrethroid-resistant An. arabiensis. However, the difference was not statistically significant. Similarly the bursting and tensile strengths, mesh size and fabric weight of the IG2 LLIN were higher than that of the OP LLIN with a decreasing trend from unwashed, laboratory washed to community usage. In general bio efficacy and fabric strength of IG2 LLIN was higher than that of OP LLIN. National malaria control programs should consider both bio-efficacy and fabric integrity of different types LLINs prior to LLINs procurement and LLIN replacement.

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CRYOPRESERVATION AND THE OPTIMIZATION OF THE DEVELOPMENT OF WOLBACHIA IN THE CULEX PIPIENS MOSQUITO CELLS

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Wolbachia is common in insects and is an intracellular, maternally transmitted bacterium symbiont. These endosymbiotic bacteria can be mutualistic by, for example, enhancing their host's nutrition and modifying immune responses to improve survival rates. Wolbachia can also act as a parasite by taking resources from their host to boost survival or by influencing host reproduction to increase their potential to proliferate in the host population. Wolbachia has recently been utilized to sterilize male mosquitoes for population control, but little is known about how it interacts with certain traits like diapause. An essential biotechnological tool for both fundamental and practical research is the insect cell culture system. This work's goal was to demonstrate the usage of a Culex cell line for multiplying

Wolbachia and developing a cryopreservation process to increase the number of Wolbachia to be utilized for diapause research and storing for prolonged use.

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HOST-FEEDING PREFERENCES AND TEMPERATURE SHAPE THE DYNAMICS OF WEST NILE VIRUS: A MATHEMATICAL MODEL ENDEAVOR

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West Nile virus (WNV) is the leading cause of mosquito-borne disease in the United States. It is most commonly spread to people by the bite of an infected mosquito. The impact of WNV on human health is widely predicted to increase in coming years as the temperature warms, since mosquito biology and disease ecology are strongly linked to environmental conditions. However, direct evidence linking these changes to the traits of mosquito and the ecological mechanisms that may underpin such changes are poorly understood topics. Transmission of WNV within the host community primarily is predicted by the relative abilities of the host to maintain and disseminate the virus and different eco-environmental factors. Related to that ability, there is an increase of evidence that shows strong preferences by mosquitoes for certain host species can dictate the dynamics of WNV and potentially govern the spill-over into mammals, such as humans, horses, and dogs. We have developed a mechanistic transmission model for WNV in one vector species (Culex pipiens) and preferred avian hosts based weather driven mosquito traits. Sensitivity analysis has revealed that feeding preference is one of the most influential parameters on intensity and timing of peak WNV infection. Our studies show that heterogeneous contact rates induced by host preference are a key factor in the WNV epizootics in multi-species host communities.

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CHARACTERIZATION OF ANOPHELINE SWARMS DURING THE DRY SEASON ALONG THE NIGER RIVER, MALI

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Previous studies in Mali have implicated riverbeds as malaria hotspots during the prolonged dry season. These Anopheline populations found on riverbeds sustain malaria transmission throughout the dry season. They also serve as inoculums for both the transmission and the spread of insecticide resistance in surrounding areas at the onset of the rainy season. Mosquito swarm physical destruction is an alternative control intervention to reduce insecticide-resistant vector population density. This study aims to characterize the swarming behavior of Anopheline populations during the dry season. This is in the prelude to their physical destruction as a control intervention along the Niger River in Mali. We conducted an active search for Anopheline swarms, starting 30 minutes before sunset during 3 successive days in and around each fishing hamlet located along the Niger River. For each detected swarm, the following characteristics were recorded: type of marker, height, size, and coordinates of the markers. In the fishing hamlets along the river, there were 84 swarming places. The main type of swarm markers was related to anthropogenic activities and included bundles of wood for cooking (30.8%), bare ground (29.1%), piles of garbage (12.8%), walls (12.8%), latrines (5.1%), and brick (4.3%). The mean number of Anopheles specimens per swarm was 31.5 (Min = 5; Max = 120). Most of the swarms were located outside human settlements. The mean height of swarming was 2.0 meters (Min = 1m, Max = 3.5m) above the ground. This study showed that most of the swarming markers were created by anthropogenic activities and were located outside of human dwellings making them easily accessible for destruction.

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PREVALENCE OF BORRELIA BURGDORFERI SENSU LATO-INFECTED IXODES SCAPULARIS TICKS IN THE UNITED STATES AND CANADA: A COMPREHENSIVE REVIEW

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Increasing densities and geographic expansion of Ixodes scapularis, the primary vector of Borrelia burgdorferi sensu lato (Bbsl), poses new risks for Lyme disease (LD). The objective of this review was to summarize tick surveillance data reported in high LD endemic areas in the US and Canada with a focus on the prevalence of Bbsl-infection in I. scapularis ticks. We conducted a literature search in PubMed from 2006 to 2023 to identify studies reporting on Bbsl-infection prevalence in questing I. scapularis ticks. Data were excluded if they were from low endemic regions (western and southern US, and western Canada), larvae, non-I. scapularis species, and studies collecting less than 50 ticks. Bbsl-infection prevalence was calculated as the number of ticks infected divided by the number of ticks tested. Descriptive analyses were performed to estimate the prevalence of Bbsl-infected I. scapularis ticks, stratified by country, surveillance type, tick life stage, and region. Of 3169 articles identified, 76 met inclusion criteria. A total of 239,161 ticks (n=156,107 in US; n=83,054 in Canada) collected between 1998-2019 were included in the analyses from 81 datasets (US=48; Canada=33). Overall, the mean prevalence of Bb-infected questing ticks was higher in the US than Canada (25.4% vs 22.3%; p<0.0001). Comparing regions and tick life stages, the mean prevalence of Bbsl-infected questing nymphs (21.1%) and adults (50.2%) in the US Northeast were significantly higher compared to those in the US Midwest (nymphs=17.7%; adults=34.7%) or Canada (nymphs=10.7%; adults=32.0%) (nymphs p=0.013; adults p=0.001). Increasing trends in the prevalence of Bbsl-infected questing ticks were observed from longitudinal data in both countries. Overall, the data reveal that the prevalence of Bbsl-infected I. scapularis ticks is high throughout high-endemic LD areas in the US and Canada. Regular assessment of densities of Bbsl-infected ticks in these areas is useful to understand the changing trends of tick infection prevalence and increasing LD incidence.

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THE POSSIBLE MICROBIAL ETIOLOGY OF ALZHEIMER'S DISEASE AND RELATED DEMENTIA

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Neurocognitive disorders are sporadic, age-related, and hereditary conditions that can lead to multiple outcomes such as progressive cognitive impairment, psychiatric and behavioral disorders, and declines in daily life functions. Observational, epidemiological, experimental, and pathological studies have generated evidence for the possible polymicrobial causality in dementia-inducing diseases. The microbial hypothesis states that pathogens and microbes act as triggers, interacting with genetic factors to initiate the accumulation of beta-amyloid plaques, hyperphosphorylated tau protein, immunosuppression, and inflammation in the brain. Evidence indicates that Borrelia spp., HSV-1, treponemal spp., Chlamydophila pneumoniae, Candida albicans, and others can lead to cytokine dysregulation, alterations in brain biochemistry and neurotransmission, neuronal degeneration, and neural death. These effects, usually manifested during aging, accumulate over time and ultimately result in neurodegeneration and dementia. In the present study, we aim to

test the possibility that polymicrobial infections exist in post-mortem brain tissue samples from patients with Alzheimer's disease using overlapping molecular methods. To establish a link between neurocognitive disorders and microbial or polymicrobial infections, autopsy samples will be examined with immunohistochemistry, highly sensitive polymerase chain reaction, and RNA in situ hybridization. The aforementioned methods were used to successfully detect Borrelia burgdorferi, Bartonella henselae, Treponema denticola, and Candida albicans in neural tissue. These findings further indicate that microbes should be considered in the etiology of neurocognitive disease. Though the etiopathogenesis of Alzheimer's disease remains controversial, this study seeks to better elucidate the multifactorial neuropathology associated with dementia-inducing disorders as well as provide compelling evidence for the existence of persistent infection in brain tissue.

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EXAMINING THE ROLE OF NYMPHAL IXODES IN THE TRANSMISSION OF BORRELIA BURGDORFERI TO DOGS

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In the United States, Lyme disease (LD) is the most commonly reported vector-borne disease among humans. LD is caused by Borrelia burgdorferi which is transmitted to mammals through the bite of infected Ixodes ticks. Nymphal Ixodes, which quest in late spring and early summer, are responsible for the majority of transmission to humans; adult ticks are responsible for a subtler peak of cases in the fall. B. burgdorferi seroprevalence among dogs has been used to estimate LD risk among humans; however, past research has suggested that dogs are less susceptible to infection from nymphal Ixodes, possibly indicating a different host preference between dogs and humans for these different life stages. To evaluate this, we reviewed LD serology results from serially tested dogs over a 9-month period to better understand timing of seroconversion and frequency of transmission by Ixodes nymphs versus adults ticks to canine hosts. In 2016, blood was collected from 215 dogs at 3 timepoints (February, August, and November). In February, blood was tested by SNAP 4Dx Plus Test and Borrelia burgdorferi C6 ELISA. Testing was limited to C6 ELISA for later timepoints. Dogs were considered serologically positive for LD if they were positive by SNAP 4Dx Plus Test or Borrelia burgdorferi C6 ELISA. Of 161 dogs serologically negative for B. burgdorferi in February, 4 seroconverted by August. All 4 dogs resided in the East region. Of 146 dogs that were serologically negative in August, 15 seroconverted by November; dogs resided in the East (10), Mid-west (3), South (1) and West (1) regions. Although the majority of canine incident cases as indicated via seroconversion occurred during adult tick season, results indicate that four dogs became infected prior to adult tick season. Future studies may be warranted to better understand the role of nymphal Ixodes ticks and B. burgdorferi transmission in dogs. Nymphal transmission of B. burgdorferi to dogs has important implications for dog-owners, veterinarians and researchers studying LD among dogs, especially in circumstances where dogs are used as proxies for human risk.

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MULTI-DRUG THERAPY IS REQUIRED TO EFFECTIVELY TREAT BARTONELLA INFECTION IN DIFFERENT ENVIRONMENTS

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Bartonella is a gram negative, facultative intracellular bacterium that manifests as different clinical syndromes collectively known as bartonellosis. The well-known diseases caused by these bacteria are cat scratch disease (B. henselae), trench fever (B. quintana) and Carrion's disease (B. bacilliformis). Excluding B. bacilliformis, which is evolutionarily more distinct than the 30+ other species, Bartonella infections result in self-limiting disease that is often undiagnosed and untreated. However, individuals with compromised immune systems may experience clinical manifestations, which can become life threatening and need to be treated with effective antibiotics. To date, there is no standard treatment course for these infections and many doctors prescribe antibiotics based on limited case studies. It has been shown that Bartonella can grow extracellularly, intracellularly, and in biofilms. To determine an effective antibiotic strategy, it is important to understand Bartonella susceptibility in each of these growth conditions. We hypothesize that combination antibiotic treatments are required to effectively eliminate B. quintana and B. henselae growth, particularly in biofilm and intracellular environments. In previous studies, B. henselae treatment with single antibiotics in different media, as well as in DH82 canine macrophages, was ineffective in preventing growth. We plan to expand this work with different antibiotics supported by case reports, as well as double and triple combination therapy in erythrocytes and biofilms. Antibiotics tested were the following: doxycycline, gentamicin, azithromycin, azlocillin, rifampin, and clarithromycin. The effectiveness of combination therapy supports the notion that Bartonella species utilize target cells and biofilms as an antibiotic evasion strategy in the treatment of bartonellosis.

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DIVERSITY AND DNA BARCODING OF IXODIDAE AND ARGASIDAE TICKS IN THE US-MEXICO BORDER REGION OF THE MUNICIPALITY OF JUAREZ, CHIHUAHUA

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Ticks are the most important arachnids for human and animal health because they are vectors of a plethora of disease-causal agents, including bacteria and arboviruses. In the border municipality of Juarez, Chihuahua, severe cases of human rickettsiosis and a high prevalence of bacteria transmitted by ticks in domestic animals have been reported in recent years. Inadequate morphological identification due to similarity between morphospecies or identification of juvenile stages is a common problem of the prevention and control programs. As a result, DNA barcode technology is a reliable support tool for completing the morphological identification of ticks at the border between Mexico and the United States. This study reports the diversity and DNA barcode of Ixodidae (hard) and Argasidae (soft) ticks collected between 2018-2022 along this Mexican border municipality. Based on morphology and confirmed species identity using DNA barcoding, 3245 ticks belonging to four species were collected along Juarez municipality in Chihuahua, state. Ticks were identified as Rhipicephalus sanguineus, Dermacentor albipictus, Otobius megnini, and Argas persicus. A Bayesian analysis was constructed with a sample of 65 Cytochrome Oxidase subunit I mitochondrial sequences of the ticks collected. The topology of Bayesian tree displayed tree groups of R. sanguineus, whereas the clades of other species were well-defined. The Markov model of nucleotide substitution for distance estimation show a mean (±SE) of 18 (±1.0) %. The intraspecific distance ranged between 0 to 0.02 %, whereas the interspecific distance was reached 11.9 to 29.5 %. Dogs were the major host of Rh. sanguineus, whereas O. megnini were predominant mostly on cows and horses. A. persicus were collected on soil, and D. albipictus were collected only on one deer. Finally, the public health importance of these species from the perspective of the public health of transboundary United States-Mexico region is also discussed.

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KNOWLEDGE, ATTITUDES, AND PRACTICES OF PARA-VETS ABOUT TICKS AND TICK-BORNE DISEASES IN PAKISTAN

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Recent global changes have accelerated the spread of ticks and tick-borne diseases, affecting animals and humans. According to a livestock survey in Pakistan, there are 41.2 million buffaloes, 49.6 million cattle, 78.2 million goats, and 30.9 million sheep. Among this massive population of ruminants, a tick infestation prevalence of 34.83% (buffalo), 57.11% (cattle), 51.97% (sheep), and 46.94% (goats) has been reported. Most livestock farmers rely on para-veterinary workers (whose training level resembles veterinary technicians in the US but can vary in quality and depth) for assistance with any animal health problem. However, little is known about the knowledge and practices of these para-veterinary workers regarding tick control and management. The objective of this study is to fill this gap using an epidemiological survey that can evaluate their knowledge and practices regarding tick-borne diseases in different regions of Pakistan. We designed a web-based knowledge, attitudes, and practices survey about ticks and tick-borne diseases. We will disseminate the questionnaire between March 2023 and June 2023 among para-veterinary workers of Pakistan to assess their awareness and response toward tick-borne disease management in animals. We will then analyze the survey to identify areas of low knowledge or ineffective practice in smallholder livestock settings. The survey has been designed and approved for dissemination, but most recruitment will be centered in May. We will use the results of this survey to design outreach and education materials for para-veterinary workers to improve their understanding and practices for managing and controlling tick-borne diseases.

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BODY LICE PATHOGEN SURVEILLANCE AMONG INDIVIDUALS EXPERIENCING HOMELESSNESS IN WINNIPEG, CANADA 2020-2021

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In 2020, Canada's largest cluster of Bartonella quintana endocarditis was described among individuals experiencing homelessness in Winnipeg, Canada. The aim of this study was to analyze ectoparasites collected from individuals experiencing homelessness in Winnipeg to confirm vector species and identify B. quintana and other pathogens. This study, Canada's first on body lice, correlates B. quintana gene cycle threshold (Ct) with louse instar and sex. Ectoparasites were collected among consenting adults seeking medical care in Winnipeg. Ectoparasites were collected from discarded infested clothing and separated into pools based on instar and sex. Ectoparasite pools were decontaminated and homogenized. DNA was extracted. Vector species, louse ecotype and pathogens were identified using real-time PCR. Louse species and ecotype were identified using the louse mitochondrial cytochrome b (cytB) and Phum_PHUM540560 genes, respectively. Pathogens were identified using the following targets: ITS3 (B. genus), yopP and fabB (B. quintana), ompB (Rickettsia prowazekii) and IS1111a (Coxiella burnetii). 7 individuals submitted ectoparasites. All ectoparasites were confirmed to be Pediculus humanus corporis using real-time PCR. Lice from one individual (14%) demonstrated B. quintana positivity: ITS3, yopP and fabB. Lice from all individuals were negative for R. prowazekii and C. burnetii. Average B. quintana Ct (combined average of ITS3, YopP and FabB) decreased from 1st and 2nd instar pools to 3rd instar pools by 6.5. Average B. quintana Ct decreased from 3rd instar pools to 4th instar pools by 1.2. Pools from female adult louse pools demonstrated lower Ct values than male pools. A minority of body lice collected from individuals experiencing homelessness in Winnipeg demonstrated molecular positivity for B. quintana. Body lice in Winnipeg do not appear be significant vectors for R. prowazekii or C. burnettii. Ct on B. quintana genes decreases with each advancing instar. Manitoban individuals with pediculosis should be evaluated for B. quintana infection.

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TICK AND TICK-BORNE DISEASE KNOWLEDGE ACROSS FRONTLINE GROUPS: A KNOWLEDGE, ATTITUDES, AND PRACTICES META-COMPARISON

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Prevention of tick bites and tick-borne diseases (TBDs) is reliant on individual-level protection measures, such as use of repellants and frequent tick checks in high-risk areas. However, these require knowledge of local spatiotemporal risk, awareness of basic prevention measures, and concern sufficient to implement protection measures. Since 2018, we have conducted Knowledge, Attitudes, and Practices surveys within multiple populations for which ticks and TBDs are a concern in the state of Illinois, USA. These populations include employees of local public health departments (n=42), veterinary professionals (n=72), and medical professionals (n=346). We will compare knowledge scores, subscores and TBD concern levels among these different populations, and compare their responses to existing tick presence and abundance and TBD prevalence data at the county and regional level. For instance, medical professionals had a higher median tick knowledge score (69%) than veterinarians (59%) or public health officials (52%), but veterinarians had a higher median disease score (47%) than the other two groups (30%). These scores varied significantly by time since last training for both veterinarians and medical professionals. These findings can serve as the basis of a One Health approach to tick prevention outreach and training for those at the front lines of TBD prevention.

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IDENTIFICATION OF PULEX IRRITANS VERTEBRATE HOSTS IN PLAGUE-ENDEMIC AREAS OF MADAGASCAR USING MULTIPLEX POLYMERASE CHAIN REACTION

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Plague is a zoonotic disease, transmitted to humans by flea bites infected with the Yersinia pestis bacterium. The plague transmission cycle is complex and can involve several mammal hosts with various susceptibilities to the disease, including humans. Fleas acquire the infection while feeding on the septicemic host and transmit it upon the next feeding. Thus, host specificity and preference determine the flea's role in pathogen transmission, for the host blood can affect the flea's ability to transmit Y. pestis. Pulex irritans, the "human flea," is one of the probable vectors in Madagascar where plague is endemic. Previous investigations demonstrated that P. irritans is the most abundant species in households and it has been found infected with Y. pestis during epidemics. Identifying P. irritans host blood source will give a new insight into better understanding the plague transmission cycle in Madagascar. Here we report the preliminary results from a study aiming to identify the host blood source of P. irritans collected from households in a plague-endemic area of Madagascar. The DNA of individual blood-engorged P. irritans was extracted and amplified using conventional multiplex PCR, with a primer set that can amplify DNA from humans, birds, and non-human mammals DNA. The amplified DNA was visualized using gel electrophoresis to identify which P. irritans samples were positive for the three types of hosts. Our results showed that from 376 individual P. irritans, 79.25% fed on human hosts, 6% fed on avian hosts, and 1% fed on

non-human mammal hosts. All avian DNA-positive samples were positive with human DNA, and all non-human mammal-positive samples were positive with human and avian DNA. We could not detect host DNA from the remaining 20.75% of the fleas. We demonstrated that although this flea species is mostly anthropophilic, it can also feed on other hosts such as birds and mammals in Madagascar. Our finding raises concern about plague transmission, especially if P. irritans would take a blood meal from rodents, the main reservoir of plague in Madagascar. Our next step will be to identify the species involved for each non-human host.

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SPATIAL DISTRIBUTION AND MOLECULAR DETECTION OF RICKETTSIA SPP. IN RAT FLEAS IN MADAGASCAR

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Rickettsioses are infectious diseases caused by bacteria of the genus Rickettsia and are mainly transmitted by arthropod vectors. Most of them are transmitted by ticks but R. typhi (murine typhus) and R. felis (flea-borne spotted fever) are transmitted by fleas and can cause severe illness and death. The aim of this study was to detect Rickettsia spp. from the fleas infesting small mammals in areas with different bioclimatic in Madagascar. The study was conducted in 28 districts across Madagascar. Urban and rural areas are randomly chosen for each district and small mammal traps were set across different habitats including house, vegetation, field, market and abattoir. Fleas were collected from small mammals and identified. The presence of Rickettsia spp. was assessed by qPCR specific for R. typhi and R. felis. A total of 3694 fleas belonging to Xenopsylla cheopis (97.0%) and an endemic flea Synopsyllus fonquerniei (3.0%) were collected from 2046 small mammals captured from 56 localities. Rattus rattus represented 71.3% of the total animals captured and R. norvegicus had high flea infestation of X. cheopis (61.2%). In this study, 1323 oriental fleas X. cheopis and 100 endemic fleas S. fonquerniei were randomly tested. Rickettsia spp. was identified in 16,4% of X. cheopis (217/1323) and 5% of S. fonquerniei (5/100). For Rickettsia species, 5.6% and 3.9% of X. cheopis were positive for R. typhi and R. felis respectively. For the endemic flea S. fonquerniei, 4% were positif for R. felis and none for R. typhi. Coinfection was found in 2 small mammals. Sixteen districts of the 28 were found infested with Rickettsia spp.. Infected fleas were found in all habitats mainly inside houses and in market place and the prevalence was higher in urban areas. Although no clinical case has been described in Madagascar, R. typhi was detected in naturally infected fleas from rats in Madagascar. The geographic distribution of the pathogen emphasizes the potential risk of flea-transmitted infections and the risk is high when animal carries many fleas. Investigations are needed to further understand the ecology of Rickettsia in fleas and their implications for human health.

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STATUS EPILEPTICUS AND MULTIORGAN INJURY IN A PATIENT WITH MURINE TYPHUS

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A 40 year old man with a history of epilepsy, well controlled on valproic acid for over a decade, presented with 2 weeks of fevers, headaches, and cough. Initial lab results showed leukocytosis, thrombocytopenia, and elevated transaminase, alkaline phosphatase, and creatinine levels. The patient developed generalized tonic-clonic seizures in the emergency room that progressed to status epilepticus, necessitating intubation and mechanical ventilation. A lumbar puncture (LP) was performed, showing an elevated opening pressure, a decreased cerebrospinal fluid (CSF) glucose level, elevated CSF protein, and an elevated CSF pleocytosis with neutrophil predominance. CSF cytologic exam showed plasma cells and plasmacytoid lymphocytes. MRI brain and CT chest returned unremarkable. CT abdomen showed hepatosplenomegaly and wall thickening of the distal ileum and ascending colon. The patient initially received vancomycin, ceftriaxone, doxycycline, acyclovir, and antiepileptic drugs. Rickettsia typhi IgM and IgG titers both returned elevated at 1:1024. Therapy was narrowed to doxycycline, and fevers and seizures resolved. A repeat LP showed improved opening pressure and cell counts, and after extubation, the patient was alert and oriented with a persistent headache but no focal neurologic deficits. He reported two dogs and one cat at home (not on flea prevention). He also had traveled to Panama and Colombia 4 weeks prior to symptom onset and spent time outdoors without insect repellant. Flea-borne typhus (FBT), caused by Rickettsia typhi, can often cause a headache as a primary symptom but encephalitis and status epilepticus are rare presentations. Our patient, fortunately, made a full recovery, but the complications of FBT encephalitis can be devastating, with one study showing mortality or neurologic sequelae at 27%. Case numbers of FBT and geographic ranges in Texas and California are expanding, so it is increasingly urgent to study rare presentations of this infection and recognize them promptly to reduce morbidity and mortality.

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MOLECULAR DETECTION, CYTOLOGICAL CHARACTERIZATION, AND GENETIC HETEROGENEITY OF 16S RDNA OF HEMOTROPIC MYCOPLASMAS IN POPULATIONS OF SMALL MAMMALS IN TWO STATES OF BRAZIL

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Hemotropic mycoplasmas are pleomorphic, non-cultivable bacteria attached to the red blood cell surface. They have been detected in human patients with immunodeficiency conditions or co-infected with other infectious agents. New species and genotypes have been described in wild animals. This study aimed to perform molecular detection, cytological characterization, and genetic heterogeneity of 16S rDNA of hemotropic mycoplasmas in small mammals from Rio de Janeiro and Parana, Brazil. A total of 258 small mammals were captured. The cytological analysis was performed using a blood smear stained with Giemsa solution. Molecular detection of agents from the Family Mycoplasmataceae was based on the 16S rRNA gene. The products amplified in the polymerase chain reaction (PCR) were selected and purified for subsequent sequencing and construction of the phylogenetic tree. There were 11 Mycoplasma spp. of small wild mammals from this study. They were joined to another 32 sequences, with Mycoplasmoides fastidiosum as an outgroup, in a dataset of 1050 positions. Among the 258 samples of small wild mammals analyzed, 23.2% (n=60) presented structures compatible with Mycoplasma sp. in erythrocytes. 33.7% (n=87) samples amplified Mycoplasma sp. in conventional PCR. The region with the highest frequency of positivity was Cruz Machado (46.15%, n = 24/52), followed by Ponta Grossa (43.10%, n=25/58), Nova Friburgo (30.56%, n= 33/108), and Lidianopolis (12.50%, n=5/40). Oligoryzomys had the highest percentage of positivity (78.05%), statistically differing from Oxymycterus spp. (42.11%), Akodon spp. (27.59%) and Sooretamys (9.09%). Males were more frequently parasitized with Mycoplasma spp. than females ($p<0.001$). Regarding the phylogenetic analysis, Mycoplasma spp. from this study grouped together with Oligoryzomys nigripes from São Paulo and Minas Gerais, forming a clade with these sequences. This study revealed the morphological, eco-epidemiological, and phylogenetic aspects of Mycoplasma spp. in small non-flying wild mammals in regions of the states of Parana and Rio de Janeiro, Brazil.

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VIRAL AND BACTERIAL SEQUENCING OF FEBRILE PATIENT PLASMA REVEALS HIGH PREVALENCE OF TICK-BORNE BACTERIAL PATHOGENS IN THIÈS, SENEGAL

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While the incidence of malaria infection in Senegal has decreased rapidly in recent years, febrile disease continues to be a major cause of morbidity and mortality. In order to better understand causes of non-malarial febrile illness (NMFI) in Thiès, Senegal, we collected plasma samples and clinical metadata from febrile patients (n = 563) and healthy controls (n = 500) across both dry and rainy seasons from 2018-2019. We optimized amplicon sequencing of the 16S rRNA V1-2 region to screen for bacterial pathogens and unbiased RNA sequencing to screen for viral pathogens. Unbiased RNA sequencing detected Dengue virus, Hepatitis B virus, and Parvovirus B 19 infections in our cohort. 16S sequencing revealed a high prevalence of Borrelia spp. and Rickettsia spp. in febrile patients, but not in controls. As compared to qPCR, 16S sequencing was sensitive and specific for detection of bacterial infections. Patients infected with Borrelia spp. experienced a range of symptoms, many of which overlapped with common symptoms of malaria, and had a unique immune response, characterized by decreased lymphocyte count and increased granulocyte count. These data demonstrate that 16S sequencing is a useful tool for detecting bacterial pathogens across a large number of plasma samples and could be employed for future surveillance. Further, the results indicate that arthropod-borne bacterial pathogens are a significant contributor to NMFI in Senegal, suggesting the need for improved diagnostics, increased access to treatment, and vector control efforts in the region.

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SPOTLIGHT REPORT: HISTORIC TICK SURVEILLANCE OF SIERRA LEONE

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Using a systematic review, the goal of this study was to better characterize the distribution of ticks and the microbial species they carry within Sierra Leone. Nineteen search terms, and their corresponding MeSH terms, were used to compile scientific literature from the PubMed, Scopus, and WOS search engines published between 1901–2022, resulting in an initial capture of 109 articles. These results were screened for relevance according to title and abstract, after which only six articles met the final inclusion criteria. Two additional articles were captured from searches of the reference sections of included articles as well as from the search results of another West African country, for a total of eight articles selected for data extraction. Information captured during the data extraction process included tick species, collection locality, collection host, and pathogen detections. A total of seven genera of ticks were reported from the articles, including Amblyomma (5 species/subspecies), Dermacentor (1), Haemaphysalis (4), Hyalomma (1), Ixodes (2), Ornithodoros (1), and Rhipicephalus (9). Most ticks were collected feeding on host animals, of which 66.2% (51/77) were collected from domestic animals. Wildlife hosts included African buffalo, ball pythons, bush elephants, chimpanzee, duikers, pangolins, and mongoose. Of note, no pathogen testing was conducted in any of the ticks collected in these studies. These results identify major gaps in tick surveillance information within Sierra Leone, with much more tick surveying needed from the environment and wildlife. Findings from this study emphasize the need for future studies to assess the prevalence of tick-borne pathogens within the tick populations of Sierra Leone.

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SARS-CO-V2 INFECTION AND RISK FACTORS AMONG HEALTH WORKERS IN BAMAKO, MALI: A LONGITUDINAL STUDY

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Health workers (HW) on the front lines of the COVID-19 pandemic control are at high risk of SARS-Co-V2 infection and could contribute to its spread at the community level. This study aimed to estimate the prevalence of SARS-Co-V2 infection and associated factors among HWs to strengthen the prevention measures. A longitudinal study was conducted from November 2021 to February 2023 in six health districts and two university hospitals of Bamako, the capital city of Mali and epicenter of the pandemic. Sociodemographic characteristics, clinical data and nasopharyngeal swabs were collected during four rounds. RT-PCR was used to determine SARS CoV 2 infection. Mixed-effects Cox regression models were used to estimate the risk of SARS CoV 2 infection with a threshold at 5%. A total of 1098 participants were enrolled with 63.5% female and 36.5% male. The nurses (34.7%) and administrative staff (20.5%) were common. Over the study period, 9.8% of participants declared to have had a contact with COVID 19 patients and 20.7% with the COVID-19 samples. The prevalence of SARS-Co-V2 infection was 3.4%, 0%, 1.3% and 5.1% in Round 1, Round 2, Round 3 and Round 4, respectively. Chronic diseases (AOR=2.08, 95%CI [1.20 3.61]), contacts with COVID-19 samples (AOR=1.72, 95%CI [1.10 2.68]) or with COVID 19 patients (AOR=2,95%CI [1.16 3.44]), and participation to indoor events with more than 10 people (AOR=1.66, 95%CI [1.02 2.70]), were associated with higher risk to develop COVID 19 symptoms. COVID-19 vaccines seem to reduce confirmed cases, but the change was not statistically significant (AOR=0.68, 95%CI [0.28 1.68]). In conclusion, the study showed a high prevalence of SARS CoV 2 infection during Rounds 1 (at inclusion) and 4 and identified some factors associated to COVID 19. No protective effect of COVID-19 vaccines was observed. Further studies are needed to assess the effectiveness of COVID 19 vaccines and how to strengthen COVID 19 prevention measures in Mali.

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IMMUNE CROSSED REACTIVITY BETWEEN SARS-CO-V2 AND PLASMODIUM FALCIPARUM ANTIGENS IN SERA FROM COVID-19 PATIENTS AND PRE-COVID-19 DONORS IN MALI WEST AFRICA

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While Western countries suffered severely of the COVID-19 pandemic, Sub-Saharan Africa countries registered low cases of the disease. In malaria endemic areas, cross-immunity betweenSARS-CoV-2 and Plasmodium is thought to exist. In 2022, we reported a significant cross-reactionof three SARS-CoV-2 proteins to pre-COVID-19 sera (asymptomatic malaria) including Spike(21.9%), RBD (6.7%), and peptide RBM (8.8%) proteins. Here, we have determined the cross-reactivity between the three SARS-CoV-2 proteins (Spike, RBD, RBM) and P. falciparum bloodstages antigens (Pf27 and LR253) in sera from COVID-19 patients and pre-COVID-19 volunteersin Mali. COVID-19 samples were collected in 2020 amongst

COVID-19 patients (n = 188) at the Dermatology Hospital of Bamako. Pre-COVID-19 sera from Nioro du Sahel (clinical malariacases, n = 51) and Dangassa (asymptomatic and healthy donors, n = 157), were collected in 2013and 2018, respectively, before the onset of COVID-19 in Mali. Samples were tested using ELISAassay to assess IgG antibodies level against each antigen. Overall, seroprevalence was higher inclinical malaria samples compared to COVID-19 samples for Spike (65.9% vs 53.19%, p = 0.01),RBD (61.1% vs 23.9%, p = 0.001), RBM (29.1% vs 37.5%, p = 0.08), LR253 (71.1% vs 32.4, p =0.001), and Pf27 (38.5% vs 28.2, p = 0.03). A significant low correlation was found betweenantibodies anti-P27 and anti-Spike (r = 0.27, p = 0.002), anti-P27 and ant-RBD (r = 0.34, p =0.001), anti-P27 and RBM (r = 0.26, p = 0.001) in pre-COVID-19 samples. The highseroprevalence of antibodies against SARS-CoV-2 proteins in malaria endemic areas may suggestcross-reactivity with malaria parasite and further investigation is needed to better understand therole of Plasmodium in COVID-19 spreading in these areas.

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DEVELOPMENT OF A DIAGNOSTIC IGM-ANTIBODY CAPTURE ELISA FOR DETECTION OF ANTI-CACHE VALLEY VIRUS HUMAN IGM

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Cache Valley virus (CVV) is a mosquito-borne virus in the genus Orthobunyavirus, family Peribunyaviridae that has been identified as a teratogen in ruminants causing fetal death and severe malformations during epizootics in the United States. CVV has recently emerged as a potential viral pathogen causing severe disease in humans. Limited information exists on its potential as a human teratogen. The only serological diagnostic assay available to detect recent CVV infections is the plaque reduction neutralization test (PRNT) which requires the use of live virus in biosafety level 2 (BSL-2) biocontainment. In order to expand human serological diagnostic capacity for CVV we have developed an immunoglobulin M (IgM)-antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) for detection of anti-CVV human IgM in diagnostic specimens. In conjunction, a HEK-293 cell line constitutively expressing a human-murine chimeric antibody with the variable regions of murine monoclonal antibody (MAb) CVV17 and the constant regions of the human IgM was developed to overcome the lack of human positive sera used as controls in the assay. The new cell line produced antibody with higher reactivity (≥3-fold) in the assay compared to a human serum sample positive for anti-CVV IgM. Previously collected human diagnostic specimens from the United States and Mexico from patients with acute febrile illness with no known etiologic agent will be tested in MAC-ELISA and PRNT to determine the utility of the assay in CVV-serodiagnostics. These results will be summarized and discussed.

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USING REGIONAL SERO-EPIDEMIOLOGY SARS-COV-2 ANTI-S ANTIBODIES IN THE DOMINICAN REPUBLIC TO INFORM TARGETED PUBLIC HEALTH RESPONSE

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Higher incidence of COVID-19 has been associated with sociodemographic factors such as living in an urban setting, high population density, and household crowding. In this study, we investigated variations in SARS-CoV-2 seroprevalence at regional and cluster levels in the Dominican Republic (DR) and assessed potential sociodemographic factors influencing the geographical distribution of COVID-19 at the regional level. Data were collected in a three-stage cross-sectional national serosurvey conducted in the DR from June to October 2021. Seroprevalence of antibodies against the SARS-CoV-2 spike protein (anti-S) was estimated and adjusted for selection probability, age, and sex. Multilevel logistic regression was used to estimate the effect of covariates on seropositivity for anti-S and correlates of 80% protection against symptomatic infection (PT80) for ancestral and Delta strains. A total of 6,683 participants from 134 clusters in all 10 administrative regions of the DR were enrolled in the survey. The adjusted anti-S prevalence ranged from 80.5% (95%CI 78.1-82.9) to 89.8% (95%CI 88.8-93.8) between regions, and from 25.7% (95%CI 24.3-27.1) to 100% (95%CI 91.2-100.0) between clusters. At the national level, Enriquillo and El Valle had the highest odds ratios (OR) for anti-S positivity (OR of 1.86 for both with 95%CI 1.24-2.80 and 1.14-3.10, respectively). Also, receiving three doses of COVID-19 vaccine was associated with anti-S positivity (OR of 121.56, 95%CI 16.85-876.60), PT80 for ancestral (OR of 15.76, 95%CI 10.12-24.26) and Delta strains (OR of 19.59, 95%CI 14.22-27.01). At the regional level, models identified that associations between covariates and outcomes varied between regions. However, vaccination was consistently associated with highest odds of seropositivity and correlates of protection in most regions. Our results can help inform more targeted regional-level public health response such as strategies to increase vaccination coverage in areas with low population immunity.

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DENGUE FEVER OUTBREAK AT THE KENYAN SOUTH COAST INVOLVING SEROTYPE 3, GENOTYPES III AND V

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Dengue fever (DF), caused by four distinct serotypes of dengue virus (DENV-1-4) is transmitted by the Aedes mosquito. There have been increasing reports of DF outbreaks in Africa, including Kenya, yet very little information is available on the virus, for instance diversity of circulating genotypes. The study aimed at characterizing DENV-3 strains from the March 2019 DF outbreak at the Kenyan south Coast. RNA was isolated from 37 human plasma samples and screened for the presence of DENV serotypes by RT-PCR. Only DENV-3 was identified. RNA from DENV-3 positive samples was used for cDNA synthesis using sequence-independent single-primer amplification (SISPA). Libraries were prepared using the NexteraXT kit, and sequenced on the Miseq. Quality filtering, sequence assembly and annotation was done using CLC Genomics v.8.5, while phylogenetic analysis was conducted in MEGA v10. A targeted sequencing approach for envelop gene was used on samples that failed to yield complete genomes. 21/37 samples tested positive for DENV-3. On sequencing, 4 samples produced complete genome (10,173 bp) and 3 had partial sequences with complete env genes (1479 bp). Partial sequences with incomplete env genes were generated from 14 samples which were re-sequenced by targeted amplification. This approach produced ten complete env genes (1439-1479 bp). Maximum likelihood analysis of the 4 complete genomes and the 17 env genes confirmed DENV-3 (GIII=15 and V=2) as the cause of the March 2019. The estimated time-to-most-common recent ancestor for the two genotypes was in 2015. Genotype III's origin was estimated to have been introduced from Pakistan. The origin of genotype V could not be ascertained due to rarity of these sequences globally, but was related to 2006 Brazilian isolate. Unlike genotype III that has been described in East and West Africa multiple times, this was the

second description of genotype V in Kenya. The generated data adds DENV-3 genome sequences to the GenBank, thus remedying the scarcity of African DENV sequences in public database. Lastly, the study will contribute to the understanding of the cyclical transmission of DENV at the Kenya coast.

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DEVELOPMENT OF A DNA HYBRIDIZATION PROBE-BASED SURVEILLANCE ASSAY FOR DETECTION OF ARBOVIRUSES IN ARTHROPOD POOLS

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Vector-borne pathogens continue to burden public health, thus advanced detection and surveillance methods are needed. Sensitivity and specificity constraints have limited development of multi-pathogen detection assays. Metagenomic sequencing has been used for microbial detection, but often lacks sensitivity for detection of low-abundance nucleic acid species. Here we present Comprehensive Molecular Entomological Surveillance (CMES)-viral, a method for enhanced detection of nucleic acids through probe-based enrichment. DNA hybridization probes were designed to cover full genomes and account for genetic diversity of 24 arboviruses of concern in CONUS. We developed a method for next generation sequencing detection of low quantity viral nucleic acids from arthropod pools. We optimized library preparation protocols and probe panel design using spiked arthropod pools for each target virus and assessed sensitivity compared with qRT-PCR and plaque titration. Additional efforts focused on creation of a simplified and standardized pipeline using the free and publicly available genetic data analysis platform, Galaxy. CMES-viral demonstrated higher sensitivity than viral titration and could detect viral genetic diversity. This assay demonstrates the ability to use NGS as a method of surveillance to successfully detect multiple arboviruses within vector samples in a single run. This approach supports the goal of reducing the global burden of arboviruses by providing an additional tool for comprehensive surveillance of arboviral vectors.

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COLORIMETRIC RT-LAMP ASSAY FOR DETECTION OF LA CROSSE VIRUS IN ARTHROPOD POOLS

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La Crosse virus (LACV) is the leading cause of arboviral pediatric encephalitis and is likely underdiagnosed. Due to the nonspecific symptoms early diagnosis is lacking, as are available treatments. The virus is primarily transmitted by Aedes triseriatus; though invasive container inhabiting mosquitoes, Ae. japonicus and Ae. albopictus, are also recognized vectors. Due to focal circulation of this virus, surveillance in mosquitoes is not consistently performed across the geographic range of LACV. Technical expertise and funding required for qRT-PCR testing is often not available in locales where transmission foci exist. To bridge the gap between field personnel collecting vector mosquitoes and state health departments with the capacity for qRT-PCR testing, we developed a reverse transcription loop-mediated isothermal amplification assay (RT-LAMP) for detection of LACV using a colorimetric indicator. Five sets of four primers were designed to the LACV S segment utilizing the NEB® LAMP Primer Design Tool and initial analysis in silico indicated two of the five sets to be ideal candidates. Primer sets were assessed for sensitivity and specificity in comparison to qRT-PCR utilizing multiple LACV strains and other orthobunyavirids spiked into mosquito pools. In summary, we developed a sensitive colorimetric assay that requires minimal technical experience or advanced machinery and can be easily deployed in local settings for arthropod surveillance of LACV. By making surveillance more accessible, these transferable assays have the potential to improve early recognition of circulating LACV and improve human health outcomes.

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HIGH TRANSMISSION OF ENDEMIC HUMAN CORONAVIRUSES DURING THE COVID-19 PANDEMIC IN ADOLESCENTS IN CEBU, PHILIPPINES

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SARS-CoV-2, the causative agent of COVID-19, is a betacoronavirus closely related to human endemic coronaviruses (hCoVs) OC43 and HKU1 and more distantly related to alphacoronaviruses 229E and NL63. For other pandemic respiratory pathogens, the emergence of novel subtypes leads to the extinction of others; it is unknown whether the same phenomenon may occur for hCoVs. We evaluated if pre-pandemic hCoV immunity affected the risk of contracting SARS-CoV-2 and whether SARS-CoV-2 infection affected the transmission of hCoVs among adolescents in the Philippines participating in a longitudinal dengue cohort study. We tested a random set of 499 out of 2035 study participants for positivity to SARS-CoV-2 receptor binding domain (RBD) by enzyme-linked immunosorbent assay (ELISA) in 2021. From this group, we randomly selected n=120 SARS-CoV-2 RBD negative and positive individuals for further study. ELISAs were used to measure binding antibodies (optical densities, OD) to RBD and spike proteins for all four hCoVs and SARS-CoV-2 for samples collected before the COVID-19 pandemic and after the spread of COVID-19 but before vaccination. We observed 79 to 91% seropositivity to the four hCoVs before the pandemic. ELISA ODs increased with age for 229E and OC43, suggesting endemic circulation, while immunity was flat across ages for HKU1 and NL63. High alphacoronavirus immunity at baseline correlated with an increased probability of SARS-CoV-2 infection, possibly indicating greater exposure to coronaviruses in general. Antibodies increased significantly to the RBDs of OC43, NL63, and 229E and spikes of all four hCoVs in both SARS-CoV-2 negative and positive adolescents. Those aged 13-15 years old in 2021 had higher antibodies to RBD and spike of OC43, NL63, and 229E than children the same age in 2019, further indicating intense transmission. Overall, we observe a limited effect of the COVID-19 pandemic or SARS-CoV-2 infection on endemic hCoV transmission. This study provides insight into the co-circulation of hCoVs as SARS-CoV-2 becomes an endemic pathogen.

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IDENTIFICATION OF IMMUNODOMINANT B AND T-CELL EPITOPES OF KYASANUR FOREST DISEASE VIRUS AND THEIR EXPRESSION FOR DEVELOPING RAPID DIAGNOSTICS AND POTENT SUBUNIT VACCINE

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The Kyasanur Forest Disease (KFD), which is also known as 'Monkey Fever' is caused by KFD Virus (KFDV) that belongs to the family Flaviviridae. KFD is a highly neglected and emerging tropical disease endemic to Western Ghat region of Karnataka, India, which is fatal with a mortality rate of 2-10%. Recently, KFD has been alarmingly spreading from its epicenter to neighboring districts and states also. The current ELISA based KFD diagnosis involves the detection of antibody in the patient's blood which is relevant only after the development of antibody following the infection and is non-specific due to cross-reactivity with other flaviviruses. Further, currently available formalin-inactivated vaccine developed in the 1970s has now been found to be less effective leading to increased disease susceptibility and

severity. To address these, the present study was aimed at identification of specific B and T-cell epitopes of KFDV immunogenic marker antigens using diverse computational tools to develop precise diagnosis and a potent subunit vaccine. Here, we have chosen E, NS1 and NS5 proteins as markers of KFDV by taking into account of their differential and non-overlapping sequences with selected arboviruses. Based on the linear and nonlinear epitope prediction tools and distinct biophysical parameters, we have identified three potential linear and ten nonlinear B-cell epitopes. Soon after the infection, NS1 protein is secreted heavily into the blood and protein E is expressed on the host cell surface. These two proteins have been expressed in bacteria and the antibody has been produced successfully in rabbit. For developing vaccine, the molecular docking and molecular dynamics simulation analysis has identified six different TH-cell epitopes based on the distribution frequency of MHC-II haplotypes in the human population and one TC-cell epitope from NS5 protein that has maximum interaction with class-I MHC. By using all these data, we are developing a precise and rapid KFD diagnostic tool and a potent subunit vaccine.

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A COHORT-BASED PILOT STUDY OF DETECTION OF LASSA VIRUS INTO THE ODONTOGENIC FIBROUS TUMOR IN KINSHASA, DEMOCRATIC REPUBLIC OF CONGO

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Lassa virus (LASV) belongs to the arenavirus genus and Arenaviridae family. It is highly pathogenic to humans, causing hemorrhagic fever. LASV has been reported to be endemic in several sub-Saharan countries where various tumors such as Odontogenic tumors (OTs) are also prevalent. A recent study has documented the presence of an arenavirus-like virus in human OT-like, odontogenic fibromyoma in a snake captive-bred red-tail boa (Boa constrictor). However, the association between OTs and LASV has not been established in humans yet. Here, we investigate the presence of LASV in tumor tissue samples from pilot cohort patients with OTs in Kinshasa. Tissue samples were collected from enrolled participants (n=29) and were tested for the detection of LASV using RT-qPCR. 83% (24/29) of analyzed tissue samples were LASV-positive. Furthermore, we found that not only the ameloblastoma was LASV positive, but also the bone close to the tumor and the oral mucosa lining the tumor This result is the first report of the presence of LASV in human OT tissues and highlights the potential contribution of LASV in the etiopathogenesis of human odontogenic tumors. Thus, deep molecular, immunological, and histological studies in the large cohorts are ongoing to characterize this cooccurrence of LASV and OTs.

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SEVERE FEVER WITH THROMBOCYTOPENIA SYNDROME VIRUS: AN UNDIAGNOSED EMERGING VIRAL INFECTION IN THAILAND

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Severe fever with thrombocytopenia syndrome virus (SFTSV) is an emerging tick-borne viral infection in China and other Asian countries. Due to its high fatality rate and its pandemic potential, SFTSV is listed among the top 10 priority infectious diseases requiring urgent research by the World Health Organization. Four cases of SFTSV were recently reported in Thailand. We performed unbiased metagenomic next generation sequencing (mNGS) coupled to viral target enrichment to identify known and novel viruses from 1,000 patients with undiagnosed, acute undifferentiated febrile illness (AUFI), hospitalized between 2014 and 2021 at Siriraj Hospital, Bangkok, Thailand. Three patients with SFTSV were detected, including a 61 -year female, 75 -year male and 77- year male with durations of illness of 7, 6 and 7 days, respectively. They presented with non-specific symptoms such as fever, myalgia, and their complete blood count (CBC) revealed marked leukopenia and thrombocytopenia. The initial diagnosis was dengue hemorrhagic fever in two individuals and sepsis with septic encephalopathy in the other who also presented with alteration of consciousness. Dengue NS1, IgM, IgG markers and antibodies against Rickettsia typhi and Orientia tsutsugamushi were not detected. All cases were treated with empirical ceftriaxone and azithromycin for 7 days. Two of them developed severe complications, including gastrointestinal bleeding, acute kidney injury and hospital acquired pneumonia. Their WBC count and platelets were normal prior to discharge. All cases of SFTSV (4 cases previously reported and 3 cases in this study) in Thailand were diagnosed between 2019 and 2020. We are conducting additional studies with AUFI specimens from as early as 2001 to determine if there has been an earlier introduction of SFTSV into Thailand. Our findings reinforce the need for rapid and accurate laboratory tests for the diagnosis of SFTVS in Thailand among febrile patients presenting with thrombocytopenia after dengue infection has been excluded.

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SPATIO TEMPORAL DYNAMICS OF MEASLES IN THE PROVINCE OF WESTERN KASAI IN DEMOCRATIC REPUBLIC OF CONGO FROM 2000 TO 2014

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Despite immunization efforts since 2000, measles remains a major public health problem in the DRC. The upsurge of outbreaks throughout the country in general and in the province of the western Kasaï especially motivated the realization of this study.To start understanding of recurrence of these outbreaks.Measles cases and deaths reported in Kasai Occidental between 2000 and 2014 were used to calculate the attack rate and develop thematic maps for possible spatial heterogeneities. The outbreaks occurred during the period were analyzed together with an assessment of measles surveillance system.A total of 33,126 cases 3.82% deaths have been reported on all that ZS Luebo, Mweka and Benaleka were more at risk. Children less than 5 years unvaccinated 65.8% were more affected and no difference in sex.The identification of the epicenter formed of the 3 ZS opens a perspective to lead the studies to the scale of health areas in order to search for the factors explaining these heterogeneities.

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CLINICAL PRESENTATION AND LABORATORY ABNORMALITIES AMONG DENGUE SEROPOSITIVE AND SERONEGATIVE FEBRILE NIGERIAN ADULTS

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Dengue is a neglected tropical disease with outbreak potentials and a low index of suspicion. We compared the clinical and laboratory abnormalities between dengue seropositive and seronegative febrile adults at the Federal Medical Centre, Owerri, South-East Nigeria. This was a cross-sectional study of 90 febrile adults aged ≥18 years recruited consecutively between 1st February and 30th September 2020. Epidemiological, clinical, and laboratory data including dengue IgM and IgG antibodies (by ELISA), dengue non-structural protein 1 (NS1) antigen by two-step chromatography, complete blood count, liver enzymes, bilirubin, and prothrombin time were

obtained. Dengue seropositivity was defined as a positive IgM, IgG, or NS1. The mean age of the participants was 39.3 ± 16.4 and 48/90 (53.3%) were females. Dengue seropositivity was observed in 65⁄90 (72.2%) participants. The pattern of positivity for dengue markers comprised IgG only (38.9%), IgM only (10%), IgG and IgM, (23.3%), and IgM and NS1 (1.1%). There was no statistically significant difference in the frequently reported symptoms/signs between dengue seropositive and seronegative febrile adults: headache (71.9% vs.28.1%), muscle pain (73.7% vs. 26.3%), nausea/vomiting (68.4% vs. 31.6%), joint pain (73.5% vs. 26.5%), fatigue (88.9% vs. 11.1%), pallor (66.7% vs. 33.3%) and abdominal tenderness (75.0% vs. 25.0%), all p>0.05. Dengue seropositive and seronegative febrile adults had comparable laboratory parameters. The proportion of seropositive adults with hematological abnormalities compared to seronegative were: anemia (66.7% vs. 33.3%), leucopenia (73.7% vs. 26.3%), and thrombocytopenia (69.6% vs. 30.4%), all p>0.05. We found a high prevalence of dengue seropositivity in this febrile population. Constitutional symptoms and laboratory investigations were comparable between dengue seropositive and seronegative participants Our findings suggest the limited value of clinical and ancillary laboratory parameters in dengue surveillance which justifies a call for improved access to dengue diagnostic assays in endemic regions.

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OROPOUCHE VIRUS AS AN EMERGING CAUSE OF ACUTE FEBRILE ILLNESS IN COLOMBIA

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Arbovirus infections are frequent causes of acute febrile illness (AFI) in tropical countries. We conducted health facility based AFI surveillance at four sites in Colombia (Cucuta, Cali, Villavicencio, Leticia) during 2019-2022. Demographic, clinical and risk factor data were collected from persons with AFI that consented to participate in the study (n=2,967). Serologic specimens were obtained and tested for multiple pathogens by RT-PCR and rapid test (Antigen/IgM), with 20.7% identified as dengue positive from combined testing. Oropouche virus (OROV) was initially detected in serum by metagenomic next generation sequencing(mNGS) and virus target capture in a patient from Cúcuta. Three additional infections from Leticia were confirmed by conventional PCR, sequenced, and isolated in tissue culture. Phylogenetic analysis determined there have been at least two independent OROV introductions into Colombia. To assess OROV spread, a RT-qPCR dual-target assay was developed which identified 87/791 (10.9%) viremic cases in AFI specimens from Cali (3/53), Cucuta (3/19), Villavicencio (38/566), and Leticia (43/153). In parallel, an automated anti-nucleocapsid antibody assay detected IgM in 27/503 (5.4%) and IgG in 92/568 (16.2%) patients screened, for which 24/68 (35.3%) of PCR positives had antibodies. Dengue was found primarily in children (<18 yr) and linked to several clinical manifestations (weakness, skin rash and petechiae), whereas Oropouche cases were associated with the location, climate phase, and odynophagia symptom. Our results confirm OROV as an emerging pathogen and recommend increased surveillance to determine its burden as a cause of AFI in Colombia.

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IMPACT OF SARS-COV-2 VARIANTS AND VIRAL LOAD DYNAMICS ON SEVERE COVID-19 AND MORTALITY IN HOSPITALIZED KENYAN ADULT PATIENTS

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While there are a plethora of studies examining factors associated with severe COVID-19 from the Global North, few studies exist for low- and medium-income countries, particularly in sub-Saharan Africa. Such studies are important in the context of differing demographics, co-morbidities, co-infections, and limited pharmaceutical (i.e., remdesivir) and non-pharmaceutical (e.g., mechanical ventilation) interventions. As such, we are conducting a prospective observational study on hospitalized COVID-19 patients (n=246, PCR-confirmed) at Siaya County Referral Hospital, Kenya (6/2020 to present): a high-burden infectious disease region (i.e., malaria, HIV&AIDS, tuberculosis, bacterial infections, etc.). Complete demographic, laboratory, and clinical variables were obtained. Viral load (VL) measurements (log10 copies/1,000 cells) were determined for upper respiratory tract (URT) and peripheral blood (PB) samples on days 0, 3, 6, and 9 (n=193 to present) using RT-qPCR with N1 and RNase P primers and probes. SARS-CoV-2 variants were determined through sequencing and temporal imputation. Disease severity was defined as: severe (SpO2≤90% and/or death), moderate (90%<SpO2≤95%/survival), and mild (95%<SpO2/survival). Mean URT VL was highest for the Omicron variant (P=1.0x10-8), while mean PB VL was highest for the Delta variant (P=1.03x10-6). AIC-based logistic-regression model selection with demographic, clinical, viral variants, and co-morbidities as covariates revealed that PB VL was the strongest predictor of external oxygen requirements (OR=1.58, P=2.16x10-3), severe disease (OR=3.33, P=4.96x10-3), and mortality (OR=1.43, P=0.032). Collectively, these results identify PB VL as the most significant factor associated with adverse outcomes. Interventions aimed at reducing/preventing the SARS-CoV-2 burden in blood, therefore, offer a viable therapeutic option for improved clinical outcomes in this population.

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DEVELOPMENT OF A FULLY AUTOMATED PCR ASSAY FOR THE DETECTION OF MPOX VIRUS

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In May of 2022 an outbreak of Clade IIb mpox Virus spread to multiple countries around the world and on July 23rd the WHO declared mpox a public health emergency of international concern due to its spreading to more than 70 non-endemic countries. Due to the rapid and global spread of the disease it became important to rapidly develop high throughput molecular diagnostic assays. Here we report the development of a Research Use Only (RUO) molecular assay (MPXV+) for the detection of mpox virus from lesion swabs and saliva. The MPXV+ assay was developed for the Abbott Molecular m2000 automated platform and employs a dual-target approach in E9L and B6R genes, with internal and external

controls to ensure expected extraction and amplification efficiency. In silico analysis of the MPXV+ oligos predicted 100% sensitivity for both mpox clades and detection of smallpox and vaccinia viruses. Exclusivity analysis at the time of writing predicted no cross-reactivity for 60 other organisms. Two commercially available mpox cultures (NR-2500 and NR-27, BEI) were serially diluted and tested in triplicate to estimate assay limits of detection in pfu/mL and TCID50/mL. Virus cultures were spiked into either UTM or a 1:1 mixture of UTM:saliva to confirm matrix inclusivity. UTM samples from lesions of 35 US CDC confirmed cases and a commercially available longitudinal mpox lesion panel (SLR) were diluted in UTM and tested to assess assay performance against known positive patient samples. Molecular detection of virus culture dilutions showed comparable performance of the MPXV+ assay in both UTM and UTM:saliva. Assay sensitivity was determined to be 1 TCID50/mL suggesting infectious levels of virus are detected. 1:50 dilutions of 35 CDC confirmed mpox lesion swab samples were detected and 1:100 dilutions of commercially sourced samples were detected with the MPXV+ assay. Here we demonstrated the development of a fully automated assay for the detection of mpox virus with sufficient sensitivity to detect infectious levels of virus and 100% concordance to CDC confirmed infections, confirming robust assay performance.

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THE ECONOMIC BURDEN OF ILLNESS OF THE GLOBALLY SPREADING CHIKUNGUNYA VIRUS (CHIKV): A SYSTEMATIC LITERATURE REVIEW

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Chikungunya is a disease caused by the arbovirus Chikungunya Virus (CHIKV), which is transmitted to humans by the mosquito species Aedes albopictus and Ae. aegypti. Over the last decades, the geographic spread of these vectors, and therefore the dissemination of CHIKV, has increased due to climate change-related factors. The clinical development of chikungunya has been shown to heavily impact the life quality of the patients, which has led to raised public health concerns. An SLR was performed to identify the evidence of the costs and resource use associated with chikungunya as the impact of the disease remains unclear. The search was conducted on the electronic databases Medline and Embase, and congress abstract repositories. Of the 1,140 records identified, 33 studies reporting outcomes from eleven world regions were included. The most reported study sites were Reunion Island, Colombia, and India. Estimated costs for chikungunya's direct and indirect effects varied greatly between studies and countries. Consultation costs, followed by hospitalization expenditures, were found to constitute the largest proportion of the total direct chikungunya costs. The frequency and duration of hospitalization also ranged significantly across studies. Indirect costs were primarily linked to absenteeism: The highest reported absenteeism rate for a CHIKV-positive population was 62.9%, with the longest median number of days patients were absent from work being 35. In conclusion, chikungunya was found to be associated with a substantial economic burden when considering the costs and frequency of inpatient and outpatient care—as well as absenteeism—for patients reporting symptoms of acute and chronic chikungunya. Moreover, misdiagnosis and mistreatment were identified as confounders to measure the economic disease burden. This highlights the need for more standardized approaches to diagnosing and treating chikungunya.

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DEVELOPMENT OF AN INTERDISCIPLINARY, MULTIAGENCY COLLABORATION TO COORDINATE LOCAL RAPID RESPONSES TO DENGUE CASE CLUSTERS IDENTIFIED AND MONITORED THROUGH UNIFIED VECTOR AND HUMAN SURVEILLANCE — PUERTO RICO, JANUARY 2021-2023

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In 2021, the Puerto Rico Dep of Health (PRDH), the Puerto Rico Vector Control Unit, and the CDC Dengue Branch established a collaborative process for identifying and mapping dengue case clusters in Puerto Rico (PR) to develop coordinated local responses aimed at interrupting transmission before an outbreak occured. This group identified clusters based on confirmed or probable dengue cases (2015 CSTE case definition) reported to PRDH or mosquito pools positive by RT-PCR for dengue virus (DENV) 1-4. We defined clusters as 3 DENV detections (including ≥1 case) with disease onset or trap collection date within 21 days and located within 500 meters. Clusters were inactivated when no new detections occurred 6 weeks after the last detection. An analysis of January 2021-2023 identified 63 clusters comprising 409 cases and 97 positive pools. Twenty-six clusters (41%) started in 2021 and 37 (59%) in 2022, with 47 (75%) beginning during June-December. The median size and duration were 5 persons or mosquito pools (IQR 3-8) and 23 days (IQR 13-62). Fifteen clusters (24%) occurred in high-density public housing. Of 78 municipalities, 15 (19%) had ≥1 cluster. As cluster frequency increased during peak months, the group reached a consensus on prioritizing clusters based on size, newly circulating serotypes, public housing, minimal reporting delay, locations with historically high cases, and high-risk neighboring communities. Interventions developed and piloted included placement of autocidal gravid ovitraps, wide-area larvicide spraying, debris clean-up, home inspections, removal of mosquito egg-laying sites, and risk messaging to local authorities. Twenty-seven (43%) clusters received ≥1 intervention. Analyses of mosquito populations in intervention clusters are ongoing and will be included at the time of presentation. This collaboration facilitated rapid response to dengue clusters and highlights the disproportionate burden in public housing. Next steps include automating cluster identification and reporting, standardizing interventions, and critically evaluating unified surveillance and integrated intervention effectiveness.

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CORRELATION OF DENGUE TRENDS BETWEEN SENTINEL AND PASSIVE SURVEILLANCE SYSTEMS IN PUERTO RICO, 2012 - 2022

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The Sentinel Enhanced Dengue Surveillance System (SEDSS) is an ongoing hospital-based active surveillance program for acute febrile illness implemented in 2012 in Southern Puerto Rico and 2019 in the San Juan metropolitan area; however, the representativeness of sentinel surveillance for broader trends is often unknown. We compared laboratory-confirmed dengue cases identified in SEDSS to those reported in the passive arboviral disease surveillance system (PADSS) to determine whether SEDSS could serve as an early warning system and whether dengue trends were similar for both surveillance systems. We analyzed data from dengue epidemic (2012-2014) and non-epidemic (2019-2021) periods to determine the utility of SEDSS under different transmission scenarios. To assess the utility of SEDSS as an early warning system we 1) tested whether the distribution of SEDSS cases was shifted earlier in time relative to PADSS using Cramer-von Mises tests of equality (CvM), and 2) used cross-correlations of lagged SEDSS data relative to PADSS to examine whether cases reported to SEDSS could anticipate those reported to PADSS. During the epidemic period, 738 SEDSS and 10,592 PADSS laboratory-confirmed dengue cases were reported. We observed a trend towards earlier reporting in SEDSS compared to PADSS (CvM p=0.06). The highest cross-correlations in case counts between the two systems were at SEDSS lags of -2, -1, and 0 weeks. During the non-epidemic period, 179 and 1,348 laboratory-confirmed dengue cases were reported to SEDSS and PADSS, respectively. The cumulative distribution of cases in SEDSS was reported earlier compared to PADSS (CvM p=0.02). The highest cross-correlations between counts were at SEDSS lags of -2, -1, and 0 weeks. Plotted together, SEDSS and PADSS followed the same peaks and troughs in dengue cases in both study periods. During epidemic and non-epidemic periods, dengue trends in SEDSS were representative of island-wide trends. SEDSS may serve as an early warning system by detecting increases in incidence up to two weeks before passive surveillance.

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COMMUNITY-BASED SERO-PREVALENCE OF CHIKUNGUNYA AND YELLOW FEVER IN THE SOUTH OMO VALLEY OF SOUTHERN ETHIOPIA

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Chikungunya (CHIK) and yellow fever (YF) are becoming major public health threats in East African countries including Ethiopia. This study aimed to assess a community-based sero-prevalence of CHIK and YF in the South Omo Valley of Ethiopia, an endemic area for YF. Between February and June 2018, blood samples were collected from study participants and screened for IgG antibody against CHIK virus (CHIKV) and YF virus (YFV) infections using ELISA. Data were computerized using Epi Data Software v.3.1 and analyzed using SPSS. A total of 360 participants (51.7% males, age range from 6 to 80) participated in this study. The overall sero-prevalence of IgG antibody was 43.6% (157/360) against CHIKV, while it was 49.5% (155/313) against YFV. There was a significant positive correlation between IgG antibodies to CHIKV and YFV (sr = 0.82; P<0.01). Residency in the Debub Ari district (AOR = 8.47; 95% CI: 1.50, 47.74) and travel history to sylvatic areas (AOR = 2.21; 95% CI: 1.02, 4.81) were significantly and positively associated with high sero-prevalence of IgG antibody to CHIKV and YFV, respectively. High sero-prevalence of IgG antibody to CHIKV shows circulation of the virus in the present study area. A low sero-prevalence of IgG antibody to YFV in YF vaccine received individuals is highly concerning from a public health point of view as waning of immune response to YFV infection could result in a periodic outbreak of YF in endemic areas. Nevertheless, the present study has not investigated for possible cross-reactivity of antibody to CHIKV with other alphaviruses and YFV with other flaviviruses and these warrants further studies in the present study area.

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SUPERSPREADING OF SARS-COV-2: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Superspreading events have been a prominent driver of the COVID-19 pandemic, contributing to rapid spread and outbreaks of SARS-CoV-2. Superspreading occurs in settings where transmission is highly efficient and/or when an individual infects many others. We have limited knowledge on the epidemiological contexts and individual-level factors that contribute to SARS-CoV-2 superspreading. To better quantify heterogeneity in SARS-CoV-2 transmission, we performed a systematic review and meta-analysis of transmission events with data on secondary attack rates or contact tracing data for individual index cases published before 9 September 2021, prior to the emergence of variants of concern and widespread vaccination. We reviewed 592 distinct events and 9,883 index cases from 491 papers. “Superspreaders” were identified as index cases causing more than five secondary cases. Meta-analysis of secondary attack rates identified substantial variation across 12 event types/settings: the highest rates were estimated for co-living situations including congregate housing (35%), households (29%), and nursing homes (25%); the lowest rates were estimated for schools (9%), hospital/healthcare (8%), and shopping (1%). There was also substantial variation in attack rates within event types. Among index cases, 67% produced zero secondary cases, 17% had one, and only 3% (287) were superspreaders. Characteristics of index cases were scarce: only 46% reported age, 48% gender, 10% presence/absence of symptoms, and 2% had Ct value. Compared to non-superspreaders, superspreaders were more likely to be adults; only 2 out of 91 superspreaders with data available were aged 12-18 years and none were under 12 years. Extreme heterogeneity in SARS-CoV-2 transmission exists, including between individuals, which remains largely unexplained. Enhanced reporting on transmission events and contact tracing in the literature could help explain some of these differences, but additional research is necessary to gain further insight on the causes of superspreading.

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VIRAL ETIOLOGY OF LOWER RESPIRATORY TRACT INFECTIONS IN CHILDREN <5 YEARS OF AGE IN ETHIOPIA: A PROSPECTIVE CASE-CONTROL STUDY

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Lower respiratory tract infections (LRTIs) are a major cause of morbidity and mortality in children worldwide and disproportionally affects Sub-Saharan Africa. Despite the heaviest burden of LRIs in Ethiopia, to date, we have found no published studies reporting comprehensive viral etiology of LRTIs among children in Ethiopia. The objective of this study is to estimate the etiological contribution of respiratory viruses for LRTIs in < 5 years children in Ethiopia. A hospital based prospective case-control study was conducted from September 2019 to May 2022. A one-step Multiplex real-time PCR (Allplex™ Respiratory Panel Assays 1-3) was done to detect respiratory viruses from Naso/Oropharyngeal (NP/OP) swab samples. STATA software version 17 was used for the data analysis. We perform Odds ratio (OR), Attributable fraction among exposed (AFE) and population attributable fraction (PAF) analysis to measure the association of the detected viruses with LRTIs. A total of 210 LRTIs cases and 210 non-LRTI controls were included in the study. The likelihood of detecting one or more viruses from NP/OP was higher among cases than controls (83.8% vs. 50.3%). The multivariate logistic regression showed significantly higher detection rate for RSV A (OR: 14.6, 95% CI: 4.1-52.3), RSV B (OR: 8.1, 95% CI: 2.3-29.1), influenza A virus (OR: 5.8, 95% CI: 1.5-22.9), and PIV 1 (OR:

4.3, 95% CI: 1.1-16.4), among cases when compared with controls. The overall AFE and PAF for RSV A were (93.2% and 17.3%), RSV B (87.7% and 10.4%) and Influenza A virus (82.8% and 6.3%), respectively. Only 2 children were positive for SARS-CoV-2. The mean CT values were lower for all the viruses detected in the cases group with the exception of corona viruses and human rhino viruses. In conclusion, based on our finding, 27.7% LRTIs could be eliminated from children in Ethiopia if RSV were eliminated. Regarding SARS-CoV-2, Children are less likely to get infected by it; therefore in resource limited countries like Ethiopia, the cost-benefit balance of vaccinating under 5 years children against SARS-CoV-2 should be carefully done before launching a vaccination campaign.

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SEROPREVALENCE OF DENGUE, CHIKUNGUNYA AND ZIKA AT THE EPICENTER OF THE CONGENITAL MICROCEPHALY EPIDEMIC IN NORTHEAST BRAZIL: A POPULATION-BASED SURVEY

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The Dengue viruses (DENV) serotypes 1, 2, 3 and 4 were re-introduced in the Northeast Brazil one by one from the 1980's until 2010's. Zika (ZIKV) and Chikungunya (CHIKV) viruses were introduced early 2010's and caused large outbreaks in 2015 and 2016. However, the extent of the ZIKV and CHIV outbreaks and the risk factors associated with exposure remains vague. We conducted a stratified multistage household serosurvey among residents aged between 5 and 65 years, in the city of Recife, Northeastern Brazil, from August 2018 to February 2019. The city neighborhoods were stratified according to high, intermediate, and low socioeconomic strata (SES). Previous infections (ZIKV, DENV and CHIKV IgG) were detected by enzyme linked immunosorbent assay (ELISA). Recent ZIKV and CHIKV infections were assessed through IgG3 and IgM ELISA, respectively. Design-adjusted seroprevalence were estimated by age group, sex, and SES. The ZIKV seroprevalences were adjusted according to the accuracy of the tests. Individual and household-related risk factors were analyzed through regression models to calculate the force of infection . Odds Ratio (OR) were estimated as measure of effect. A total of 2,070 residents were investigated. The forces of infection for high SES were lower for all three viruses as compared to intermediary and low SES. Overall DENV seroprevalence was 88.7%. The overall adjusted Zika seroprevalence was 35.6%, 47.4% in the low SES and 23.4% in the high. The overall CHIKV seroprevalence was 35.7 %, with the low SES with a seroprevalence of 38.6% and the high SES with 22.3%. ZIKV seroprevalence increases fast with age while CHIV seroprevalence almost constant through all ages. The serological markers of recent infections for ZIKV and CHIKV were 5% and 3.5 % respectively. In conclusion, our results confirmed continued DENV transmission and intense ZIKV and CHIKV transmission during the 2015/2016 epidemics followed by continued baseline transmission. The study also shows that there is a significant proportion of the population that still susceptible to infections by ZIKV and CHIKV in the region.

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INVESTIGATION OF THE MEASLES OUTBREAK IN DJIBOUTI

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Measles is one of the vaccine-preventable diseases. There are an estimated 9,484,000 cases with 128,000 deaths worldwide in 2021 of which nearly half have been reported in Africa. In addition to this morbidity and mortality, the total cost of a measles epidemic is estimated on average between $9862 and $1,063,936 per outbreak, thus constituting a significant economic burden. The aim of our study was therefore to describe the outbreak of cases and to analyse the epidemiological and spatio-temporal characteristics in order to be able to propose recommendations for measles surveillance and prevention. We therefore undertook a retrospective descriptive study that was conducted on data from measles cases investigated in Djibouti during the period February 2022 to December 2022. A total of 603 cases have been reported throughout Djibouti, of which 326 have been investigated. Of these 326, 204 (63.1%) were biologically confirmed by IgM serology and 2 (0.6%) cases by epidemiological link. The annual incidence of the disease was 171 cases per 1,000,000 population. The sex ratio was 0.91 with mean age of cases of 3 years and 9 months and extremes ranging from 3 months to 50 years. The most represented age group was 1-4 years with 110 (54.2%) cases, and children under 5 years of age accounted for 81.8% of cases. The most observed clinical signs were fever in 98.5% of cases, maculo-papular rash in 98.5% of cases and cough in 92.2% of cases. Among vaccine-age cases, 107 (61.1%) cases were unvaccinated, of which the most represented were 1-4 years of age with 72 (67.3%) cases. One death was reported during this period. In sum, the country's immunization coverage needs to be improved to prevent potential measles outbreaks with a strengthened surveillance system based on systematic early reporting and biological confirmation of all cases.

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MOLECULAR EPIDEMIOLOGY OF ACUTE DENGUE AND CHIKUNGUNYA INFECTIONS AMONG FEBRILE PATIENTS VISITING FOUR HOSPITALS IN BOTH URBAN (YAOUNDÉ) AND RURAL (DIZANGUE) SETTINGS FROM CAMEROON

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Dengue and chikungunya are widely distributed in Cameroon but there information on their prevalence in different epidemiological settings are still lacking. This study was undertaken to assess dengue and chikungunya prevalence among febrile patients in urban and rural settings. From December 2019 to September 2021, willing febrile (axillary temperature >38°C) outpatients visiting 4 healthcare facilities in the cities of Yaoundé and Dizangué were screened for malaria, dengue and chikungunya. Patients' clinical symptoms were recorded and their blood samples collected in EDTA tubes were centrifuged at 2000rpm for 10 min in order to obtain plasma, then analyzed using CDC-real-time PCR protocols. A Giemsa-stained tick blood smear was formed for malaria microscopy. Odds ratios were

used to determine the level of association between socio-demographic factors, clinical features and the infection status. Overall, 301 patients were recruited: 198 in Yaoundé and 103 in Dizangue. For dengue, 110 patients were positive 90 (45.45%) in Yaoundé and 20 (19.42%) in Dizangué and the disease' prevalence was higher in urban compared to rural setting. Important prevalence (n= 50, 16.61%) of dengue-malaria co-infection was recorded. For chikungunya, one (0.5 %) patient (Yaoundé) was tested positive after rtRT-PCR. Abdominal and retro-orbital pains were significantly associated to acute dengue infection. All the four dengue serotypes were recorded with a predominance of DENV-3 (35.45%) and DENV-4 (25.45%), with DENV-4 reported for the first time in Cameroon as well as Central Africa Region. In conclusion, this study further confirms endemicity of both dengue and chikungunya in Yaoundé and Dizangue. These data stress the need for active surveillance of cases to prevent outbreaks occurrence across the country.

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SEROPREVALENCE OF SARS-COV-2 NEUTRALISING ANTIBODIES AMONG TRAVELERS ENTERING GHANA THROUGH THE MAJOR LAND BORDERS, 2022

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High mortality, morbidity, and transmission of circulating SARS-CoV-2 variants have been reported worldwide. The progression of the pandemic in Africa differs based on the pattern of death and the relative contagiousness of the virus. SARS-CoV-2 was introduced into Ghana by travellers followed by subsequent community transmission. Lockdown of air and land borders were two key control strategies. Timely interventions to test and control air border users were implemented, however, land borders remained closed. This cross-sectional study aimed to determine the seroprevalence of SARS-CoV-2 amongst travellers entering Ghana through 10 approved land borders. Persons aged ≥ 18 years into this study. Truck drivers using the land borders and providing goods and services during the pandemic were the main focus in phase one of the study. Sampling later expanded to include all individuals aged ≥ 18 years using the land borders. A questionnaire was administered to each consenting participant and blood samples collected were processed to obtain serum for detection of neutralising antibodies using the WANTAI ELISA kit. Overall seroprevalence was 92.26% (4172/4522). This however varied across the different POEs with the highest in Oseikojokrom (13.74%) and the lowest in Hamile (2.11%). Students and people whose businesses required direct contact with others had 1.84 and 1.16 times higher odds of seropositivity respectively (aOR 1.84: 95% CI 1.04 - 3.24, p= 0.04 and aOR 1.64: 95% CI 1.16-2.32, p=0.005). The odds of seropositivity were 2.19 times higher among vaccinated compared to unvaccinated travellers (aOR 2.19: 95% CI 1.69-2.78, p<0.001). The high neutralising antibodies detected indicates that the majority of persons entering Ghana through the land borders pose little to no risk of community spread. Nearly half of the travellers had received the COIVD-19 vaccination irrespective of which vaccine was administered and travellers' occupation and POE used influenced the seropositivity rates. These findings supported information on the opening of the land borders in Ghana.

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ELIMINATION OF HEPATITIS B VIRUS USING ANTIVIRAL PROPHYLAXIS AND VACCINATION IN REMOTE SETTINGS THROUGH LOCALLY ADAPTED, INTEGRATED SERVICES: A MATHEMATICAL MODEL

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The Dolpa district of Nepal, has remote geographic landscape, low vaccination coverage, and high prevalence of hepatitis B (HBV) in pregnant women, which creates a condition for perpetuation of high mother to child transmission of the virus. This modeling study assessed the impact of vaccination and third-trimester tenofovir disoproxil fumarate (TDF) prophylaxis on HBV burden and elimination in Dolpa district. This deterministic compartmental model used four possible treatment scenarios: baseline 50% vaccination coverage (scenario I), 50% TDF and baseline vaccination coverage (scenario II), 90% TDF plus baseline vaccination (scenario III), and 90% TDF and birth-dose plus 95% vaccination coverage (scenario IV). The main outcomes for the study were burden of HBV, incidence of HBV, and time to elimination. The study highlights that HBV elimination may not be achieved in Dolpa district by 2100 using the baseline interventions. The use of 90% TDF coverage with the baseline vaccination significantly reduces HBV prevalence and HBV-related mortality and elimination is possible in less than 60 years. Combined implementation and scale-up of 90% TDF and birth-dose and 95% infant HBV vaccination leads to HBV elimination by 2047. In the setting of geographical inaccessibility, a micro-elimination approach for HBV in the remote Dolpa district of Nepal using third-trimester TDF is an effective and equitable approach. This approach is likely to significantly reduce HBV burden and HBV-related mortality even before achieving elimination and partly avoids challenges from the need for cold chain and unaffordable cost of immunoprophylaxis.

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THE EPIDEMIOLOGY OF INFLUENZA B VIRUS IN GHANA, 2017 TO 2021

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Influenza B is characterized by two antigenic lineages: B/Victoria and B/Yamagata. These lineages circulate together with influenza A during seasonal flu epidemics with variation of the year-to-year incidence rates and geographic distribution. This study described the epidemiologic trends of influenza B in Ghana from 2017 to 2021 using surveillance data from the Ghana National Influenza Centre (NIC) sentinel sites. Demographic and laboratory-confirmed influenza data from influenza-like-illness (ILI) cases in Ghana between 2017 and 2021 was obtained from the Ghana NIC. Data was analyzed as detection rates, trends, and regional distribution. The Ghana NIC confirmed 21,539 influenza cases. The detection rate of influenza B was 2,935 per 100,000 (632/21539) and was highest in age groups 0-to-5 years-old and 6-to-15 years-old. Over this five-year period, the detection rate of influenza B was highest in the years 2018 and 2019. However, the years 2017, 2020 and 2021 were below the average rate of 16,028 per 100,000 population (p-value <0.0001). The trend analysis showed that influenza B cases increased from epidemiological week 35

(in the month September) for the years under review. In 2017 and 2018, both influenza B lineages were co-circulating, but from 2019 to 2020, the B/Victoria lineage dominated. Few influenza B infections (Victoria=1; Yamagata=1) were detected in 2021. Influenza B infections were sporadic with variable geographic (regional) distribution in Ghana. Secondary analysis of data from this five-year period helped better understand the frequency and distribution of influenza B in Ghana. Additionally, information from this five-year period was shared with the World Health Organization (WHO) Global Influenza Surveillance and Response System (GISRS) and contributed to recommendations for which influenza strains were incorporated into the southern hemisphere seasonal influenza vaccine. Findings from this surveillance activity highlight the importance for ongoing influenza surveillance and monitoring of the antigenic strains in circulation

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A PROPOSAL FOR UTILIZATION OF PREGNANCY AS AN OPPORTUNITY FOR HCV ELIMINATION AND ERADICATION

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Hepatitis C Virus (HCV) is a major cause of morbidity and mortality globally. Since the development of highly effective direct acting antivirals, the WHO has set a goal of HCV elimination by 2030. Key to this strategy are increased screening and treatment for HCV. Pregnancy and the postpartum period represent a unique time when underserved populations globally have increased contact with the healthcare system. We propose a model in which antenatal care is used to maximize case identification, treatment, and prevention. Pregnant individuals are an ideal sentinel population for HCV surveillance. Contact with the healthcare system is driven by the pregnancy, rather than disease, and thus asymptomatic carriers can be identified. The population is well distributed geographically and socioeconomically, reducing potential sampling bias. Additionally, the infrastructure already exists, as antenatal centers routinely screen for other diseases like HIV. Universal screening in pregnancy can provide data on population level disease exposure and be used to identify geographic hot spots. Once cases are identified, we argue that pregnancy presents an opportunity for intervention. While treatment during pregnancy is not currently WHO approved, clinical trials are underway examining the safety of the direct acting antivirals antepartum. In the interim, identification of infection during pregnancy allows for optimization of the treatment cascade postpartum. It also ensures the exposed newborn and other close contacts can be identified and connected with HCV screening. Finally, we propose that pregnancy can be used as a time for prevention measures, connecting patients to needle exchanges, counseling on risk reduction and providing education on the disease. As new technologies are developed, it may also represent an ideal time to perform vaccination. Taking advantage of patient engagement and existing infrastructure, pregnancy presents a unique opportunity to intervene in the fight for HCV eradication.

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ASSESSING JAPANESE ENCEPHALITIS VIRUS RISK IN ASIA USING HIGH-RESOLUTION REMOTELY SENSED DATA AND MACHINE LEARNING

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Japanese encephalitis virus (JEV) is a mosquito-borne virus endemic to large parts of Asia and the western Pacific and is the predominant cause of vaccine-preventable encephalitis in the region. JEV is estimated to have caused more than 20,000 deaths in 2019, but fewer than 1% of infections result in symptomatic disease. Occurrence data is sparse despite acute encephalitis syndrome (AES) surveillance in most countries, as cases are not always laboratory confirmed and spatially detailed data is typically not published. To enhance our understanding of the prevalence and distribution of JEV in Asia we conducted a literature review of available occurrence data and compiled all records which could be geocoded. We use this occurrence data with high-resolution remotely sensed covariates and a convolutional neural network (CNN)-based approach to model probability of occurrence at significantly improved resolution and scale over past research. The CNN method has been demonstrated to excel in similar spatial prediction tasks with sparse data and allows us to predict probability of occurrence at 100m x 100m resolution, a first for the region. Our 13 covariates include climatic and population data, as well as land use, vector habitat, and animal density rasters. Preliminary results are promising, with a 0.72 probability of occurrence predicted for the validation dataset, which contains 15% of total JEV observations withheld from model training and testing. These preliminary outputs focus on a subset of the region including the Indian subcontinent and surrounding area, successfully predicting higher probability in Uttar Pradesh, Bihar, and Bangladesh where we have high density of occurrence records, but also in Andhra Pradesh, Telangana, and parts of Myanmar where data is severely lacking. We expect further improvement in model accuracy as we incorporate more data and further develop the model. Our approach provides a more detailed view of the spatial distribution of JEV and has the potential to inform targeted intervention and control strategies for the disease, ultimately helping to reduce the burden of Japanese Encephalitis in these endemic regions.

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INVESTIGATION OF SEVERE DENGUE OUTBREAK IN MAUMERE, EAST NUSA TENGGARA, INDONESIA IN 2020: CLINICAL, SEROLOGY, AND VIROLOGICAL FEATURES

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Dengue, an acute febrile disease caused by dengue virus (DENV) infection, is endemic to Indonesia. The country continues to see cyclical outbreaks throughout the years. During early 2020, outbreak of severe dengue occurred in Maumere, Sikka district, East Nusa Tenggara province. Investigation was conducted to understand the cause and characteristics of the outbreak. During the outbreak from February to June 2020, dengue patients were recruited in TC Hillers Hospital, Maumere and sera were collected. Clinical and hematological data were acquired from the patients and DENV infection was confirmed using NS1 antigen and/or RT-PCR detection. The patients' serological status was determined using IgG/IgM ELISA and plaque reduction neutralization test (PRNT). DENV serotyping and Envelope gene sequencing were performed to identify the serotype and genotype of the viruses causing outbreak. Dengue infections were virologically confirmed in 96 (72.2%) out of 133 patients enrolled. Most patients (88.7%) were children under the age of 18 years. Most cases were dengue hemorrhagic fever/dengue shock syndrome while only 5.8% were dengue fever. A majority (92.6%) of these cases were secondary infections. The dominant serotype was DENV-3 (87.3%), followed by DENV-4 (7.0%), DENV-1 (2.8%), and DENV-2 (2.8%). PRNT on DENV-3 secondary infections patients detected the presence of DENV-2 and DENV-4 neutralizing antibodies. Phylogenetic analysis revealed close evolutionary relationship of Maumere DENV to viruses from other Indonesian regions, especially Bali and Kupang. The presence of anti-dengue antibodies for multiple serotypes suggests a history of dengue transmission, with the serotype shift, likely from introduction through travel, as a possible contributor to this outbreak. The high proportion of anti-dengue IgG in young children also demonstrates a high infection rate in the area which may contribute to disease severity. The severe dengue outbreak in Maumere is caused by DENV-3 which were introduced from nearby islands. The secondary infection of this serotype most likely contributes to the severity of the disease during the outbreak.

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PREVALENCE OF ANTI-VZV AMONG SAMPLE OF MEDICAL UNDERGRADUATES IN SRI LANKA: EXPLORING THE VALUE OF 'RECALLED HISTORY OF CHICKENPOX' AS AN INDICATOR OF IMMUNITY

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Immunity to varicella zoster virus (VZV) is indicated by the presence of antibody to VZV (anti-VZV). Chickenpox vaccine is not included in the National Immunization Program of Sri Lanka and immunity to VZV usually develops following natural infection, unless an individual receives vaccination in the private sector. Recalled history of chickenpox is often used as an indicator of immunity when deciding post-exposure prophylaxis. The objective of this study was to determine the performance of 'Recalled history of chickenpox' as an indicator of immunity. A cross-sectional study was carried out with convenient sampling involving medical undergraduates at a state university in Sri Lanka from August to October 2020. Epidemiological data and blood sample for anti-VZV (by anti-VZV IgG ELISA, Euroimmune, Germany) was collected. Total of 142 undergraduates participated in the study. Median age was 22 years (IQR 22 -23). Almost half (45.1%, 64/142) gave history of chickenpox without history of vaccination. Another 7% (10/142) undergraduates who had no history of illness had taken chickenpox vaccination, with 60% (6/10) of them getting a single dose of vaccine. The balance 47.9% (68/142) had neither history of chickenpox nor vaccination. Of the 64 undergraduates who had chickenpox, 43.8% (28/64) had it at the age < 10 years, 18.8% (12/64) at 10 to 15 years and 34.4% (22/64) at > 15 years. Anti-VZV was detected in 48.6% (69/142) indicating immunity to chickenpox, including 91.3% (63/69) with history of chickenpox and 7.2% (5/69) with history of vaccination. Anti-VZV was detected in one (1.4%) who had no history of chickenpox or vaccination. Positive recalled history of chickenpox had a sensitivity 98.4%, specificity 98.5%, positive predictive value 98.4% and negative predictive value 98.5% for the presence of anti-VZV. Immunity to VZV is detected in less than 50% of the medical undergraduates at a state university in Sri Lanka, in majority following natural infection. Positive recalled history of chickenpox has a good predictive value of immunity and recalled history of chickenpox can be used in deciding the post exposure prophylaxis.

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HIGH RISK OF DENGUE AND CHIKUNGUNYA VIRUS FOUND AMONGST CHILDREN LIVING IN INFORMAL URBAN SETTLEMENTS IN MAKASSAR, INDONESIA

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Increases in dengue (DENV) and chikungunya (CHIKV), viruses transmitted by Aedes aegypti and Aedes albopictus, have been highlighted as one of the most alarming health impacts of climate change. Increasing temperatures are ideal for Aedes life stages and extreme weather events, such as droughts and floods, increase water insecurity and promote Aedes breeding habitats. Additionally, the built environment and under-resourced water and trash management systems in informal settlements likely play critical roles in mediating the risk of Aedes-transmitted arboviruses. However, dengue and chikungunya risk in informal settlements with these dual risks from the built environment and climate vulnerability have not been well studied. In 12 informal settlements in Makassar, Indonesia, we conducted annual testing for prior dengue and chikungunya infection by Abcam IgG ELISA in children under 5 years old. We then calculated annual incidence using the catalytic formula with age stratified seropositivity rates and using the seroconversion rate in children tested both years. Amongst 154 children tested during at least one of two testing campaigns in 2019 and 2020, seropositivity was 32% for dengue and 3% for chikungunya. We estimated the dengue annual incidence to be approximately 10-18%. We also found that children living in houses made of porous wall or floor materials were less likely to have evidence of a past dengue or chikungunya infection (OR=0.5; p<0.05). Additionally, children living in households with trash collection were less likely to be seropositive (OR=0.4; p<0.05) compared to those that disposed of their household trash locally in the settlement Changes in house construction and trash disposal practices offer opportunities for interventions to reduce dengue and chikungunya transmission in this highly vulnerable population.

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GENOMIC CHARACTERIZATION OF SARS-COV-2 FROM AN INDIGENOUS RESERVE IN MATO GROSSO DO SUL, BRAZIL

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The COVID-19 pandemic had a major impact on indigenous populations. Understanding the viral dynamics within this population is essential to create targeted protection measures. A total of 204 SARS-CoV-2 positive samples collected between May 2020 and November 2021 from an indigenous area in Mato Grosso do Sul (MS), Midwestern Brazil, were screened. Samples were submitted to whole genome sequencing using the Nanopore sequencing platform. Clinical, demographic, and phylogenetic data were analyzed. We found the co-circulation of six main SARS-CoV-2 lineages in the indigenous population, with the Zeta lineage being the most prevalent, followed by B.1.1 (an ancestral strain), Gamma, and Delta. The estimated indigenous population mortality rate was 1.47%. Our results revealed that multiple independent SARS-CoV-2 introduction events had occurred over time, probably due to indigenous mobility since the villages studied here are close to urban areas in MS, and people are in constant movement between both areas. The mortality rate was slightly below the estimation for the state in the period studied, which we believe could be related to the low number of samples evaluated, the underreporting of cases and deaths among the indigenous population, and the inconsistency of secondary data available for this stud. In this study, we showed the circulation of multiple SARS-CoV-2 variants in the indigenous population, which should be isolated and protected as they belong to the most fragile group due to their socioeconomic and cultural disparities. We reinforce the need for constant genomic surveillance to monitor and prevent the spread of new emerging viruses and to better understand the viral dynamics in these populations, making it possible to direct specific actions.

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METAGENOMIC SEQUENCING REVEALS EXTENSIVE DIVERSITY OF RNA VIRUSES IN WESTERN AUSTRALIAN MOSQUITOES

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Mosquitoes harbour a wide diversity of microorganisms, including insect-specific viruses and viruses of public health importance. In recent years, metagenomic approaches have enhanced the study of these widely diverse and complex virus populations in field-collected mosquitoes. We used metagenomics to characterize the infectome in mosquitoes trapped as part of the Western Australia (WA) arbovirus surveillance program. Firstly, we performed high-resolution metagenomic sequencing on six mosquito species associated with medically important viruses: Aedes vigilax, Culex annulirostris, Cx. australicus, Cx. globocoxitus, Cx. molestus and Cx. quinquefasciatus. We identified 41 RNA and one DNA viral species from 19 families, including 13 novel viruses. Culex mosquitoes exhibited a significantly higher diversity of viruses than Aedes; no virus was shared between the two genera. We observed heterogeneous distribution of viruses between geographical regions and between closely related species suggesting the possible role of geography and host species in shaping virome composition. Wolbachia bacteria were detected in three members of the C. pipiens complex, excluding C. globocoxitus. Secondly, we characterized viruses from cytopathic effect (CPE)-positive tissue culture supernatants obtained by inoculation of mosquito homogenate, in which flaviviruses and alphaviruses were excluded via fixed-cell ELISA using virus-specific monoclonal antibodies. We characterized whole genomes of 91 RNA viruses belonging to 11 species from five viral families. The viruses included Gan Gan virus, associated with mild human disease, and Batai, Wallal and Warrego viruses, known to cause animal disease. We also identified one Murray Valley encephalitis virus and a Ross River virus, both known to cause human disease and a possible limitation of the screening ELISA. Follow-up epidemiological investigations are needed to determine whether the other identified viruses infect humans or other animals. In summary, we have used an unbiased approach to expand and understand the diversity of RNA viruses and other microorganisms in WA mosquitoes.

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GENETIC CHARACTERIZATION OF INFLUENZA AND SARS-COV-2 IN DOD BENEFICIARIES DURING THE 2021-2022 SEASON

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The Department of Defense (DoD) Global Respiratory Pathogen Surveillance Program conducts testing on respiratory specimens from a worldwide network of sentinel sites using PCR-based assays and next-generation sequencing (NGS) to detect and characterize respiratory pathogens. Analyses aid in the annual selection of influenza vaccine strains and help define the impact of influenza and SARS-CoV-2 in the DoD. The program collects respiratory specimens and metadata from DoD active duty and beneficiaries with influenza-like or COVID-19-like illness symptoms across 100+ global sentinel sites. PCR confirmed influenza and SARS-CoV-2 positive specimens are further characterized by NGS. In combination with partner laboratory data, phylogenetic analyses and lineage determinations are performed to assess the genetic changes occurring in these viruses. 1,348 influenza viruses were analyzed, with 1,337 A(H3N2), 10 A(H1N1) pdm09, and one B/Yamagata. Among A(H3N2) viruses, one was clade 3C.2a1b.1a and the rest were clade 3C.2a1b.2a2, with 963 sharing D53G, 309 sharing D53N, 23 sharing E50K, 24 sharing S205F, and 17 with no further subgrouping. Two of the A(H1N1)pdm09 viruses were clade 6B.1A.5a1 and 8 were clade 6B.1A.5a2. The B/Yamagata virus was clade Y3. For SARS-CoV-2, lineages were determined for 10,381 sequences, including 1 Alpha, 1,864 Delta, 3,794 BA.1, 1,950 BA.2, 622 BA.2.12.1, 18 BA.3, 259 BA.4, 65 BA.4.6, 1,802 BA.5, and 6 recombinant viruses. Influenza activity during the 2021-2022 season was elevated from the previous season but lower than seasons before that. Strains for the 2022-2023 Northern Hemisphere vaccine include a clade 3C.2a1b.2a2 virus for A(H3N2), a clade 6B.1A.5a2 virus for A(H1N1)pdm09, a clade V1A.3a1 virus for B/Victoria, and a clade Y3 virus for B/Yamagata. 99.9% of A(H3N2) viruses, 80% of A(H1N1)pdm09 viruses, and the one B/Yamagata virus were the same clade as these vaccine strains. Many A(H3N2) clade 3C.2a1b.2a2 subgroups emerged. Predominance of SARS-CoV-2 variants throughout the season shifted from Delta to BA.1 to BA.2 to BA.5, with most of the circulation and diversity falling within the Omicron lineage.

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A UNIQUE AMPLICON SEQUENCING TECHNOLOGY FOR INFECTIOUS DISEASE: LONG AND SHORT-READ SOLUTIONS

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The COVID-19 pandemic demonstrated that accurate, rapid, and sensitive viral genome sequencing is critical to directing the global response to disease and pandemics. IDT's xGen™ Amplicon technology allows over 3,500 target specific primers in a single multiplexed PCR reaction. This design can generate super-amplicons that maintain target coverage when a primer drop-out occurs due to novel viral mutations. Super-amplicons form when amplicon primers produce 2X or greater sized amplicons. A single Wuhan-1-based panel design for SARS-CoV-2 provided complete coverage for all known SARS-CoV-2 variants. The xGen Amplicon technology was initially developed for short read sequencing (PE-150) with Illumina platforms. Here we show that the xGen Amplicon technology also provides sequencing solutions with long read sequencing (up to 4kb read length) using the Oxford Nanopore MinIon (ONT). For HIV we developed an xGen Amplicon panel using the reference genome HXB2. We tested five variants with 91-94.3% identity to HXB2. Coverage for the short read panel ranged from 77-90%. Gaps in coverage were mainly in the env region. We hypothesized that super-amplicons are produced but are too long for Illumina sequencing. To confirm this, HIV amplicon products of the multiplex PCR were subjected to fragmentation and library prep followed by Illumina sequencing. Coverage was improved to greater than 96% for all variants; however a significant drop in viral mapping resulted. To circumvent the low mapping rate, an xGen Amplicon ONT panel for HIV was designed using the same panel design described above. Long read sequencing with the MinIon generated coverage greater than 90% for the four HIV variants that were tested, while a high viral mapping rate was maintained. This demonstrates the ability of the panel to generate amplicons that can be used to sequence highly divergent regions of rapidly evolving viruses even when regions of the genome diverge significantly from the design genome. We are continuing with this approach for a number of other viruses, including Chikungunya, Zika, and Dengue.

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RE-EMERGENCE OF COSMOPOLITAN GENOTYPE OF DENGUE VIRUS SEROTYPE 2 IN SOUTHERN VIETNAM

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Dengue is a mosquito-borne viral infection caused by one of the four dengue serotypes (DENV1-4). Each serotype is subdivided into several genotypes. Asian 1 of dengue virus serotype-2 (DENV-2), has been the dominant genotype in southern Vietnam for the last decade. In this study, we have identified new DENV-2 lineages of cosmopolitan genotype in Ho Chi Minh City, not previously detected in Vietnam before (samples from 2017-2022). We infer the likely transmission routes of these new DENV-2 lineages into Vietnam from other South and Southeast Asian countries and when these events occurred. Of 45 DENV-2 samples, taken between 2017 and 2022, we identified 28 (62%) were Cosmopolitan genotype and 17 (37.7%) were Asian I genotype. The full DENV-2 phylogeny analysis will be presented, including the probable route of introduction of these viruses into Ho Chi Minh City and surrounding areas, the approximate timing of these events, and current outbreak dynamics. This re-emergence of the Cosmopolitan genotype, with new lineages, prompts an urgent need to update dengue serotyping techniques for surveillance in the region as well as set up studies on evolution, and transmission dynamics of this virus.

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DENGUESEQ: DEVELOPMENT AND VALIDATION OF A PAN-SEROTYPE WHOLE GENOME AMPLICON SEQUENCING APPROACH FOR DENGUE VIRUS

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Amplicon-based sequencing (PrimalSeq) was developed in response to the Zika virus epidemic due to difficulties generating complete genomes using metagenomic approaches. Later this approach was adapted as the primary sequencing method for SARS-CoV-2 (i.e. the "ARTIC" protocol). Investments in global genomic infrastructure resulted in a significant increase in amplicon sequencing capacity that can be utilized beyond SARS-COV-2, by swapping out virus-specific components such as primer schemes. Increased genomic surveillance of other viruses of public health concern, such as dengue virus, is needed to reduce the future burden of disease. Particularly, genomic surveillance of dengue virus can help to monitor the roll out of novel control strategies such as vaccines and release of mosquitoes carrying the virus-inhibiting Wolbachia bacterium. However, the majority of currently available sequences are partial, while complete genomes are needed to monitor and refine novel control tools. In this study, we developed and validated a pan-serotype whole genome amplicon sequencing approach for dengue virus. We sequenced a panel of virus stocks as well as clinical specimens from Florida to validate our approach with genetically diverse dengue viruses spanning the defined genotypes within each of the four serotypes. We show that the dengue primer schemes can be "plugged" into existing amplicon sequencing workflows, with high genome coverage across all four serotypes at a range of RNA titers (threshold of ~100 RNA copies/µL). The primer schemes can be either used as a serotype-specific assay (serotype known) or mixed into a unified pan-serotype assay (serotype unknown), with similar sensitivity. Our approach can help laboratories to quickly adapt their existing amplicon sequencing workflows to improve genomic surveillance of dengue virus.

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EVOLUTION AND CIRCULATION OF SARS-CO-V2 OMICRON SUBVARIANTS IN ODISHA STATE, INDIA, NOVEMBER 2021 TO NOVEMBER 2022

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Omicron Variant of Concern (VOC) & its subvariants are characterized by immune evasion and reinfection. We present 1 year data (November 2021 to November 2022) of circulating SARS CoV2 variants in Odisha, India. We included 855 samples from SARS CoV2 positive patients by real-time RT-PCR referred to the Virus Research & Diagnostic Laboratory at the ICMR Regional Medical Research Centre, Bhubaneswar. Next-generation sequencing for SARS-CoV-2 was performed on Oxford Nanopore MinION Mk1C with Midnight protocol for library preparation. Bioinformatic pipeline included ARTIC field bioinformatics, lineage classification was done with PANGOLIN and Nextclade. Demographic data, history of vaccination & prior SARS CoV2 infection was included for analysis. Predominant circulating VOC in Odisha in November & December 2021 was B.1.617.2 in 87.3% and 58.8% respectively of sequenced samples while Omicron (B.1.1.159) VOC was detected in 3.23% of specimens in December 2021. BA.1 and BA.2 subvariants dominated between January-May 2022 and corresponded to a peak in COVID19 cases & high positivity between January-March 2022. A shorter peak in reported cases in July-August 2022 corresponded with predominance of BA.2.75 subvariant (40.3% and 60% of sequenced samples July & August 2022 respectively). BA.4, BA.5 were detected in limited samples (5% and 1% July 2022). XBB and further subvariants (XBB.1, XBB.2, XBB.3) were detected from September-November 2022 but did not correspond with increased cases or hospitalization. In cases of SARS CoV2 reinfection(N=166), the commonest subvariants were BA.2 (24.1%), BA.2.75 (24.7%) & XBB (10.8%) corresponding to the months in which these were the predominant subvariants. Reinfections were more common in ages 20-40 yrs and 40-60 yrs with few cases in >60 yrs. Primary 2-dose vaccination against SARS CoV2 was complete in all the reinfection cases, but in 39.2% of reinfections, booster 3rd dose had not been administered. In conclusion, Omicron and its evolving sub-variants are the current circulating VOC in our region in India and associated with considerable number of SARS CoV2 reinfections.

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DEVELOPING A DENGUE VIRUS LINEAGE CLASSIFICATION SYSTEM TO IMPROVE GENOMIC SURVEILLANCE

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Last year, dengue virus caused nearly three million cases in the Americas. As climate change continues and Aedes species increase their geographical range, more populations are at risk of infection, leading to an increase in the disease burden. Interventions, including Wolbachia infection and vaccinations, are likely to be impacted by viral genetic diversity but dengue virus genetic diversity is currently not well described. Dengue virus genomes are categorized as one of four serotypes, and each of those have several

genotypes. However, some sequenced dengue viruses do not cluster with the defined genotypes, and they do not capture most transmission dynamics. For example, most of the DENV1 sequences in the Americas fall into the DENV1-V genotype, and so details of how DENV1 spreads between and within countries using only the genotype designations are obscured. Further, any impact of pharmaceutical or biological interventions is not easily monitored, and both would require slower and more complex phylodynamic analyses. Following previous work on SARS-CoV-2 and Rabies virus, we proposed a hierarchical lineage classification system to address this issue. We built on the existing serotype-genotype system to maintain ties with the existing dengue virus research community; and designated all publicly available dengue virus genomes, including new genomes from the Caribbean and Florida. We have also written an accompanying software tool to enable other groups to assign new sequenced viruses for genomic surveillance programs. We then apply this lineage system to explore local and regional dengue virus transmission dynamics without the need for complex phylodynamic analyses.

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IDENTIFICATION OF GENES INVOLVED IN THE TYPE-I INTERFERON RESPONSE ELICITED BY THE LIVE-ATTENUATED JAPANESE ENCEPHALITIS VIRUS SA14-14-2 VACCINE

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Japanese encephalitis virus (JEV) is a mosquito-borne flavivirus that has both human and veterinary public health significance. The safe and highly effective SA14-14-2 live-attenuated vaccine (LAV) can elicit protective immunity with one single immunization and plays a major role in the control of human JE. To date, little is known about the mechanism(s) contributing to the high immunogenicity of JEV SA14-14-2 LAV. Such knowledge can be translated to support the development of next-generation candidate JEV LAV and has important implication for the development of candidate LAVs for encephalitic flaviviruses. We undertook the genome wide CRISPR-Cas9 knock-out screening of human A549 (GeCKO-A549) cells infected with the JEV SA14-14-2 strain, as a model system to investigate the host responses following immunization with JEV LAVs. Surviving cells were harvested, followed by the extraction of genomic DNA and next-generation sequencing analysis. Unique genes were selected based on the gene enrichment in the JEV resistant GeCKO-549 cells as compared to the control cells. There was correlation between survival of GeCKO-A549 cells and deletion of tyrosine kinase 2, interferon alpha subunit 1, interferon beta receptor subunit 2, and signal transducer and activator of transcription 1 (STAT1). All four genes are associated with type-I interferon response against JEV. Although STAT1 knockout did not result in the surviving phenotype, STAT1 gene was highly ranked. In comparison with wild-type JEV strains, the SA14-14-2 vaccine strain is capable of eliciting a broader spectrum of type-I IFN responses, providing a putative molecular basis for the high immunogenicity of the empirically developed human JE live-attenuated vaccine (LAV). The knowledge can be translated to support the rational design of second-generation candidate LAVs to control human and swine JE.

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DOES TIME MATTER IN EBOLAVIRUS RESURGENCE? ELUCIDATING TIMEFRAME REQUIRED FOR REACTIVATION OF EBOV WITHIN HUMAN SURVIVORS AND BATS POPULATION

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Ebolaviruses (EBOV) have caused more than 40 outbreaks since its discovery in 1976, with a high case fatality rate of 50-80% per outbreak. A budding mystery in the epidemiology of EBOV is the reactivation of the virus within EVD survivors after a prolonged latency period, a phenomenon responsible for most of the recent outbreaks. However, it is unclear how long this latency period last and whether different bat species, identified as EBOV's reservoir host, experience this latency before the spillover event. To explore these questions, we assembled a genome dataset that spans the known history of EBOV outbreaks from GenBank. Based on bat surveillance in the location where EVD outbreaks have been reported, we identified several candidate bat species that tested positive for EBOV antibody, and we narrowed it down to three that tested positive for EBOV on PCR. Analysis was done by partitioning the genomes into codon regions and assigning each partition an HKY model with gamma-distributed specific rates. We set the bat's species as traits and estimated the latency process using the explicit latency model implemented in BEAST as a molecular clock. All three fruit bats species showed evidence of involvement in the transmission dynamics of the virus. Their pattern of involvement suggested that earlier EBOV outbreaks occurring between 1976 to 2000 originated from central Africa and most likely spilt over from Epomops franquetti. The subsequent epidemics from 2003 to 2021 spilt over from Hypsignathus monstrous and Myonycteris torquata. We used the estimated proportion of the latency across various branches to deduce the virus's diffusion process during quiescent stages in bat populations providing valuable insight into the virus's molecular evolution outside of human hosts. We further predicted the approximate period for the likely resurgence of EBOV in both human and nonhuman hosts, considering if the virus started off from persistent or latent EBOV. This study is crucial for devising timely follow-up strategies for EVD survivors and initiating EBOV surveillance among bat populations.

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MOLECULAR PHYLOGENY AND SEROTYPE DISTRIBUTION OF DENGUE VIRUS IN THE PHILIPPINES, 2015-2022

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Dengue is the most prevalent arboviral disease in humans and it has caused tremendous burden to the tropical and sub-tropical countries. In the Philippines, dengue is considered as a major public health problem and is probably the most well-known arboviral infection and feared tropical disease. Despite being endemic in the Philippines with all four Dengue virus (DENV) serotypes, there is a limited information available about the circulating viral serotypes and genotypes. Serum samples (n = 30,594) from dengue suspected patients for the years 2015 to 2022 were sent to the Research Institute for Tropical Medicine (RITM) to detect DENV serotype by Real-time RT-PCR. The E gene was amplified using one-step RT-PCR and followed by direct Sanger sequencing. Phylogenetic analysis was done using Maximum Likelihood and General Time-Reversible +G model with 1,000 replicates for bootstrap (1,500+nt) by MEGA 7.0 for genotype identification of positive DENV samples. Dengue RNA was detected in 15,367 samples, 1,364 of these were successfully sequenced for the whole E gene. The predominant serotypes for 2015 were DENV 1 and 2. Subsequently, a shift to DENV 3 serotype from 2016 to 2019 was observed. However, in the year 2022, DENV 1 and 2 were detected again to be the dominant serotypes. It is also notable that in the same year, DENV 4 detection have increased compared to the previous years. Phylogenetic analysis showed that the Philippine DENV samples existing genotypes were: DENV 1 (GI = 5, GIV = 490), DENV 2 (Cosmopolitan = 292), DENV 3 (GI = 474), and DENV 4 (GII = 103). The eight-year phylogenetic data suggested that the existing genotypes for DENV 1 to DENV 4 in the Philippines originated mostly from Asian countries and French Polynesia. Constant monitoring of circulating strains is vital in understanding the phylodynamic patterns of disease outbreaks. This will aid in the development of future regional vaccines with antigenic and genetic compositions based on the surveillance.

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PERSISTENCE OF SERUM IGM ANTIBODIES ANTI-CHIKUNGUNYA VIRUS FOR MORE THAN 24 MONTHS AFTER THE ONSET OF ACUTE SYMPTOMS

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How long anti-chikungunya virus (CHIKV) IgM antibodies remain detectable in the bloodstream is not well established. Thus, our objective was to assess the frequency of detection of anti-CHIKV IgM antibodies over time using a commercial ELISA (CHIKjjDetect™ IgM ELISA kits; InBios International Inc., Seattle, USA) in 148 serum samples obtained sequentially from 45 patients with CHIKV infection who developed chronic joint pain. Infection was confirmed by qRT-PCR (N=43) or IgM seroconversion (N=2) during an outbreak in Salvador, Brazil, between June 2019 and February 2020. Each patient had a minimum of three and a maximum of six serum samples available for testing. Among the samples obtained within 7 or between 11-30 days post-symptoms onset (DPSO), 13.3% (6/45) and 97.5% (39/40) were positive for anti-CHIKV IgM, respectively. All the samples obtained between 31-60 (N=11), 61-90 (N=9), 91-120 (N=2), or 121-180 (N=5) DPSO were positive for anti-CHIKV IgM. Among 19, 7, and 4 samples obtained between 721-900, 901-1080, or 1081-1260 DPSO, 6 (31.5%), 1 (14.2%), and 1 (25.0%), respectively, remained CHIKV IgM-positive. Considering the 23 patients with at least one serum sample collected >720 DPSO, we found that 7 (30.4%) still had IgM detectable. These results indicate that, in contrast to the typical duration of IgM following acute viral infections of only a few months, a significant proportion of chikungunya patients that develop chronic joint pain can maintain CHIKV IgM detectable for more than two years after acute disease. Thus, the application of CHIKV IgM serological tests for diagnosis of acute illness in settings where large CHIKV epidemics occurred and endemic transmission ensued may be misleading due to detection of antibodies that may represent infections from previous years. This possibility is especially concerning if our findings are also valid for patients that do not develop chronic symptoms. Further studies should verify whether our results hold for patients without chronic symptoms and evaluate whether maintenance of anti-CHIKV IgM antibodies correlates with the duration of arthralgia, which would suggest viral persistence.

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CROSS-SECTIONAL EVALUATION OF ANTI-SARS-COV-2 ANTIBODY RESPONSE TO AZD1222 RECOMBINANT VACCINE DEPLOYMENT IN THE BONO REGION, GHANA

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Preliminary data across the globe shows that the AZD1222 recombinant vaccine was highly effective in preventing not only the symptoms but also the transmission of the SARS-CoV-2 virus. In Ghana, data on the immune response generated by different vaccination doses is lacking. The present study aimed to compare the anti-SARS-CoV-2 antibody response among single and double-vaccinated versus unvaccinated individuals. A case-control design was employed for this study. Seventy-nine participants (35 vaccinated, 44 unvaccinated) were recruited from the Sunyani West Municipality and screened for the presence of SARS-CoV-2 specific IgG and IgM antibodies in plasma samples using a Standard COVID IgG and IgM Combo FIA test. Data analysis was carried out with STATA (Version 21). The current study showed that mean IgG levels among vaccine groups (Group 1: Not vaccinated, Group 2: 1 dose, Group 3: 2 doses) differed significantly ($F_{2, 76}=11.457$, $p<.001$) between Group 1 and Group 3; and between Group 2 and Group 3. Participants in Group 2 and Group 3 were 4.1 and 12.5 times more likely to develop more antibody responses compared to their counterparts in Group 1 respectively.This baseline study demonstrated that in the short term, individuals who received either one or two doses of the AZD1222 recombinant vaccine generated a higher antibody response compared to individuals who did not receive any dose of the vaccine. It remains to be seen how long the generated immune response will last in this population and whether a booster shot could be a useful strategy

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TO MODULATE OR NOT TO MODULATE: INCREASING IMMUNOGENICITY AND REDUCING IMMUNE EVASION OF SARS-COV-2 VIA NEXT GENERATION VACCINES

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Coronaviridae is a notable family of viruses that are responsible for multiple epidemics and pandemics throughout the 20th and 21st centuries. The SARS-CoV-2 pandemic and its generation of subsequent variants have magnified the importance of researching and understanding highly pathogenic emerging viruses and forging the advancement of vaccines to combat future pandemics that are likely to occur. The vaccines developed to combat the SARS-CoV-2 pandemic have significantly reduced the likelihood of hospitalizations and death in vaccinated individuals infected with the virus, however as the virus mutates to create emerging variants that evade prior immunity, the need for a robust and efficacious vaccine is the utmost importance. The type I interferon (IFN) response plays a dichotomous role in mRNA vaccines. Type I IFN has been shown to both inhibit and enhance the mRNA vaccine-driven response. Here we provide data showing our investigation of a type I IFN antagonist on mRNA vaccine immunogenicity and protection. As a model system, we developed an mRNA vaccine that expresses stabilized pre-fusion spike protein of SARS-CoV-2 and a type I interferon antagonist for immune modulation to confer robust immunity and protection against SARS-CoV-2 variants while reducing intra-host viral diversity relative to a vaccine encoding spike protein only. We have generated and validated our mRNA vaccine in vivo, leading to the demonstration of vaccine immunogenicity and protective capacity against SARS-CoV-2. Our results indicate that type I IFN antagonists improve vaccine immunogenicity and protective capacity against lethal challenge in comparison to parental mRNA vaccine (spike only). We intend to investigate the immune-modulated vaccine's ability to alter viral population dynamics using SARS-CoV-2 barcode viruses in vaccinated mice post-infection to understand mechanisms of protection and control. Our findings on mRNA vaccine immunogenicity, vaccine efficacy through ancestral and variant challenges, and their impact on virus population dynamics will lead to advancements in the fields of virology, immunology, and evolutionary biology.

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SEROPREVALENCE OF HUMAN CORONAVIRUSES IN PEDIATRIC SAMPLES COLLECTED BEFORE COVID-19 PANDEMIC IN THE PHILIPPINES AND JAPAN

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Infections of four seasonal human coronaviruses (HCoVs); 229E, NL63, HKU1, and OC43, are common in children, and COVID-19 infections in

children are generally mild. This feature might be associated with protection conferred by recent seasonal HCoVs infection. This study aimed to determine the seroprevalence of HCoVs and SARS-CoV-2 neutralizing antibodies in children less than 5 years old. A total of 419 (Philippines: 315 and Japan: 104) serum samples collected before COVID-19 pandemic period (2015—2019) were tested for IgG antibodies against four seasonal HCoVs and SARS-CoV-2 using recombinant spike ectodomain proteins by enzyme-linked immunosorbent assay (ELISA). Neutralization antibodies against SARS-CoV-2 (wild-type) were also measured for samples collected in the Philippines that were positive for anti-SARS-CoV-2 IgG. As a result, about 90% of children less than 2 months old in the Philippines had IgG antibodies against four seasonal HCoVs. Then, the antibody prevalence were less than 20-47% between 6-11 months old and reached up to 80% by 2-3 years old. The seroprevalence of SARS-CoV-2 was low at about 3% between 6-11 months old and then reached about 50% at 4 years old. The seroprevalence of NL63, HKU1, and OC43 in samples collected in Japan showed a similar trend, although the seropositivity against 229E stayed low (63%) in those aged 4 years. The median age of children in the Philippines who showed positive for anti-SARS-CoV-2 IgG antibodies were older and had significantly higher IgG antibody titer against four seasonal HCoVs, compared with those negative for SARS-CoV-2 IgG antibodies (age: 2.2 years vs. 0.9 years, $p < 0.0001$, antibody titer in each antigen: 7.7-13.5 vs. 1.3-6.13, $p < 0.0001$). These results suggest some cross-reactivity between SARS-CoV-2 and seasonal HCoVs. However, only one of the 69 reactive samples had a neutralization antibody against SARS-CoV-2. Although there is no neutralization capability in samples positive for anti-SARS-CoV-2 IgG antibodies, there might be some cross-reactive antibodies between SARS-CoV-2 and seasonal HCoVs, which might explain lower severity of COVID-19 infections among children.

5301

ASSESSING THE ROLE OF NON-NEUTRALIZING ANTIBODIES IN ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY OF DENGUE VIRUS INFECTED CELLS

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Dengue virus (DENV) is endemic in over 100 countries causing widespread morbidity and mortality. 400 million people are infected annually, resulting in 100 million symptomatic cases and at least 40,000 deaths. It has been previously described that antibodies against DENV E protein can cause antibody dependent enhancement during secondary DENV infection, increasing infection. However, there are other potential antigen targets created during DENV infection. Non-structural protein 1 (NS1) is a non-structural protein that is both secreted from and expressed on the surface of DENV infected cells. IgM, IgG, and IgA isotype antibodies against NS1 can be readily detected after DENV infection. Our study aims to determine: the capability of NK cells to clear NS1 expressing cells opsonized by αNS1 antibodies via antibody-dependent cellular cytotoxicity (ADCC), confirm cytotoxic activation of NK cells with opsonized NS1-expressing cells, what receptors are used in both IgG and IgA isotype mediated killing of NS1 expressing cells, and if secreted NS1 functions to protect DENV-infected cells from ADCC. To this end, we will analyze ADCC using a flow cytometry based ADCC assay. We will assess the death of NS1-expressing cells in the presence of NS1-reactive antibodies and NK cells, and we will also assess the activation of NK cells using CD107a as a cytotoxic activation marker on NK cells. We will also assess receptor utilization of NK cells for IgG or IgA mediated ADCC. Using an αCD89 antibody known to block FcαR binding to IgA, we can assess potential reduced ADCC of opsonized NS1-expressing cells with an IgA monoclonal antibody. Similarly, using αCD16, 32, and 64 antibodies known to block FcγRs binding to IgG, we can assess reduced ADCC of opsonized NS1-expressing cells with an IgG monoclonal antibody. We have previously shown that secreted NS1 can block monocytic phagocytosis of NS1-expressing cells. We will also investigate the ability of secreted NS1 to block ADCC by NK cells and NK cells to decrease viral proliferation by killing infected cells.

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MODULATION OF COMPLEMENT REGULATORY MOLECULES IN INFECTED AND BYSTANDER CELLS DURING DENGUE VIRUS INFECTION

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Dengue virus (DENV) is a flavivirus with four known circulating serotypes (DENV 1-4). Infection with DENV can result in a wide spectrum of disease: primary infections tend to produce milder disease while secondary infections can be associated with more severe disease, though the mechanisms behind this phenomenon are not well defined. The complement cascade seems to play an important role during DENV infection, as cleaved complement factors such as the anaphylatoxins C3a and C5a have a potent effect on the permeability of the capillary vasculature. Recent studies suggest that complement dysregulation and overactivation may play a role in the development of severe dengue disease. In this study, we aimed to investigate the effect of infection on the expression of complement regulatory molecules on both infected and bystander cells. HepG2 and Bewo cells were infected with DENV-2 16681 (MOI = 1) for 48 and 72 hours post infection (hpi). Cells were then stained with anti-CD55, anti-CD46, and anti-DENV antibodies and analyzed by flow cytometry to determine the expression of CD55 and CD46. Infection with DENV-2 resulted in 13-18% of total cells expressing DENV E protein. During DENV-2 infection, a significant decrease in the expression of complement regulatory molecules CD55 and CD46 was observed at both 48 and 72 hpi in bystander cells, while expression levels in mock-infected and DENV-infected cells remained normal. Our results suggest that DENV-infected cells can augment expression of complement regulatory molecules and prevent cell death. Going forward, we plan to utilize a human skin explant model to investigate the mechanism by which DENV modulates expression of these complement regulatory molecules on infected cells while inhibiting their expression on bystander cells.

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THE DIFFERENTIATION OF TREG AND TH17 CELLS IN PATIENTS WITH CHRONIC HEPATITIS B IN DIFFERENT STAGES

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Regulatory T (Treg) and T helper 17 (Th17) cells modulate the immune response in chronic hepatitis B virus infection by promoting immune tolerance, restricting liver damage, stimulating inflammatory responses, and inducing hepatocyte injury. These cells act by signaling transcription factors and secreting cytokines. Our study aimed to observe the percentages of Treg and Th17 cells, as well as their mRNA levels of Foxp3 and RORγt, in chronic hepatitis B (CHB)-infected groups and CHB patients experiencing hepatitis flare (HF). We recruited 159 participants, including 137 CHB-infected cases and 22 healthy controls (HC) from Ho Chi Minh City. CHB cases were divided into three groups: HBeAg+ CHB infection (e+CHBI, n=52), HBeAg+ CHB (e+CHB, n=24), and HF (n=61). Treg and Th17 cells were measured by flow cytometry, and the mRNA levels of Foxp3 and RORγt were analyzed by Realtime PCR. The percentages of Treg, Th17, and a special subset - IL17A(+)Foxp3(+)Treg cells - were significantly higher in the HF group compared to the e+CHBI group. Meanwhile, there was no significant difference in the mRNA levels of Foxp3 and RORγt in CHB groups. These findings reveal that these immune cells increase with the severity of the liver injury, and the mRNA levels of transcription factors do not correlate with the percentages of their cells. Our results explain the diversity of T cells and their subsets in the immune response in CHB and suggest that the new subset should be further investigated as a specific tool in the HBV immune response.

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INDIRECT IGG ELISA AND SEROTYPE-SPECIFIC NEUTRALIZING ANTIBODY TITERS ARE ASSOCIATED WITH DENGUE IN CHILDREN IN CEBU, PHILIPPINES

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Standard measures of dengue virus (DENV) antibodies have not been consistently associated with dengue disease. We assess whether an indirect dengue IgG ELISA (PanBio; Brisbane, QLD, Australia), plaque reduction neutralization test (PRNT) to DENV1-4, and preparation of virus used in this assay (standard vs. mature) are associated with dengue risk and protection. Healthy children (n = 1,214) aged 9-14 years in Cebu, Philippines were enrolled in a prospective cohort study in May - June 2017, and febrile illness prompted dengue diagnostic testing through March 2020. At enrollment, all sera were tested for binding antibodies by ELISA, and random subsets were tested for neutralizing antibodies by PRNT to DENV1-4 using WHO reference (standard, n = 737) and mature clinical strains (n = 77). The probability of dengue was modeled as a function of baseline antibodies using logistic regression and generalized additive models adjusted for age, sex, and enrollment site. Inverse probability weighting was used to account for subset size. The probability of symptomatic dengue was 11.1% (95% CI: 5.6-20.9) in the naïve group vs. 3.6% (2.0-6.3) for those with ELISA >= 3 (p = 0.005). By standard PRNT, geometric mean titers to DENV1-4 (GMTs) > 200 were protective (1.4% [0.6-3.1], p<0.0001) with no enhancement at lower GMTs. Baseline standard PRNT titers to DENV2 and DENV3 were protective against a homotypic dengue case (DENV2: OR 0.28, 95% CI 0.12 to 0.65; DENV3: OR 0.27, 95% CI 0.13 to 0.57), but not heterotypic dengue. Among children who entered the cohort with multitypic immunity, none had GMTs < 40 by the standard PRNT, but 49% had GMTs < 40 by the mature PRNT. Using the mature PRNT, GMTs between 40-100 were enhancing compared to GMTs <40 (probability of dengue: 15.4% [8.2-27.1] vs. 7.1% [3.7-13.3], p = 0.024) while GMTs >100 were protective (1.4% [0.3-5.4], p = 0.024). In sum, a commercial ELISA and neutralizing antibodies are associated with dengue. We hypothesize that the mature PRNT has a higher threshold for antibody binding and thus more accurately identifies enhancing and neutralizing antibodies. These assays may be valuable for use in population and vaccine trials.

5305

DETECTION OF ENVELOPE-DIMER EPITOPE-LIKE BROADLY PROTECTIVE ANTIBODIES IN DENGUE-IMMUNE CHILDREN IN THE PHILIPPINES FOLLOWING VACCINATION AND NATURAL INFECTION

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The dengue vaccine, Dengvaxia, has been described as inducing antibody-dependent enhancement (ADE) in dengue-naive individuals. There is an urgent need to develop an effective dengue vaccine that elicits protective, cross-reactive neutralizing antibodies (Abs) like envelope-dimer epitope (EDE) Abs, which target quaternary epitopes on the E protein dimer and neutralize dengue viruses 1-4 (DENV1-4) without triggering ADE. Here, we investigated natural infection and vaccine-induced cross-reactive neutralizing Abs in children with prior DENV infection histories in a longitudinal vaccine cohort in Cebu, Philippines. In total, 1,214 children remained unvaccinated while 1,782 children received a single dose of Dengvaxia in June of 2017 during a mass vaccination campaign. Serum samples were collected one month before and one year (12-18 months) after the vaccine campaign. We selected a random subset of n=223 polytypic DENV-immune children to measure baseline status and change in EDE-like Abs due to natural infection and vaccination. Paired samples were tested by Plaque Reduction Neutralization Test (PRNT) with mature DENV1-4 low passage clinical isolates and a Blockade-of-Binding (BOB) assay to detect Abs that prevent EDE Ab C8 from binding a DENV2 E protein dimer. An IgG ELISA against the DENV1-4 E protein monomer and DENV2 E protein dimer were also performed on the same participants for comparison to the mature PRNT and BOB. Both vaccinated and unvaccinated groups had high levels of EDE C8-like Abs at baseline. We also observed a significant increase in Ab level after one year in both groups across all assays. The level of C8-like Abs in a sample was correlated with how well the sera were able to neutralize mature DENV1-4 in PRNT assays. This correlation was stronger in naturally infected sera than vaccinated sera, indicating differences in Ab quality. These results highlight the presence of EDE-like Abs that could possibly protect against the four DENV serotypes and provide insights for future vaccine candidates.

5306

THE MAGNITUDE AND QUALITY OF NEUTRALIZING ANTIBODIES CORRELATE WITH PROTECTION AGAINST SYMPTOMATIC DENGUE VIRUS INFECTION AND DIFFER BY SEROTYPE, IMMUNE STATUS, AND ASSAY CONDITION

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Neutralizing antibodies (nAbs) are considered an essential component of the protective response against the four serotypes of dengue virus (DENV1-4), yet measurement of their potency is primarily performed using a single cellular substrate and partially mature virions. This does not capture the full breadth of nAb activity and may lead to biased estimations of nAb potency and repertoire. Here, we evaluated the nAb response associated with protection against symptomatic DENV infection using samples collected after one or more DENV infections but prior to a subsequent symptomatic or inapparent DENV1, DENV2 or DENV3 infection in a long-standing pediatric cohort study in Nicaragua. We compared nAb titers in pre-inapparent and pre-symptomatic infection samples measured in Vero cells with or without DC-SIGN expression infected with mature or partially mature virions. This allowed us to measure the magnitude and the quality of the nAb response and revealed that nAb correlates of protection are dependent on the individual's prior DENV immune status (primary vs. secondary) and the infecting serotype. Higher cross-reactive nAb titers were associated with protection against DENV1 and DENV2 disease in participants with one prior infection (DENV1 and DENV2) or multiple prior infections (DENV2), while no difference was observed between the pre-DENV3 infection groups. The nAb potency and the protective NT50 correlate were greatly impacted by virion maturation state and cell substrate. For all serotypes combined, the median NT50 to partially mature virions in Vero cells was 202, compared with 42 to mature virions in Vero-DC-SIGN cells. nAbs to mature virions with Vero

DC-SIGN cells had the lowest threshold (NT50 = 180) for detecting 90% of the individuals with subsequent symptomatic disease and was correlated with protection (Odds Ratio 0.85, 95% Confidence Interval 0.73-0.96), in comparison with partially mature virions and mature virions in Vero cells (threshold NT50 = 898 and 476, respectively). These results have important implications for determination of antibody correlates of protection for vaccines and natural infections.

5307

NEUTRALIZING IGM CONTRIBUTE SUBSTANTIALLY TO BOTH PRIMARY AND SECONDARY DENGUE SEROTYPE 1 IMMUNITY

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IgM antibodies can contribute to virus neutralization, but their role in immunity to dengue virus serotypes 1-4 (DENV1-4) remains a gap. DENV1-4 cause ~100 million infections per year, with 25-50% symptomatic cases. Using children's plasma from our long-standing hospital-based study in Nicaragua, we compared DENV-neutralizing IgM antibodies in primary (1º; n=10) and secondary (2º; n=19) DENV1 infections. Plasma from ~14-30 days post-symptom onset were IgM- vs mock-depleted, and polyclonal IgM was eluted. We found that plasma IgM antibodies in both 1º (Mean NT50=0.23µg/mL) and 2º (Mean NT50= 2.6µg/mL) DENV1 cases demonstrated potent neutralizing activity against DENV1, the infecting serotype. Surprisingly, in 55% (10/18) of 2º DENV1 cases, plasma IgM contributed an average of 30% (range 8-76%) of total plasma DENV1-neutralizing activity at early convalescence, which is the peak antibody response. In this subset, mean DENV1-neutralizing titer in plasma with IgM was higher than plasma without IgM (NT50 = 63,831 vs 49,458; $p<0.05$, Wilcoxon paired rank test). Even after controlling for IgG in each fraction, the DENV1-neutralizing titer of plasma with IgM was 21% higher than that without IgM. This demonstrates a substantial role of IgM in 2º DENV1 cases. As a benchmark, plasma IgM from 1º DENV1 cases (n=8/9) contributed to a mean of 54% (24-76%) of total plasma DENV1-neutralizing activity. Additionally, we found that eluted plasma IgM from 2º vs 1° DENV1 cases were phenotypically distinct, with more cross-neutralization of DENV2 and DENV3 in 2° (Mean NT50 DENV2 =3.8; DENV3 = 2.4 µg/mL) compared to 1º (Mean NT50 DENV2 = 4.6; DENV3 = 12 µg/mL) DENV1 cases ($p<0.05$; Mann Whitney Test). Thus, plasma IgM from the early convalescence of both 1º and 2º DENV1 cases demonstrate substantial antiviral activity, and breadth of IgM DENV-neutralization is greater in 2º DENV1 immunity. Contribution of IgM to 2º DENV immunity is particularly intriguing since this is a time at risk for enhanced dengue. Neutralizing IgM may have an underappreciated role in controlling DENV infection.

5308

TYPE-SPECIFIC ENVELOPE-DOMAIN EPITOPES OF NEUTRALIZING ANTIBODIES AFTER PRIMARY DENV2: SUMMARY OF FINDINGS FROM NATURAL INFECTION, HUMAN CHALLENGE MODELS, AND YOUNGER AND OLDER CHILDREN FROM A PEDIATRIC OBSERVATIONAL COHORT

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After primary dengue (DENV) infection or vaccination, individuals develop antibodies to different epitopes and domains on the DENV envelope (E) and pre-membrane (prM) glycoproteins. Of these, serotype-specific (TS) antibodies typically target E domains, while serotype cross-reactive (CR) antibodies typically the target pre-membrane (prM) protein and conserved regions of E. Age-dependent vaccine efficacy has been observed in Phase III trials of pediatric live-attenuated vaccination against DENV, where younger children have lower protection after vaccination compared to older children. A possible component of this difference may be variation in epitopes of neutralizing antibodies elicited by maturing immune systems. To identify and quantify E-domain, neutralizing TS antibody responses in polyclonal sera, we developed a panel of chimeric DENV4/2 viruses that incorporate DENV2 envelope domain I, II, and III (DENV4/2-EDI, EDII, EDIII, respectively) into the DENV4 E glycoprotein. The recovery of viable DENV4/2-EDII recombinants was dependent on the inclusion of chimeric DENV4/2 prM protein that maintained critical interactions with chimeric E. The ED-chimeric virions preserved epitopes of TS and envelope dimer epitope (EDE) CR mAbs and had similar sensitivity to CR polyclonal responses as the parental strains. In natural infection and human challenge samples, the neutralizing activity of polyclonal sera predominantly targets EDIII. To evaluate age-based differences in antibody domain-level epitope targets controlling for prior exposure, we also present an analysis of primary DENV2 convalescent sera from the Pediatric Dengue Cohort Study located in Managua, Nicaragua. Additional studies in controlled experimental studies and well-described observational cohorts will examine if ED epitope targets correlate with protection against subsequent infection.

5309

NEUTRALIZING ANTIBODY TITERS DIFFER BY STRAIN AND MATURATION STATE AMONG MULTITYPIC CHILDREN IN THE PHILIPPINES

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Dengue virus seropositivity is often measured by plaque reduction neutralization test (PRNT), which assesses the antibody response of a patient against one or more of the dengue virus serotypes 1-4 (DENV1-4). These tests consist of serum from a patient and an infectious virus, but the high antigenic diversity of dengue virus may mean that the neutralizing capacity of an individuals' serum is variable by strain. Additionally, viruses can emerge from cells at different stages of maturity (defined by the cleavage of the precursor membrane protein), with mature viruses possessing a more homogeneous structure and fewer antibody-accessible epitopes. To assess the effect of these variables on neutralization assays, we grew both standard and mature preparations of highly passaged DENV1-4 WHO reference strains, where lab adaptation may increase antibody cross-reactivity, and low-passage DENV1-4 clinical isolates from Southeast Asia (SEA). All strains were tested with sera from 26 children aged 9-14 participating in a cohort study in Cebu, Philippines with evidence of multiple prior dengue virus infections. As anticipated, antibody titers were

highest against the WHO-standard strains, but surprisingly, we also found that the WHO-mature strains had the lowest titers. When we scrutinized this trend by serotype, the WHO-standard strains consistently had the highest titers, while the titers of the other three virus preparations relative to one another were variable by serotype. Overall, the geometric mean titers of the SEA strains were significantly different from the titers of the WHO strains irrespective of maturation preparation ($p < 0.001$), but the SEA strains were less sensitive to changes in maturity ($p=0.09$) than the WHO strains ($p<0.0001$). Our results suggest that careful consideration should be given before selecting a viral strain for neutralization assays. A mature isolate may be more useful as a correlate of protection. However, for identifying any prior DENV infection, a standard lab-adapted virus may better detect weakly neutralizing antibodies.

5310

LINKING MULTIPLE SEROLOGICAL ASSAYS TO INFER DENGUE INFECTION HISTORY ACROSS PAIRED SAMPLES USING MIXTURE MODELS

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Dengue virus (DENV) is an increasingly important human pathogen, with half of the globe living in environments where DENV transmission may one day occur. Since only a minority of infections are captured by direct detection methods (PCR or antigen tests), serological assays play an important role in the diagnostic process. However, interpreting results from serological assays across different platforms remains challenging, particularly because interpretations from multiple assays may differ, creating uncertainty over how to generate finalized interpretations. Here we utilize mixture models, which provide a probabilistic framework to separate data into multiple distinct components, to infer infected vs. uninfected individuals from longitudinal serological samples. We develop a Bayesian mixture model that can jointly model data from multiple serological assays, and that can incorporate information from serum sampled at multiple time points. We fit to 3479 sampled pairs of acute and convalescent serum collected as a part of illness and household investigations across three longitudinal cohort studies in Kamphaeng Phet, Thailand which contained 298 from gold standard PCR confirmed infections. We compare the classification of the new model to prior standard interpretations that independently utilize information from either the hemagglutination inhibition assay (HAI) or enzyme-linked immunosorbent assay (ELISA). Our results provide a probabilistic framework through which multiple serological assays across different platforms can be combined across sequential serum samples to provide insight into whether individuals have recently experienced DENV. As the differences in results across these platforms reflect performance as well as biological differences, future work will explore the clinical and immunological differences that shape these heterogeneous immune responses to DENV and whether distinct phenotypes may shape subsequent clinical outcomes.

5311

CIRCULATORY T FOLLICULAR HELPER CELL AND MEMORY B CELL FREQUENCIES IN A CONVALESCENT DENV IMMUNE COHORT

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Dengue virus (DENV) is the cause of the most prevalent mosquito-borne viral disease worldwide, with an estimated 400 million cases and 21,000 deaths per year. Circulatory T follicular helper cells (cTfh) activation, a CD4+ T cell subset that helps B cells, requires antigen presentation through specific human leukocyte antigen (HLA). In some populations, HLA alleles are associated with DENV protection, with robust and multifunctional T-cell responses, supporting a role for T-cells during DENV infection mediated through individual HLA alleles. However, studies identifying conserved HLA alleles specific to DENV epitopes and HLA-restricted T cells (DENV-specific HLA-restricted T cells) across multiple DENV endemic populations, including Puerto Rico, still need to be included. In this context, we aim to characterize the breadth and magnitude of DENV-specific HLA-restricted cTfh cell responses in a convalescent DENV immune cohort to access specific cellular and host genetic factors mediating the adaptive immune response to DENV infection. Here we test the hypothesis that DENV-specific HLA-restricted cTfh cells persist over the convalescent period with heightened breadth and magnitude. HLA class II alleles from stored buccal samples will be genotyped by Next-Generation Sequencing using the MHC Core Library Prep and Capture Kit. We aim to describe the HLA alleles from a Puerto Rico cohort. The HLA alleles selected for the study will be the most frequent alleles worldwide for each locus and the unique alleles in the population. The investigators anticipate that DENV-specific HLA-restricted cTfh cells circulating in blood persist over convalescent infection with heightened breadth and magnitude.

5312

MALARIA ABOLISHES ONNV-INDUCED ARTHRITIS BY ALTERING THE KINETICS OF VIRUS-SPECIFIC CD4 T CELL DEVELOPMENT IN THE FOOTPAD-DRAINING LYMPH NODES

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O'nyongnyong virus (ONNV) is a re-emerging Alphavirus known to be transmitted by main malaria vectors, suggesting the possibility of co-infections with Plasmodium species in areas of co-transmission. However, the immunopathological consequences of such infections remain unexplored. Using experimental murine co-infection models, we demonstrated that a pre-existing blood-stage Plasmodium infection abolishes ONNV-induced footpad swelling by suppressing the infiltration pathogenic CD4 T cells into the footpads of co-infected mice. T cell profiling of footpad-draining lymph nodes (LN) upon ONNV inoculation revealed altered expansion of swelling-driving CD4 T cells but not CD8 T cells. Assessment of LN migratory dendritic cells (mDC) in co-infected mice revealed impaired mDC numbers and activation capacity which was restored upon blockade of Plasmodium-induced interferon gamma (IFNg) and restitution of viral antigen availability in the footpads. However, the restoration of mDC numbers and, consequently, CD4 T cell expansion in footpad-draining LN of co-infected animals did not restore footpad swelling suggesting an IFNg-independent mechanism. Importantly, lymph nodes from malaric mice displayed increased numbers of PD-1+ICOS+ and TFH-like CD4 T cells during the first 72 hours post-ONNV inoculation which correlated with the induction of germinal center (GC) responses in footpad-draining lymph nodes. These preliminary data suggest that the suppression of ONNV-induced footpad swelling during murine malaria could be linked to the shifting of virus-specific T cell responses towards a TFH-like phenotype.

Additional experiments aiming at identifying soluble immune factors that could explain the development of TFH responses in in footpad-draining LN of co-infected mice are being carried out.

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EVALUATING THE CONTRIBUTION OF NS1 ANTIGENEMIA TO DENGUE-ELICITED NEUTROPENIA

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Neutrophils are an important part of the innate immune response and host protection from invading pathogens. One way pathogens try to impede this innate response is decreasing the number of neutrophils available, causing neutropenia. Neutropenia is a common clinical manifestation in viral infections, including dengue infection. Dengue virus (DENV) is responsible for dengue disease, a tropical disease responsible for an estimated 400 million infections per year and significant healthcare burden. The cause of dengue-elicited neutropenia is unknown but is an important question in the field due to culpability of activated neutrophils and their byproducts in the risk of hemorrhage in severe dengue. Neutropenia has a variety of causes, one prospect in the context of dengue infection is a cell death pathway known as NETosis. The cell releases its nuclear content complexed with antimicrobial proteins to immobilize invading pathogens; evidence of this process has been found during dengue infection. Using data collected from the Dengue Human Infection Model challenge study, our lab analyzed the early viral kinetics of dengue infection and identified the secreted form of DENV non-structural protein 1 (sNS1) in serum as a potential contributor to neutropenia. sNS1 plays an important role in dengue pathogenesis and is implicated in disrupting endothelial cell monolayer integrity and platelet activation, both important components of vascular destabilization during severe disease through interaction with TLR4. TLR4 engagement can induce NETosis, providing a potential link between sNS1 and neutrophils. To test sNS1 involvement in NETosis, we stimulated isolated neutrophils with vary concentrations of NS1 for three hours. Using fluorescent microscopy, we found that sNS1 appears to trigger cell death in neutrophils. We plan to preincubate neutrophils with a TLR4 blocking antibody to determine if TLR4 mediates sNS1 induction of neutrophil death. This begins to address the question of whether secreted NS1 interaction with neutrophils plays an important role in mediating dengue-elicited neutropenia through triggering of cell death pathways.

5314

ARBOVIRUS TRANSMISSION AND DISEASE PATHOGENESIS IN OBESE AND TYPE II DIABETIC MICE

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In the last century, anthropogenic factors such as human movement to new ecotypes, agricultural expansion, and uncontrolled urbanization, have significantly contributed to zoonotic emergence and spillover at a global scale. Arthropod-borne viruses (arboviruses), maintained in nature through transmission cycles involving hematophagous arthropod vectors, are the most important contributors to disease and a public health concern worldwide. Concomitantly, another contemporary public health concern is the prevalence of chronic underlying conditions. According to the World Health Organization (WHO), chronic diseases kill approximately 41 million people each year, with cardiovascular disease, cancer, respiratory diseases, and diabetes accounting for the most deaths. Strikingly, clinical data indicate that patients with preexisting conditions such as diabetes infected with mosquito-borne viruses are prone to severe disease outcomes and mortality. It is reasonable to hypothesize that such conditions will impact the progression of arboviral replication and transmission in and from human hosts. In the present study, we aim to understand the arbovirus disease pathogenesis, viral kinetics, and mosquito acquisition of arboviruses in infected mice suffering from an obese state approximating a Type II diabetes mellitus (T2DM) phenotype. 10-week-old LEPRDB/DB, LEPRWT/DB, wild type C57BL/6J mice were pretreated with IFNAR blockading antibodies to render them permissive to MAYV infection through Aedes aegypti bite. No significant difference in viral load was observed during early infection (3 to 5 days post-infection) by MAYV among the three genotypes (media ranging from 2.1 log10 to 3.1 log10 FFU/mL). This lack of significant difference in the viral load suggests that further histopathological and cytokine analysis must be conducted to analyze if there are differences in the MAYV infection outcome related to TSDM and the wild-type genotypes.

5315

EXPLORING MICRORNA AS POTENTIAL DIAGNOSTIC BIOMARKER FOR ZIKA VIRUS INFECTION

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Zika virus (ZIKV) has emerged as a serious public health concern, which accurate diagnosis is of crucial importance, since it impacts pregnancy outcome and has lifelong consequences for newborns from infected mothers. However, current diagnostic tests are challenging for nucleic acid testing due to short-lived viremia and low viral loads, and for serological testing due to antibody cross-reactivity with other flaviviruses leading to misdiagnosis. This study aimed to identify and evaluate microRNAs (miRNAs) in plasma as biomarkers for accurate ZIKV diagnosis. In the discovery phase miRNA profiles were determined by Next-Generation sequencing using plasma samples from pre- and post-seroconversion phase of ZIKV infection, and from non-infected subjects as a control group. Analysis of miRNA results from the discovery phase led to the identification of 110 differentially expressed miRNAs (68 up- and 42 down-regulated) in ZIKV-infected subjects as compared to the control group. We selected 20 miRNAs with high levels of differential magnitude (up or down modulation) between ZIKV-infected and control groups for further evaluation and validation by qRT-PCR using sample from 72 subjects, including 48 ZIKV-infected (26 pre- and 22 post-seroconversion) and 24 from non-infected controls. A total of 5 miRNAs (miR-3929, miR-3615, miR-17-3p, miR-497-5p, and miR-1224-5p) exhibited the highest differential expression to discriminate ZIKV-infected from control, from which 2 (miR-3929 and miR-3615) were identified using the logit model as a signature-panel to distinguish infected from non-infected subjects. To verify and validate the identified signature-panel we performed blind-coded testing in a cohort of 36 plasma samples composed of ZIKV-infected pre- (n=12) and post-seroconversion (n=12) and non-infected control (n=12). Decoded analysis of results revealed that 19/24 infected samples and all uninfected were correctly identified, demonstrating feasibility of the miRNA signature-panel to be used as non-viral and non-immune biomarkers to diagnose ZIKV infection and potentially for monitoring pregnant women in endemic areas.

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CARDIAC ELECTROMECHANICAL ALTERATIONS DURING CHIKUNGUNYA VIRUS INFECTION

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Chikungunya virus (CHIKV) is a re-emerging arbovirus that is endemic to several parts of the world, including Africa, Asia, South America, and Central America. CHIKV has been shown to infect several tissue systems, resulting in a spectrum of symptoms. While it is generally considered an abnormal presentation, there is significant clinical evidence of CHIKV infection of human cardiac tissues, including myocarditis, arrythmia, and cardiac arrest. These reports span over five decades and include all lineages that were and are currently circulating in the world. As climate change increases the range of CHIKV and more people are at risk of infection, there is a need to understand how CHIKV can affect the heart. In this study, six lines of human pluripotent stem cell derived cardiomyocytes

(hiPSC-CMs) were infected with seven different strains of CHIKV, including field strains of East Central South African, Indian Ocean, Asian, and West African lineages. Microelectrode Array (MEA) was used to assess electromechanical alterations of the cardiomyocytes, including beat rhythm, conduction, and contractility changes. All strains of CHIKV directly infected hiPSC-CMs within two days of infection. MEA analysis revealed differences between impact of CHIKV infection on female hiPSC-CMs and specific CHIKV strains. Multiple linear regression analysis showed that gender was a significant predictor for several electromechanical factors. Statistical analysis did not indicate that any CHIKV lineage caused significant electrophysiological changes. The data show significant changes in electrophysiology of CHIKV infected hiPSC-CMs, where specific CHIKV lineage does not appear to play a role, which is supported by previous clinical data. Further, the experiments conducted here support past mouse model work and reveal hiPSC-CMs as a relevant study model for CHIKV infection of the human heart, allowing for novel discoveries to be made.

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SOLUBLE UROKINASE PLASMINOGEN ACTIVATOR RECEPTOR AS PROGNOSTIC BIOMARKER FOR SEVERE DENGUE IN ADULTS

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Dengue is the most common arboviral disease with an estimated 100 million symptomatic infections annually, and cases is expected to increase with warmer climate. Dengue associated illness requiring hospitalization is estimated at 19.0% in Asia, which may strain healthcare facilities during outbreaks. Current biomarkers are inconsistent in predicting SD in early disease, and a combination of biomarkers to predict SD are less feasible in resource limited settings. Together, poses a challenge in the management of dengue patients. In a longitudinal cohort (febrile, critical and recovery phases) of adult dengue patients recruited in Singapore (2016-1019), we evaluated on the utility of soluble urokinase plasminogen activator receptor (suPAR) as a prognostic biomarker of SD. A total 129 patients: 40 dengue fever (DF), 46 dengue warning signs (DWS), 13 SD and 30 controls, were assayed for plasma suPAR levels by ELISA. In the febrile, critical and recovery phases, suPAR levels were significantly elevated in the dengue group compared with controls, and levels were significantly raised with increasing severity (all, P<0.001). By pairwise comparisons, suPAR concentrations were significantly raised in SD versus either DWS or DF in all disease phases, but no significant difference between the DWS and DF groups was observed. By logistic regression, a unit increase in suPAR level was associated with an increased risk of SD in the febrile phase [OR: 2.1, 95%CI (1.2-3.7), P = 0.009] and critical phase [OR: 1.70, 95%CI (1.27-2.28), P < 0.001]. In the febrile and critical phases, the AUROC for suPAR to predict SD was 0.82 (95%CI 0.63-0.99) and 0.86 (95%CI 0.75-0.97), respectively. Using a cut-off, suPAR levels at >4ng/ml, to predict SD, the sensitivity was 86.0% with a specificity of 69.0% in the febrile phase, and 91.0% sensitive and 68.0% specific in the critical phase. The PPV for SD in febrile and critical phases were 35.0% and 42.0%, respectively, and the corresponding NPV was 97.0% (febrile) and 98.0% (critical). In conclusion, plasma suPAR levels were elevated in adult dengue patients in proportion to disease severity and maybe a reliable predictor of SD.

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ATTENUATED CHIKUNGUNYA VIRUS STRAIN 181 CLONE 25 INFECTION IN IMMUNOSUPPRESSED RHESUS MACAQUES

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Chikungunya is a mosquito-borne infection caused by Chikungunya virus (CHIKV) which is transmitted to humans by the bite of infected mosquitos. CHIKV is a rapid-onset febrile disease characterized by fever, headache, lethargy, arthralgia, muscle pain, and rash. The attenuated CHIKV 181/clone 25 was developed for live vaccine production for human use in 1986 using CHIKV 15561 strain isolated from an infected patient from Thailand. CHIKV 181/clone 25 induced great protection against challenge and highest antibody titers in weanling mice and monkeys; however, it was withdrawn because 8% of volunteers in Phase II human clinical trials developed transient arthralgia. In this study, we studied the ability of attenuated CHIKV strain 181/25 to cause disease in immunosuppressed rhesus macaques (RM) using cyclophosphamide and dexamethasone. The immunosuppressed monkeys were inoculated with 107 PFU of CHIKV strain 181/25. After the infection, all animals exhibited asymptomatic infection as evidenced by lacking of core temperature change, joint swelling and/or lymph node enlargement. No critical changes in blood cell counts were observed following the infection. Viral RNA was detectable in the circulation from day 1 after intravenous infection, and longer bacteremia period was observed in an animal in the immunosuppressed group. Anti-CHIKV IgM and IgG were induced by day 4 post infection. CHIKV-specific cellular immune responses were determined by IFN-γ ELISpot assay and showed the cellular responses during 7 to 14 days post infection. Cytokine profiling was different between the immunosuppressed and control groups. Viral RNA dissemination was found predominantly in lymph nodes and spleen with greater level in the immunosuppressed group. Infectious virus was detected after 1 to 2 days post infection in one animal in each group at relative low level. This study provided laboratory tools to evaluate CHIKV rhesus model for pre-clinical study or drug and vaccine testing. However, to establish symptomatic CHIKV illness, longer immunosuppression treatment may require.

5319

A MACHINE LEARNING AIDED COMPARISON OF LIVER PATHOLOGY AMONG FILOVIRUSES

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Ebolavirus and Marburg virus are filoviruses known for causing hemorrhagic fever. Pathologic changes in the liver are abundant and develop early after infection. However, model specific differences in liver pathology are poorly understood. We performed a retrospective study of the liver pathology resulting from different filoviral models, using machine learning approaches, to investigate model specific differences. Liver slides and blocks were examined from rhesus monkeys infected with Ebola virus (EBOV Kikwit and EBOV Makona), and Marburg virus (MARV), and compared to clinical chemistries obtained during the experiment. All samples were from previous experiments on animals that did not receive treatment or vaccination and were infected intramuscularly with similar inoculant. A board-certified pathologist annotated slides for areas of parenchyma and necrosis in QuPath. Model training was done using a customized multi-class U-Net implemented in Tensorflow. Clinical chemistries showed higher levels of the liver enzyme ALT in animals ifected with MARV (mean 1411) compared to EBOV Makona (mean 666, p= 0.001) or EBOV Kikwit (mean 387, p=<0.001), but lowest levels of AST in animals infected with MARV compared to EBOV Makona or EBOV Kikwit. The percentage of parenchymal area with necrosis was highest in animals infected with MARV

(Mean 35.6%) compared to EBOV Makona (mean=1.7%, p=0.008), or EBOV Kikwit (mean=0.7%, p=0.0013). ALT values and percent necrosis trended higher in EBOV Makona compared to EBOV Kikwit without reaching statistical significance (p=0.08, p=0.08). Linear regression showed a significant association between ALT levels and percent necrosis (p=0.003), but an overall poor fit (R squared=0.34). Histopathologic review of liver samples revealed viral specific differences in presentation between tissues from MARV infected animals compared to EBOV infected animals. No statistical difference was seen between EBOV Kikwit and EBOV Makona. This initial machine learning model development has shown promising results for automated whole slide liver tissue segmentation to provide quantitative data.

5320

A CONSISTENT NONHUMAN PRIMATE MODEL FOR EARLY ZIKV-ASSOCIATED PREGNANCY LOSS

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The 2016 Zika virus (ZIKV) outbreak in the Americas revealed a previously unidentified risk of birth defects in babies born to mothers infected with Asian-lineage ZIKV during pregnancy. However, the impact of African-lineage ZIKV infection during pregnancy remains less understood, despite probable origination in Africa and its presumed endemic presence in many countries for decades. Nonhuman primates serve as a valuable model for studying ZIKV in pregnancy due to their gestational similarities to humans and susceptibility to ZIKV infection but limited animal numbers and inconsistent outcomes have hindered the study of ZIKV preventives and therapeutics using this model. While examining the effects of African ZIKV co-infection on pregnancy outcomes in SIV-positive rhesus macaques, we identified a specific combination of infection timing, dose, and ZIKV strain that consistently resulted in fetal demise. Regardless of SIV co-infection or antiretroviral therapy (ART) treatment, 11 out of 14 pregnancies (78%) ended in spontaneous loss within 3 weeks following infection at approximately 30 days gestation with an African-lineage ZIKV. ZIKV was detected in the placentas and fetal tissues in all cases of pregnancy loss. Due to the high rate of pregnancy loss among all ZIKV-infected dams, we could not assess the impact of SIV co-infection. However, we serendipitously developed a model with a consistent outcome necessary for testing medical countermeasures in pregnancy and potentially uncovered an under-appreciated risk of early pregnancy loss due to infection with African-lineage ZIKV.

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GENETIC ANCESTRY DRIVES DIFFERENCES IN THE IMMUNE RESPONSE TO DENGUE VIRUS INFECTION IN HUMAN SKIN

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Epidemiological evidence supports a protective effect of African ancestry against severe dengue, but the mechanisms underlying the effects of ancestry on dengue virus (DENV) infection are unknown. We used full-thickness human skin explants from healthy individuals to define the effects of genetic ancestry on the immune response to DENV infection. We performed genotyping of a set of ancestry informative markers to estimate the proportion of European and African ancestry for each individual. Skin explants were inoculated with DENV-2 using a bifurcated needle and analyzed by confocal microscopy using antibodies to NS3 protein, cell-specific, and inflammatory/ antiviral markers. We found a strong positive correlation between European ancestry and the extent of DENV replication in the epidermis and dermis, which contained two times more infected cells than African ancestry skin. In European skin, increased replication of DENV was mediated by boosted recruitment and infection of macrophages, dermal dendritic cells, and Langerhans cells. Quantitative in situ imaging, as determined by the expression of IL-1β and IFN-α, revealed a robust inflammatory response to DENV infection in European skin, whereas a strong antiviral response was observed in African skin. Simultaneous blockage of IL-1β and addition of IFN-α using microneedle arrays before DENV inoculation inhibited DENV replication by preventing recruitment and infection of myeloid cells in the dermis of European skin. RNA-sequencing of full skin biopsies revealed ancestry-associated differences in the transcriptional response to DENV and confirmed a stronger inflammatory response to infection with increased European ancestry. Profiling of single nucleotide polymorphisms of innate immune-related genes identified several genotype variants (e.g., RXRA, OSBPL10) with higher expression in Africans that were markedly associated with reduced DENV replication in the dermis. Our findings reveal ancestry-related differences in the immune response to DENV infection and identify potential therapeutic targets that could prevent dengue dissemination in human skin.

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HCV LEADING EARLY AGE ONSET OF HCC - MULTIPLE RISK FACTORS ATTRIBUTE

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HCC development in young adults is multifactorial such as alcohol abuse, HCV, HBV infection, cirrhosis of liver, alcohol consumption, smoking, obesity , genetic and metabolic conditions. Here we report an unusual case of a 27-years-old man who presented with complain of vague right upper quadrant abdominal fullness, jaundice, non-bilious non-projectile vomiting, loss of appetite, and significant weight loss for 2-months. On examination, tenderness + in right hypochondrium , bilateral pedal edema . Patient had elevated liver enzymes (Sgpt-181, Sgot-150) with increased alpha-fetoprotein (16271). Other abnormality include urea-323, creat-9.21, USG was suggestive of chronic kidney disease (contracted kidney with lost CMD). Triple phase CT of abdomen showed a liver mass with arterial enhancement and delayed washout suggestive of HCC and cirrhosis. Patient was diagnosed as HCC at an early stage, which allowed for timely initiation of treatment. This early age onset of HCC in a young adult may be multifactorial such as HCV infection, alcoholism, cirrhosis, smoking, and CKD . Alcohol-induced liver injury increases the risk of developing HCC in persons infected with HCV, with higher risk among those who consume

alcohol heavily. The possible mechanisms of CKD causing HCC involve uremia itself, long-term dialysis status, and miscellaneous factors such as hormone alterations and dysbiosis.

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RECONSTITUTION OF HUMAN MICROGLIAL CELLS IN BRAIN CEREBRAL CORTEX AND CEREBELLUM OF HUMAN-IMMUNE-SYSTEM HUMANIZED DRAGA MICE

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Human microglial cells are a target and reservoir for human pathogens affecting the central nervous system such as HIV, SARS-CoV-2, and Zika virus leading to severe neuropathology in humans. The lack of animal models able to reconstitute human microglial cells poses a challenge for investigating human neuropathology after infection and for testing efficacy of immunotherapeutics. The humanized DRAGA mouse (HLA-A2.HLA-DR4. Rag1KO.IL2RγcKO.NOD) reconstitutes a functional human-immune-system (HIS) upon infusion with CD34+ hematopoietic stem cells (HSC) from HLA-matched human umbilical cord blood. Pluripotent HSCs infused into DRAGA mice migrate in various tissues where they can differentiate not only into hematopoietic-derived cells, but also into non-hematopoietic cells such as human epithelial/endothelial cells expressing the human angiotensin-converting enzyme 2 (hACE2), the primary receptor for the SARS-CoV-2 virus infection, as well as human hepatocytes. The DRAGA mouse, by virtue of reconstituting human cells and by eliciting specific human cellular and antibody responses following infection and vaccination, represents a surrogate "in vivo human model" able to sustain infection with human pathogens such as SARS-CoV-2, Influenza, P. falciparum, HIV, Zika virus, and dengue. Herein we show reconstitution of human microglial cells (hCD45+hCD18+) in the brain cerebral cortex and cerebellum of DRAGA mice by flow cytometry (FACS), with cell numbers averaging 6.3% of the total brain microglia. Immunofluorescence studies further indicated that the human microglial cells in the brain of DRAGA mice were organized in small patches in the cerebral cortex and cerebellum but absent in the control (non-HSC infused DRAGA) mice. The DRAGA mouse model thus represents a novel pre-clinical model to investigate infection and immunopathology of human pathogens targeting human microglia, and for testing the efficacy of novel vaccines and immunotherapeutics.

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EFFICACY OF HUMAN SERA FROM SUBJECTS VACCINATED WITH A CHIKUNGUNYA VIRUS VIRUS-LIKE PARTICLE VACCINE IN CYNOMOLGUS MACAQUES

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Chikungunya virus (CHIKV) causes acute illness characterized by fever, fatigue, and severe joint pain, which can lead to debilitating chronic manifestations including arthralgia. Emergent BioSolutions is developing a CHIKV virus-like particle (VLP) vaccine that has demonstrated a robust immune response in nonclinical and Phase 1 and 2 clinical studies. The vaccine has demonstrated protection against viremia after a virulent challenge in non-human primates. To determine the protective efficacy of antibodies induced in humans by the CHIKV VLP vaccine, sera from vaccinated volunteers was used to passively immunize cynomolgus macaques (NHPs). Four dose levels of CHIKV immune sera pooled from subjects who had been vaccinated once with 40 µg of CHIKV VLP vaccine were administered intravenously to six NHPs per group, and an additional six NHPs received negative control sera. All NHPs were challenged subcutaneously at 24 hours with a rescued clone of CHIKV outbreak strain LR2006-OPY1, a strain heterologous to the Senegal strain used to derive the CHIKV VLP. Animals were monitored for ten days following challenge. Analysis of serum immediately before challenge demonstrated that CHIKV serum neutralizing antibody (SNA) levels in NHPs increased in a dose-dependent manner. No animals that were administered CHIKV sera developed viremia at any time during the course of the study, while all animals that were administered control sera developed viremia that peaked two days post-challenge and resolved by day 4 post-challenge. Viral RNA was detected by quantitative reverse-transcriptase PCR in all control animals and in some animals in the two groups that were administered the two lowest dose levels (0.3 and 0.6 mL/kg) of CHIKV sera. No CHIKV RNA was detected in any animals that were administered the two higher CHIKV sera dose levels (1.2 and 2.4 mL/kg) or that had a pre-challenge SNA titer ≥ 25.7. This study demonstrated that sera from vaccinated individuals was sufficient to protect NHPs from viremia and the presence of viral RNA following heterologous CHIKV challenge and that an SNA titer of 25.7 was associated with that protection.

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INVESTIGATION OF A SUSPECTED CASE OF MONKEY POX, IBOKE, HEALTH DISTRICT OF TABOU, CÔTE D'IVOIRE, JULY 2022

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Monkeypox is a global public health problem. In West Africa more than 35 cases have been reported to WHO. On July 30, 2022, the health district of Tabou was informed by the detection of a suspected case of monkeypox in Iboké, a health area bordering Liberia, a country to which a confirmed case of monkeypox was reported. An investigation was carried out with the aim of describing the case, searching for other cases and proposing prevention and control measures. A cross-sectional descriptive study was conducted. A case was defined as any person presenting with an acute rash & one or more of the following signs or symptoms headache, fever, lymphadenopathy, myalgia, body aches, asthenia. The data were taken from consultation registers, interviews with identified contacts. Sociodemographic and clinical characteristics were collected. The data were analyzed in Excel & frequencies measures were calculated. 35-year-old young man with disseminated rashes on the face & the rest of the body accompanied by fever, with no notion of travel outside Iboké but having been in contact with a confirmed case. The result of his sample was negative. Ten (10) contacts were identified without signs & symptoms, of which 8(80%) linked to the suspected case and 2(20%) linked to the confirmed case in Liberia. 80% of the contacts of the suspected case live in Iboké versus 50% (1/2) for the confirmed case. The median age of contacts is 28.5 (range: 5 - 43). The sex ratio is 1.7 male to 1 female. Young man had contact with the confirmed case from Liberia. The majority of contacts lives in Cote d'Ivoire. No case of monkeypox has been detected in Cote d'Ivoire so far. Case management has been recalled and measures have been taken to strengthen cross-border surveillance between the two countries.

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SYLVATIC STRAINS OF DENGUE VIRUS HAVE DISTINCT REPLICATION KINETICS IN HUMAN CELLS

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Dengue disease is caused by each of the 4 types of dengue virus, infecting an estimated 390 million people each year and causing significant morbidity and economic burden. These viruses are endemic in tropical areas of the planet where the competent mosquito vector is available. Dengue viruses are thought to have emerged as a spillover from the dengue sylvatic cycle, where the virus is transmitted among non-human primates in Southeast Asia and Africa. Based on phylogenetic analyses, 4 independent spillover events resulted in the successful generation of the dengue virus types that

circulate in humans today. Other contemporary infections of humans with sylvatic strains have been reported, however, these have resulted in dead-end transmission chains without the generation of a new clade of viruses circulating in humans. What restricts most sylvatic strains of dengue virus to gain efficient transmission in humans remains unknown. Other scientific groups have generated conflicting data on the possible differences among the virus clades. To approach this question, we decided to use a set of complimentary methods to identify differences in replication of lab adapted, clinical isolates, and sylvatic strains of dengue viruses, using human cells as a model. Our data shows that clinical strains of dengue can initiate a complete replication cycle in primary human macrophages, although reaching lower infectious titers compared to lab adapted strains. Among the tested sylvatic strains, all presented lower infectious titers compared to the clinical isolates. As expected, all strains replicated to similar levels in mosquito cells. Currently, we are increasing the number of isolates from clinical and sylvatic origin to better understand inter-strain variability. This research will help understand what regulates the success of spillover events in flavivirus and help to anticipate if risk remains of new clades of dengue viruses entering the human transmission cycle.

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SEVERE DENGUE RISK: SPECIAL POPULATIONS WITH REPEATED HIGH-RISK EXPOSURES: CHARACTERISTICS AND A FRAMEWORK FOR RECOMMENDATIONS

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As a re-emerging tropical disease, a growing body of literature has been dedicated to the emergence of Dengue serotypes throughout the world, an increase in the vector range and seasonality, the discovery of dengue in previously unaffected populations and locations, and characteristics that place individuals at greater risk for severe dengue—the most complex and life-threatening form. However, no cohesive synthesis of the pathogenesis of the disease and its impact on specific non-traditional populations who are at a heightened risk of frequent and/or prolonged exposures. A literature review identified the comprehensive factors that determine the severity and determinates of the disease, the characteristics of non-traditional high-risk populations, and mitigation and control measures. Humanitarian aid workers, Peace Corps volunteers, missionaries, international business travelers, travelers visiting friends and relatives, and military service members are at a heightened risk for dengue infection due to recurrent and long-term travel to dengue-endemic regions, where they may have continuous or repeated exposures. A comprehensive, One Health approach should be employed to fight the spread of dengue infections. Synthesizing the clinco-epidemiology of dengue with available prevention and mitigation measures, including the use of vaccines, allows for the development of a framework for recommendations for travelers with repeated high-risk exposures. One of the best prevention methods is a tailored pre-travel health assessment covering various topics, including illness risk, primary prevention of vector contact, and health history. After establishing previous infection through a serum study, administering vaccines for travelers to endemic and hyperendemic areas should be considered. Travel health providers must be aware of barriers to prevention, such as non-compliance, inaccurate risk perception, and vaccine hesitancy, and devise strategies to mitigate these barriers. Dengue is a real and present threat whose reach will expand with travel, trade, and the expansion of the habitable range of the vector.

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HIGH CONFIDENCE AND DEMAND FOR HEPATITIS E VACCINE DURING AN OUTBREAK IN BENTIU, SOUTH SUDAN: A QUALITATIVE STUDY

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In Bentiu internally displaced persons camp, large outbreaks of hepatitis E have occurred in 2015-16, 2019, and 2021-22. In response to the 2021 outbreak, South Sudanese Ministry of Health with support from Médecins Sans Frontières implemented the first-ever mass reactive vaccination campaign with HEV239 (Hecolin; Innovax). The target population for the campaign was individuals 16-40 years old, including pregnant women, residing in Bentiu camp. We aimed to assess knowledge, attitudes, and practices related to hepatitis E and the vaccine in Bentiu camp. We conducted 8 focus group discussions (FGDs) with community leaders, the general population of vaccine-eligible adults, vaccine eligible pregnant women, and healthcare workers. The Behavioral and Social Drivers of Vaccination framework was selected a priori to develop FGD guides and organize emerging themes into four domains: thinking and feeling, social processes, motivation, and practical issues. Two coders used inductive thematic analysis to code all transcripts using NVivo software. Data were collected in November 2022. Most individuals had experiences with hepatitis E such as being infected themselves or witnessing infected family and/or community members. Hepatitis E was perceived as a dangerous disease, and general sanitation and cleanliness were frequently mentioned prevention strategies. Participants believed children, pregnant women, and elderly were the highest risk groups. Confidence in the benefits of hepatitis E vaccine was high and participants frequently made requests for additional hepatitis E vaccination campaigns and expanded eligibility criteria for vaccination (e.g. for children). The primary barriers to vaccination were practical issues related to being away from the camp during the campaign, fears about injections, social pressure, misinformation about side effects, and concerns about why some groups were not eligible for vaccination (e.g. young children). Personal experiences with hepatitis E illness and perceived severity of illness were drivers of high demand for hepatitis E vaccines in the first-ever use of the vaccine in an outbreak setting.

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POTENT NEUTRALIZING ANTIBODIES ISOLATED FROM DONORS IMMUNIZED WITH THE 17D YELLOW FEVER VACCINE

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Yellow fever virus (YFV) is a mosquito-borne flavivirus endemic in Sub-Saharan Africa and tropical South America. The disease yellow fever causes approximately 51,000 annual deaths worldwide. A live-attenuated vaccine developed in 1937 is essential to control the spread of YFV, but the shelf life and manufacturing constraints of egg-based vaccine production, the vaccine's rare severe adverse events, and the lack of effective therapeutic options for yellow fever disease create an urgency for the development of new YFV vaccines and therapeutic tools. YFV-neutralizing antibodies could be a promising passive immunization and treatment that may also guide development of effective non-replicating YFV vaccines. In this study, we captured natively paired heavy and light chain antibody libraries from two donors that were immunized with the YFV 17D vaccine and generated yeast surface display libraries for functional antibody analysis. By screening yeast libraries with YF virus-like particles purified by chromatographic techniques, we identified three anti-YFV antibodies with potent neutralizing activity against circulating strains from Western Africa and South America, including one extremely potent antibody with a neutralizing IC50 < 5 ng/mL against the 17D vaccine strain. Passive transfer of two monoclonal antibodies protected mice in the YFV neurotropic disease mouse model via intracerebral challenge with the 17D strain. The new YFV antibodies we describe here have the potential to support development of novel YFV vaccines and may also serve as YFV outbreak countermeasures for treatment or prevention.

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EXPLORING POTENTIAL INDICATIONS FOR REMDESIVIR BEYOND COVID-19

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Remdesivir (RDV; GS-5734; VEKLURY®), a monophosphoramidate prodrug of an adenosine analog, is the first FDA-approved antiviral therapy for COVID-19. Rapid approval and distribution of RDV for SARS-CoV-2 was enabled by preexisting safety, efficacy, and pharmacokinetic data generated during its initial development for RSV and Ebola. Beyond SARS-CoV-2, RDV and its parent nucleoside (GS-441524) have antiviral activity against multiple RNA viruses through potent inhibition of their viral RNA-dependent RNA polymerases (RdRp). Cell-based assays have shown that RDV is potent against viruses within the Paramyxoviridae, Pneumoviridae, Filoviridae, Coronaviridae, Flaviviridae, and Picornaviridae families. In vivo, the pharmacologically active nucleoside triphosphate is efficiently produced in lung and peripheral blood mononuclear cells, and antiviral efficacy has been demonstrated in animal models of RSV, Ebola, Marburg, Nipah, MERS-CoV, SARS-CoV, and SARS-CoV-2 infection. Because RDV requires intravenous administration, orally bioavailable prodrugs of the parent nucleoside are being evaluated for expanded use in outpatient populations. GS-621763, an orally bioavailable prototype prodrug of GS-441524, reduced SARS-CoV-2 replication in human primary lung cell cultures as well as in mouse, ferret, and nonhuman primate challenge models. GS-5245, another oral prodrug of GS-441524, has completed Phase I pharmacokinetic and safety evaluations and is currently in Phase III clinical trials for the treatment of high-risk COVID-19 patients. Expanded in vivo efficacy against other emerging viruses is an area of active research. Collectively, these data support continued exploration of the antiviral prophylactic and therapeutic indications of RDV and oral nucleoside analogs. Proactive characterization of preclinical efficacy across other priority pathogens can enable rapid deployment of an effective treatment in response to emerging viral threats.

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EVOLUTION OF A FUNCTIONALLY INTACT BUT ANTIGENICALLY DISTINCT DENGUE VIRUS (DENV) FUSION LOOP

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A hallmark of Dengue virus (DENV) pathogenesis is the potential for antibody-dependent enhancement (ADE), which is associated with deadly DENV secondary infection, complicates the identification of correlates of protection, and negatively impacts the safety and efficacy of DENV vaccines. ADE is linked to antibodies targeting the fusion loop (FL) motif of the envelope (E) protein, which is completely conserved in mosquito-borne flaviviruses and required for viral entry and fusion. In the current study, we utilized saturation mutagenesis and directed evolution to engineer a functional variant with a mutated fusion loop (D2-FL) which is not neutralized by FL-targeting monoclonal antibodies. The FL mutations were combined with our previously evolved pre-membrane (prM) cleavage site to create a mature version of D2-FL (D2-FLM), which evades both prM- and FL-antibodies but retains sensitivity to other type-specific (TS) and quaternary cross-reactive (CR) antibodies. CR serum from heterotypic (DENV4) infected non-human primates (NHPs) showed lower neutralization titers against D2-FL and D2-FLM than isogenic wildtype DENV2 while similar neutralization titers were observed in serum from homotypic (DENV2) infected NHPs. We propose D2-FL and D2-FLM as valuable tools to delineate CR antibody subtypes in serum as well as an exciting platform for safer live attenuated DENV vaccines suitable for naïve individuals and children.

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PHARMACODYNAMIC MODELS TO INFORM THE DESIGN OF PHASE 2 ANTIVIRAL THERAPEUTIC TRIALS FOR DENGUE

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There are currently no effective antiviral therapeutics for the treatment of early symptomatic dengue infection. A consensus methodology for the pharmacometric assessment of candidate dengue antiviral drugs would be important for comparing trial results and improving phase 2 trial design. The time to viral clearance and the area under log-viremia curve (AUC), assessed from serial qRT-PCR measurements in plasma samples, are the most widely reported measures of virological response in clinical trials. These endpoints have not been compared formally with other metrics, notably model-based estimates of the rate of viral clearance. We analyzed prospectively gathered viral clearance profiles from >600 patients recruited in clinical trials of repurposed drugs for dengue conducted by the Oxford University Clinical Research Unit in Viet Nam over the last 15 years. We fit different phenomenological pharmacodynamic models and summary measures (single exponential decay, bi-exponential, penalized splines, AUC) and show that the rate of viral clearance, estimated from a mixed effects single exponential decay model, is a robust pharmacodynamic summary of viral clearance. The rate of viral clearance, estimated from viral densities during the first 5 days following enrollment, provides increased statistical power (reduced type 2 error) compared with time to clearance and AUC. Using these data, we take a simulation approach to derive sample size requirements for hypothetical effective antiviral drugs with varying effects on acceleration of viral clearance. We recommend that pharmacometric antiviral assessments should be conducted in patients with early dengue illness (less than 72 hours from fever onset) with twice daily serial qRT-PCR plasma samples taken over 5 days.

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MULTIPLEX ASSAY PERFORMANCE ACROSS VARIED GEOGRAPHICAL AND RESOURCED SETTINGS: DEMOCRATIC REPUBLIC OF THE CONGO, LIBERIA, AND HAWAII

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Geographical and resource barriers may introduce biases and limitations to assay performance. Determining if assay reproducibility is compromised due to these barriers is essential for assay optimization and standardization. Sustainability is a keystone of public health equity, which includes inter-assay performance, especially for seroepidemiology or detection assays for use in local health posts, zones, or departments to direct public health interventions and policies. Multiplex technology has been used globally for seroepidemiological and vaccine response analyses; however, the performance of the assays across countries has yet to be assessed. Due to the robustness of the assay, it's hypothesized that filovirus multiplex bead-based assay performance shows limited variation across geographical and resource settings in Low Middle-Income Countries (LMICs) and High-Income Countries (HICs). On the example of "real-life" detection of filovirus-specific IgG responses using Magpix multiplex bead-based technology in laboratories in the Democratic Republic of the Congo (DRC), Liberia, and Hawai'i, United States, assay performance across countries, laboratories, and technologists has been assessed. Sources of potential variation were identified; however, there was limited variability across assays performed in each locale after assessments were conducted using correlation analyses and standardized cutoff criteria. The standardized cutoff criteria involve readouts from positive and negative control samples, population limits of detection, and validation using gaussian mixture modeling. These data suggest that our multiplex filovirus bead-based assay, used in three distinct geographical and resourced settings, performs well with reproducible results. This validated technology identifies previous exposure to filovirus antigens, including vaccine and natural infection responses, globally, with limited biases due to geographical or resourced setting changes. Sustainable and unvaried analysis of samples can not only improve local public health intervention strategies but may have global impacts as well.

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IN VITRO EFFICACY OF SELECTED ANTIMALARIALS AGAINST VARIANTS OF SARS COV 2 VIRUS CIRCULATING IN PANAMA DURING 2020 2022

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With the appearance of new variants of the Severe Acute Respiratory Syndrome virus (SARS-CoV-2) that causes COVID-19, the search for new antiviral drugs against this disease has renewed interest in the possible antiviral activity of antimalarial compounds. Even though at present several chemotherapeutic agents had been screened for activity against the SARS-CoV2 virus, only a few drugs had been approved for use in humans. Studies conducted in China early in the pandemic, demonstrated that chloroquine (CQ) and hydroxychloroquine (HCQ), inhibit SARS-CoV-2 replication in vitro in African green monkey kidney cells (Vero-E6). Since then, thousands of compounds have been screened using various cell lines including Vero-E6 and human lung cancer cells (Calu-3), but the use of CQ and HCQ in humans remains controversial. In this study, we aim to compare the in vitro efficacy of a series of selected antimalarials compounds against SARS-CoV-2 variants circulating in Panama with the hypothesis that the efficacy of the compounds is variant dependent. For this purpose, we first screened twenty-six compounds for cytotoxicity in both cell lines using the methyl thiazolyl tetrazolium (MTT) assay to determine their minimal cytotoxic concentration. Preliminary results indicated that 17/26 (65%) of the compounds had a viability $\geq$ 80% in Vero-E6 cells and 26/26 (100%) in Calu-3 cells. Of these, 13/17 (76%) showed antiviral activity in Vero-E6 cells against the Delta variant, and 15/17 (88%) against the A2.5 variant. In summary, 15 compounds including 4 and 8 aminoquinolines, quinolinomethanols, sesquiterpene lactones, among others were down selected for further analysis. The inhibitory concentration 50% (IC50), cytotoxic concentration 50% (CC50), selectivity index (SI) and pre and post infection activity will be determined for these compounds. In conclusion, in this study we demonstrate that selected antimalarial, endectocidal, antiviral and antineoplastic-immunosuppressive compounds from various classes had in vitro antiviral activity in Vero-E6 and Calu-3 cells against the Delta and A2.5 variants of SARS-Cov-2 circulating in Panama.

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QUERCETIN HYDRATE AS A POTENTIAL ANTIVIRAL AGENT AGAINST ZIKA VIRUS

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Zika virus (ZIKV) has re-emerged in recent decades, leading to outbreaks of Zika fever in Africa, Asia, and Central and South America. Despite its drastic re-emergence and clinical impact, no vaccines or antiviral compounds are available to prevent or control ZIKV infection. We performed a study to evaluated the potential antiviral activity of quercetin hydrate against ZIKV infection and demonstrated that this substance inhibits virus particle production in Vero cells under post infection condition. First, the MTT assay was used to determine the cytotoxicity of quercetin hydrate for Vero cells. Cell viability was well above 50% at the highest concentration (1000 µM), with cell viability corresponded to 101.1 ± 12.9% for Vero cells, at 1000 µM. No cytotoxicity was observed in cells treated with 0.5% DMSO. We initially tested the antiviral effect of quercetin hydrate on ZIKV in Vero cells since these cells are highly permissive to infection. Vero cells were incubated with 1000 - 15.625 µM quercetin hydrate or the equivalent volume of DMSO and infected with ZIKV (MOI = 0.1) under post infection condition for 48 hpi. Then virus yields were measured by viral titration (PFU/mL). The presence of DMSO did not affect the production of progeny infectious virus particles. In the post-infection assay in cells 1 h after virus infection, EC50 was 28.8 µM (95% CI 22.4-37.1 µM) and SI > 34.7. These results indicate a significant dose-dependent decrease in the production of infectious ZIKV particles in the presence of increasing quercetin hydrate concentrations. After observing the dose-dependent antiviral potential of quercetin hydrate in Vero cells, we performed kinetic infection in Vero cells. Viral progeny production in the cell supernatants was quantified by plaque assay at the indicated post-infection times to observe multiple rounds of replication over 72 h. In vitro antiviral activity was long-lasting (still observed 72 h post-infection), suggesting that quercetin hydrate affects multiple rounds of ZIKV replication.

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A UNIVERSAL PURIFICATION METHOD FOR SARS-COV-2 VARIANT SPIKE ANTIGENS

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Many vaccine platforms, including recombinant subunit protein vaccines, have been used to prevent severe disease subsequent to SARS-CoV-2 infection. Previously we developed an adjuvanted, lyophilized SARS-CoV-2 protein vaccine capable of preventing lung pathology in non-human primates. Immunoaffinity purification with the monoclonal antibody CR3022 was employed for antigen purification. Due to the evolution of the SARS-CoV-2 receptor binding domain in new variants, purification of current variant spike antigens with this efficient method is impossible. We demonstrate here a universal, tagless purification method applicable to all SARS-CoV-2 like spike proteins with minimal impact on the remaining antigen receptor binding sites by restoring the CR3022-binding epitope in our engineered BA.1 and BA.5 spike variant constructs. Reverted spike protein genes of BA.1 and BA.5 sub-variants were transfected into Drosophila S2 cells to produce stably expressing cell lines. Supernatants containing native BA.1 or the engineered versions of BA.1 and BA.5 were used for purification on CR3022- and ACE2-coupled affinity columns. Initial purification of native BA.1 spike construct using CR3022-immunoaffinity failed to extract measurable quantities of purified protein but purification with ACE2 resulted in low yields of purified protein. Reversion of the mAb epitope in BA.1 and BA.5 constructs allowed for efficient purification using CR3022. Binding affinity to ACE2 receptors remained the same between naive and reverted forms of BA.1 and BA.5 spike proteins. Restoring the CR3022 epitope on the Omicron variant spike therefore allows for effective immunoaffinity purification of a tagless, minimally modified antigen. This may therefore constitute a universal method for purifying SARS-CoV-2 spike proteins with minimal impact on the remaining epitopes and may streamline production of antigens for serosurveillance and rapid subunit protein vaccine production with a uniform, pre-approval process to combat new and evolving variants. It could potentially also be used for the generation of other purpose-engineered vaccine antigens.

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DESIGNING THERAPEUTICS BIOSIMILAR OF COMMERCIALIZED MABS TO MINIMIZE LETHAL EFFECTS OF DENGUE HEMORRHAGIC FEVER: IN-SILICO APPROACH

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Dengue virus (DENV) with its 4 flavivirus serotypes, is responsible for dengue hemorrhagic fever (DHF) and dengue shock syndrome and contributes to 390 M infections yearly, worldwide. Due to antibody-dependent enhancement (ADE), vaccines are worsening DHF. Unavailability of therapeutics, drive this study to design biosimilars of existing FDA-approved therapeutics mAbs to neutralize Dengue Ag-Ab immune complex and reduce the pathogenesis of DHF.Envelope protein sequence of 4 serotypes of DENV, their conserved domain, epitope regions, antigenicity were retrieved, identified, predicted and aligned respectively. The 7 selected FDA-approved therapeutic mAbs (PDB ID: 6VJA, 6TCS, 7DHA, 5GGU, 5VL3, 5UDE and Nirsevimab) and Fcγ of Anti-Dengue specific IgG sequence and structure, were retrieved. Molecular docking was conducted between therapeutics mAbs with Ag, Ab separately. Later, amino acids modification were performed on existing mAbs to design biosimilar model with a wide coverage range for blocking all serotypes of DENV, and validated them. Finally, DENV Ag-Ab immune complex with modeled biosimilar mAbs were docked for final screening.Out of the 7, both existing and modified Nirsevimab, Tremelimumab, and Omalizumab showed better binding affinity (ΔG values range -10 to -20.4 kcal/mole, where ΔG < -9.3 kcal/mole preferable for therapeutic drugs), dissociation score and smallest eigenvalue with dengue Ag-Ab immune complex. The 306-318 amino acid sequence of the E protein of DENV is the conserved epitopic domain with an antigenic score of 0.8 (where >0.7 is considered an immune response generating threshold). Among 13 amino acids, FVKEETQH amino acids are common among all serotypes, and others are unique. The modified mAbs cover the entire epitopic C terminal region of all serotypes, along with the Fc gamma region of anti-dengue IgG.The proposed 3 candidate biosimilars of commercialized mAbs fulfilled the criteria for the therapeutic potential to neutralize ADE in DHF. Further in vitro studies are required for biopotency and toxicity determination to investigate their effectiveness in immediate patient management.

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NIPAH VIRUS THERAPEUTICS: A SYSTEMATIC REVIEW FOR CLINICAL PRIORITISATION

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First identified in 1998 in Malaysia and Singapore, Nipah virus infection is a bat-borne zoonotic disease spread through contaminated body fluids of infected mammals. The case fatality rate (CFR) is 40-75% and debilitating long-term neurological complications are common in survivors. The ongoing Bangladesh outbreak is the largest since 2015 with 14 cases and 10 deaths to date. There are no specific therapeutics. In recognition of this and the high CFR, Nipah is a priority pathogen on the WHO R&D Blueprint. We conducted a systematic review to identify existing therapeutic monoclonal antibodies (mAbs) and small molecules for Nipah virus and other Henipaviridae to assess the evidence available for the safety and efficacy of each to support candidate prioritisation for potential compassionate use and clinical trials. We searched (last on 30 May 2022) 7 bibliographic databases, 3 trial registries, and the Trip database and WHO website. Studies were included if they contained minimum primary data on the safety and/or efficacy of mAbs (in vivo) or small molecules (in vitro) for the treatment of Nipah, Hendra, and related Henipaviridae. From 1469 records screened, we identified 56 eligible studies: 12 on 6 sets of mAbs and 25 on 10 groups of small molecules with in vivo data, and 19 on 18 sets of small molecules with in vitro data only. Limited data were available in humans with only one clinical trial (a phase 1 study of the anti-Hendra G glycoprotein mAb m102.4 in healthy volunteers), and 8 outbreak reports, 7 of which were case series of <10 patients and 6 of which used ribavirin. There were 23 animal studies all except one of which were challenge studies with Nipah or Hendra virus. Only m102.4, remdesivir, ribavirin, and fusion inhibitory lipopeptide have been tested in non-human primates. m102.4 and remdesivir protected all and lipopeptide 2 of 6 treated primates, while ribavirin delayed but did not prevent death. Risk of bias was critical in all clinical studies other than the one trial and high or unclear in all except one of the animal studies. A rationale is presented for clinical prioritisation.

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DENGUE ALLIANCE: ADVANCING DENGUE ANTIVIRALS FROM IN VITRO TO CLINICAL EFFICACY STUDIES OF CONCEPT

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In 2019 dengue was listed by World Health Organization (WHO) as one of the top ten global health threats, with a 30-fold increase in incidence over the last 50 years reaching 400 million infected cases per year globally with majority of the disease burden in Asia and Latin America. Climate change is predicted to contribute to expansion of the mosquito vectors to new geographical areas thus leading to further increase in the number of infections. Despite significant progress on vaccine and vector control, until now, no specific dengue therapeutics are available. The Dengue Alliance includes leading research institutions from dengue-endemic countries namely India, Thailand, Malaysia, and Brazil, and was established by the Drugs for Neglected Diseases initiative (DNDi) to provide a framework for the rapid identification and progression of antivirals for dengue to clinical proof-of-concept studies by drug repurposing strategies. Here we describe the drug repurposing approach taken by the Dengue Alliance to validate antivirals as well as the initial results and overall strategy for prioritization of compounds. The in vitro efficacy for 23 compounds with reported dengue or flavivirus antiviral data were determined using cell-culture based DENV assays available at the Dengue Alliance partner labs. These assays represent a broad coverage of the DENV1-4 serotypes as well as clinical isolates and lab strains using different infection systems. The results aligned well between the labs, with most compounds ranked similarly, independent of host cell system or DENV serotype. Compounds with EC50 in low micromolar range were further evaluated by pharmacokinetics studies in mice. Two of the compounds were finally tested in A129/AG129 model for inhibition of dengue infection.

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DEVELOPMENT OF A PSEUDOTYPED LENTIVIRAL REPORTER VIRUS SYSTEM FOR NIPAH AND HENDRA VIRUSES

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The Nipah and Hendra henipaviruses are highly virulent zoonotic paromyxoviruses, a family of negative-sense single-stranded RNA viruses. Henipaviruses have been isolated from bats in Central and South America, Asia, Oceania, and East Africa and can cause disease in humans, with fatality rates of up to 75%, and across a range of mammals. Nipah virus (NiV) infection in humans can cause respiratory illness and encephalitis and outbreaks have been reported in Malaysia and Singapore and are seen almost annually in eastern India and Bangladesh and. Hendra virus (HeV) are reported nearly annually in the eastern states of Australia, primarily infecting horses but also humans. There are no specific treatments or vaccines for NiV and HeV in humans, and they are classified as Biosafety Level-4 (BSL-4) pathogens. Their infection uses the interaction of the virus envelope G protein (for cell attachment) and F protein which performs infective membrane fusion. To provide critical reagents for analyses of antibody or serum immune responses to henipaviruses, we have developed a pseudotyped lentiviral reporter virus system for Nipah (strain Malaysia 2008) and Hendra (strain Hendra horse virus/Australia/Hendra/1994) viruses, with these reporter virus particles (RVPs) displaying both G and F proteins. These replication-incompetent RVPs perform one round of infectivity and enable safe (BSL-2) and reproducible virus neutralization assays with luminescent or fluorescent readout. We are testing the ability to neutralize the NiV and HeV RVPs using anti-G and anti-F antibodies. The use of henipavirus RVPs will overcome biosafety level restrictions on research into vaccines and therapies for these viruses.

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MAPPING ANTIBODY EPITOPES USING A COMPREHENSIVE MUTAGENESIS LIBRARY OF SARS-COV-2 S PROTEIN

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To characterize the immune response to SARS-CoV-2 infection, we created a comprehensive Ala-scan mutation library of the SARS-CoV-2 S protein. We use this library to epitope map anti-SARS-CoV-2 monoclonal antibodies (MAbs) by high-throughput, rapid screens of MAb binding to each mutant S protein. Individual mutant expression plasmids are transfected into human cells to achieve native protein expression and folding. Immunoreactivity of MAbs to each mutant S protein is quantified by high-throughput flow cytometry, allowing us to identify the S protein epitope residues with the highest energetic contributions to MAb binding. We have mapped over 150 MAbs targeting the S protein, identifying conformational epitopes in the S1 receptor binding domain (RBD) and N-terminal domain (NTD), and in S2, helping characterize MAbs that neutralize and protect in animal models of disease. To provide critical reagents for analyses of MAb or serum immune responses to SARS-CoV-2 infection, we developed a pseudotyped lentiviral reporter virus system for SARS-CoV-2, with reporter virus particles (RVPs) displaying S protein. These replication-incompetent RVPs perform one round of infectivity and enable safe (BSL-2) and reproducible virus neutralization assays with luminescent or fluorescent readout. We have produced over 70 SARS-CoV-2 RVP types incorporating variant S proteins. We also used our MPS antibody isolation platform to obtain MAbs against S protein, some of which neutralize the major Omicron variants.

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DEVELOPING NOVEL INHIBITORS AGAINST VENEZUELAN EQUINE ENCEPHALITIS VIRUS BY TARGETING VIRUS-HOST INTERACTIONS

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Venezuelan equine encephalitis virus (VEEV) remains one the most important zoonotic pathogen in the family Togaviridae. VEEV is endemic to the Americas and has been responsible for periodic outbreaks of febrile and neurological disease in both equines and humans, with an associated case fatality rate of up to 10% in humans. Moreover, it is classified as a select agent by both the CDC and USDA due to its low infectious dose and ease of aerosolization and manipulation. Concerningly, there are currently no FDA-approved therapeutics or licensed vaccines against VEEV infection in humans. The VEEV capsid protein is an essential virulence factor of VEEV. The capsid protein can simultaneously bind to the host's nuclear import receptors, importin α/β1, and the host export receptor, CRM1 to form a tetrameric complex. This complex accumulates at the nuclear pore channel, halting nucleocytoplasmic trafficking, downregulating host transcription and inhibiting cellular antiviral response. We hypothesized that chemical inhibitors capable of disrupting the interaction of capsid with importin α/β1 should increase cellular antiviral response, resulting in reduced viral titers and rescue of cells from VEEV-induced cell death. Two small molecule inhibitors, I2 and 1564, were designed to disrupt the interaction between capsid and importin α. These inhibitors were well tolerated by HMC3 microglial cells with CC50 of >250 μM and >500 μM for I2 and 1564, respectively. These compounds impacted VEEV TC83 titer with >1 log10 decrease at 9 hpi. Furthermore, I2 displayed an EC50 of 2.96 μM and 1564 an EC50 of 5.38 μM against VEEV. Both compounds also rescued infected cells from VEEV-induced cell death. In order to evaluate the impact of these compounds on the capsid-importin αinteraction, we cloned two viruses that contain a V5 tag at the N-terminus of the capsid. The replication kinetics of these new viruses were similar to that of parental viruses. Moreover, they

both expresses V5-tagged capsid at various timepoints. Future studies will evaluate the impact of these compounds on capsid-importin interaction using co-immunoprecipitation and confocal microscopy.

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FACTORS ASSOCIATED WITH ADHERENCE TO MALARIA TREATMENT GUIDELINES IN PRIVATE DRUG OUTLETS - KISUMU COUNTY, KENYA

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The malaria prevalence in Kenya is 6% and three-fold higher in the western region. The National Malaria Control Program (NMCP) seeks to avert antimalaria resistance and other adverse outcomes. We assessed the factors associated with adherence to the malaria treatment guidelines in Kisumu County private drug outlets (DOs) in 2021. A cross-sectional survey of DOs was conducted. Using a structured questionnaire to interview DO staff, we collected data on outlet characteristics (location, testing), staff factors (cadre, age, sex, training), and systemic factors (supervision, inspection). Research assistants disguised as clients used a standardized tool to record data on malaria case management observed in DOs. Analysis used proportions and measures of central tendency, dispersion. Association between independent and dependent variables was assessed using the Chi-square test. Multivariable logistic regression analysis was used to identify factors independently associated with adherence at p-value <0.05. Of the 70 participating DOs, none had a copy of the guidelines, and 60 (85.7%) were in an urban setting. Male staff were interviewed at 35 (50%) outlets, and the age group of 30-39 years constituted 30 (42.9%) of the staff. Staff adhered to the guidelines in 14 (20%) outlets. The odds of adherence to guidelines were higher among staff who had a bachelor's degree at OR 6.0 (95% CI 1.66-21.74), staff trained on malaria rapid diagnostic test (mRDT) at OR 4.4 (1.29-15.04), staff who asked about patient's symptoms at OR 3.6 (1.08-12.25), DOs with functional thermometers at OR 5.3 (1.46-19.14), DOs inspected by Pharmacy and Poisons Board (PPB) within the preceding three months at OR 9.4 (2.55-34.67), and DOs with basic infrastructure at OR 3.9 (1.01-15.00). Recent inspection by PPB (adjusted odds ratio (aOR) 4.6 (1.03-20.77) and staff trained on mRDT at aOR 4.5 (1.02-19.84) were independently associated with adherence to guidelines. Frequently inspected outlets and staff trained on mRDT tend to adhere to the guidelines. Regulatory inspection of all DOs should be done frequently. County health managers and NMCP should capacity-build DOs on mRDT use.

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RETROSPECTIVE STUDY TO DETERMINE ANTIMALARIAL RESISTANCE MARKERS PROFILE USING TAQMAN ARRAY CARD IN TAK PROVINCE THAILAND FROM 1998-2001

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One of the major contributing factors of continued transmission of malaria is the development of drug resistant Plasmodium falciparum. Although the total number of malaria cases reported in Thailand has decreased in recent years, it is important to conduct surveillance in endemic areas to understand the emergence and spread of resistance to the first-line treatments for malaria and guiding malaria control measures. A Plasmodium TaqMan Array Card (TAC), developed at the University of Virginia was employed to identify mutations of various genes associated with anti-malarial resistance in retrospective samples. These samples were collected in 1998, 1999 and 2001 from Tak province, Thailand under a protocol evaluating the BinaxNow® Malaria Rapid Diagnostic Test, which received FDA approval in 2007. A total of 808 samples were tested, and 696 samples were confirmed malaria species positive. P. falciparum was the dominant species detected, followed by mixed infections of P. falciparum/P. vivax, P. falciparum/P. malariae, P. falciparum/P. vivax/P. malariae, and P. falciparum/P. vivax/P. ovale. Mutations in kelch13, Pfcrt, pfdhfr, pfdhps, cytochrome b, and Pfmdr1 genes were the main targets of detection. The first-line of treatment for uncomplicated P. falciparum infection during the time of the collection of these samples was mefloquine alone or in combination with sulfadoxine/pyrimethamine (S/P) and with artesunate in more recent years. No PfCYTB mutations associated with atovaquone resistance were detected. We detected mutations in PfMDR 1 at positions N86Y, Y184F, and N1042D that confer mefloquine resistance. Mutations in genes that are associated with S/P resistance, pfdhfr and pfdhps, are high in these samples. A double mutation of PfDHFR at positions 59R and 108N were presented at >99% while the majority of PfDHPS had multiple mutations, 540E and 581G. The only K13 mutations detected were a mutation at position P574L (3.33%, 1/30) in a 1998 sample, position Y493H (2.49%, 5/206) in 1999 samples, and position R539T (0.22%, 1/460) in 2001 samples. Both Y493H and R539T are WHO confirmed K13 mutations conferring resistance to artemisinin.

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EMERGING PLASMODIUM FALCIPARUM WITH REDUCED SUSCEPTIBILITY TO ARTEMISININ AND LUMEFANTRINE IN AFRICA

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Clinical management of uncomplicated malaria caused by Plasmodium falciparum is reliant on the effectiveness of artemisinin-based combination therapy (ACT). New parasite genotypes encoding variants of the pfk13 gene are now emerging in Africa, and these are less susceptible to the artemisinin component drugs. This poses a risk of resistance selection against the partner drugs in ACT, such as lumefantrine. Case histories from UK travellers with documented ACT treatment failure, with and without pfk13 variants, and results from field surveys of resistance gene variants will be presented, together with newly collected in vitro susceptibility data for parasites of African origin adapted to long-term culture in 2022-23. The implications of these findings for future drug strategies for African malaria chemotherapy, and the design of appropriate therapeutic efficacy studies, will be considered. Finally, we will discuss the wider public health implications for Africa of a potential upsurge in prevalence of P. falciparum with reduced susceptibility to artemisinin.

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SANGER SEQUENCING AND DECONVOLUTION OF POLYCLONAL INFECTIONS: A QUANTITATIVE APPROACH TO MONITOR DRUG RESISTANT PLASMODIUM FALCIPARUM

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Molecular markers are used in epidemiological surveillance to monitor the emergence and spread of drug-resistant pathogens. These markers are comprised of either single nucleotide polymorphisms (SNPs) or concatenated SNPs in microbial genes that interact with drugs. Although various technical improvements in sequencing methods have been introduced to identify SNPs, current tools (conventional approach) used to measure molecular markers of anti-malarial resistance do not allow discrimination of mixed infections, and must be improved for more sensitive surveillance of anti-malarial resistance to better inform control strategies. We developed a new method to quantify molecular markers of anti-malarial

drug resistance genes [Plasmodium falciparum dihydropteorate synthase (Pfdhps) and P. falciparumdihydrofolate reductase (Pfdhfr)] by standard sequencing of amplicons and bioinformatic estimation of proportions of different genotypes in individual samples. Using parasite mixtures with known alleles, we observed a highly significant correlation between the predicted proportion of each allele with the proportion measured by sequencing and deconvolution. This was observed for Pfdhps at codons 436F, 437G and 613S/T and for Pfdhfr at codons 51I, 59R and 164L ($p < 0.001$). In studies of field samples, the mean fraction of Pfdhps was greater than 20% at codons 436F/A (95.9%,) and 437G (49.9%), but not at 431V, 540E, 581G, and 613S/T (4.7%, 0.0%, 1.2% and 1.5%, respectively); corresponding prevalences of Pfdhps were 100%, 72.5%, 50.0, 0.0%, 25.0%, and 12.5%, respectively. The mean fraction of Pfdhfr was greater than 20% at codons 51I, 59R and 108T/N (89.0%, 98.3% and 74.7%), respectively but not at 16V(0.6%), 50R(11.1%), 140L(8.6%) and 164L(8.7%); corresponding prevalences of Pfdhfr were 100%, 100%, 100%, 12.5%, 75.0%, 50.0%, and 28.6%, respectively. Our results demonstrate quantitative discrimination of varying proportions of sensitive versus resistant alleles using a cost-effective approach that incorporates Sanger sequencing of PCR amplicons with novel informatics tools for deconvolution.

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IDENTIFICATION OF NEW ANTIMALARIALS TARGETING THE PLASMODIUM FALCIPARUM PROLINE TRNA SYNTHETASE

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Identification of new antimalarials targeting the P. falciparum proline tRNA synthetase Benigno Crespo, Carlos Alemparte, Pilar Manzano, Emilia D'oria, Andrew Cliffon, Tony Choudhry, Gang Yao, Apirat Chaikuad, Audrey Tolbert, Chloe Oxford and Nathan Gittens

Malaria is one of the most devastating diseases in the world, causing around 65,0000 deaths in 2021, and almost 50% of the world population is at risk of being infected. Reports of resistance to Artemisinin in different regions, especially in South East Asia and recently also in Africa, is a major concern. There is an urgent need of new antimalarial treatments to replace those compromised due to resistance. Phenotypic screening has been the cornerstone in the search for new antimalarials in the last decade. However, the chemical diversity in the screening collections is currently exhausted, and little progress has been made in the identification of new modes of action. Thus, more target-based approaches are required to find new chemical starting points for hit to lead programs. Cytoplasmic prolyl t-RNA synthetase (ProRS) is one of the most chemically and genetically validated targets in Plasmodium falciparum (Pf). ProRS is the main target of Febrifugine, a Chinese traditional medicine used for centuries in the treatment of Malaria. However, Febrifugine and synthetic analogues like Halofuginone cannot be developed as antimalarials due to an unacceptable safety profile associated to their low selectivity against the human homologue.In this work, we present the strategy followed for the identification of new chemical inhibitors of Pf ProRS. GSK collection has been screened by affinity selection mass spectrometry (ASMS) and by encoded library technology (ELT) in different conditions, including ProRS alone as well as combinations of the protein with its different substrates (proline, ATP and tRNA). Identified binders were progressed to a biochemical assay to assess their activity against Pf ProRS and its human counterpart. Mode of action of selective compounds will be elucidated using resistant strains, thermal shift, biochemical assays and crystallography.

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SIMPLE, INEXPENSIVE IN VITRO DRUG SURVIVAL ASSAY FOR MONITORING ANTIMALARIAL DRUG SENSITIVITY IN MALARIA ENDEMIC REGIONS

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Resistance to cheap antimalarial drugs and the current artemisinin combination therapies has contributed to the sustained burden of malaria. For malaria elimination, the efficacy of current drugs needs to be monitored especially in Africa, which bears over 96% of the burden of malaria. Drug efficacy monitoring in laboratories use in vitro inhibition concentration (IC50) tests, which has been highly inconsistent and cumbersome to implement across endemic settings. Here, we present a simple and inexpensive in vitro malaria drug survival assay (mDSA) for monitoring antimalarial failure in low resource settings. In vitro drug survival assay determines the % survival and the reinvasion rate of parasite isolates exposed to a 48-hour pulse of lethal concentrations of antimalaria drugs. In this study, 32 field isolates of malaria parasites in the Gambia and the control isolates (DD2 and 3D7) were exposed to (10X IC50 cut-off) of dihydroartemisinin (DHA): 24nM, lumefantrine (LUM): 200nM, chloroquine (CQ): 200nM and piperaquine (PPQ):200nM respectively for 48h, followed by another cycle of culture in drug-free medium. The % survival and the reinvasion rate were estimated after 24h and 48h drug-free growth. Our preliminary findings show that this simple assay can consistently differentiate resistant from sensitive parasite strains for each of the antimalarial drugs. With CQ for example, the % survival was 72, 118 and 6% for the field isolates, CQ-resistant strain (DD2) and CQ-sensitive strains (3D7) respectively ($p < 0.05$). The high % survival of the field isolates, evidence of CQ resistance, was supported by the significantly higher reinvasion in the field isolate than 3D7 (0.4 vs 0, $p < 0.05$) and the no significant difference between the field isolates and DD2 (0.4 vs 1.4, $p > 0.05$). mDSA confirmed persistent CQ resistance in the Gambia. mDSA can therefore be used for surveillance of antimalarials and early detection of failure. It could facilitate drug policy to improve malaria control.

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ANALYSIS OF THE SUITABILITY OF USE OF MUTATIONS IN THE PVCRT-O AND PVMDR1 GENES AS MARKERS OF RESISTANCE OF PLASMODIUM VIVAX TO CHLOROQUINE IN AMAZONIC BASIN

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In Brazil, approximately 139,000 malaria cases were recorded in 2021, 83% of them caused by P. vivax. In the absence of an antimalarial vaccine, the control policy is based on case management through prompt diagnosis and treatment. With the rapid emergence and dispersion of parasite drug resistance, it is necessary to monitor the effectiveness of drugs used in the treatment. In Brazil, a percentage of up to 10% of vivax malaria cases resistant to chloroquine (CQ) have already been registered. Unlike P. falciparum, there are no established molecular markers of P. vivax chemoresistance (QR) to CQ. Therefore, we investigate whether the polymorphisms in the genes pvcrt-o and pvmdr1 can be markers of QR to QC. Additionally, the pvdhfr and pvdhps genes associated with QR to the sulfadoxine-pyrimethamine (SP) were analyzed to find out the potential of using this drug in cases of QR parasites to CQ. For this, 130 samples from the Amazon Basin were studied through the polymerase chain reaction followed by target DNA sequencing. In the pvcrt-o exons, the K10 insert was present in 14% of the samples. Regarding pvmdr1, the SNPs T958M and F1076L had a frequency of 95% and 3%, respectively, while the SNP Y976F was not detected in the samples. In pvdhfr, we observed the presence of double FRTHNI (76%), triple FRTHNL (21%), and quadruple

FRTRNL (8%) mutants, and the wild-type haplotype was not found. As for pvdhps, we detected the wild type (38%) and single SGKAEV (50%), and double mutants CGKAEV (12%). Allelic combination of the pvdhfr/pvdhps genes showed that the triple FRTHNI + SGKAEV (42%) and the double FRTHNI + SAKAEV (31%) mutants were the most prevalent. Thus, it is concluded that: i) mutations in the pvcrt-o gene seem to have a low potential for association with the phenotype of QR to CQ because K10-pvcrt-o and F1076L/Y976F/T958M-pvmdr1 polymorphisms were detected in samples from patients who responded well to CQ treatment and; ii) the frequencies of double and triple pvdhfr and pvdhps mutants associated with the low percentage of non-mutated parasites seems to indicate that SP cannot be introduced as an alternative drug in cases of QR to CQ in P. vivax.

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IDENTIFICATION OF B-CARBOLINE DERIVATIVES ACTIVE AGAINST QUIESCENT ARTEMISININ-RESISTANT PLASMODIUM FALCIPARUM

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Malaria is a devastating disease that caused 619,000 deaths in 2021 worldwide. Cases of malaria have increased from previous years in part by the quick development of resistance to current antimalarials. Due to the rising resistance to current antimalarial drugs such as chloroquine and artemisinin, there is an urgent need to discover and develop new chemotherapeutic agents that engage new targets in the malaria parasite. This research focuses on a novel antimalarial with a unique β-carboline scaffold known as PRC1584. It is known that exposure to dihydroartemisinin (DHA) induces a quiescent state in Plasmodium falciparum ring stage. Quiescence is a mechanism of Plasmodium survival especially from drug treatment. This phenomenon increases the risk of clinical failures following artemisinin-based combination therapies by slowing parasite clearance and allowing the selection of parasites resistant to partner drugs. We investigated if short exposure of PRC1584 also induces quiescent and/or kills the proliferating ring stage and if PRC1584 has activity against DHA-induced quiescent ring stage in the presence or absence of DHA-resistance. We used the ring survival assay (RSA) and the quiescent-stage survival assay (QSA) to assess the antiplasmodial activity of PRC1584 and its analogs in the presence and absence of DHA resistance. Our studies revealed that only 8 hours of exposure to PRC1584 kills both the proliferating ring stage and the DHA-induced quiescent rings of P. falciparum independently of the presence of DHA-resistance. In addition, we are using these assays to guide optimization of this series as preclinical leads. Altogether, these results revealed that PRC1584 displays a fast-killing profile and that it may act through a novel mechanism of action. Identifying if new antimalarials may also facilitate the development of quiescent-ring stage is extremely important, as this could result in recrudescence and treatment failure.

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PLASMODIUM FALCIPARUM KELCH13 R561H SPREAD AND EMERGENCE OF OTHER ARTEMISININ PARTIAL RESISTANT MUTATIONS ACROSS RWANDA USING A SITE AND TEMPORAL RAPID POOLING STRATEGY

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Recent monitoring has detected multiple emerging Plasmodium falciparum kelch13 (K13) propeller gene mutations across East Africa. Mutations, such as R561H in Rwanda and C469Y/F, and A675V in Uganda, have been increasing and are associated with artemisinin partial resistance mainly manifesting as delayed clearance after treatment with ACTs and recrudescence. Coordinated surveillance efforts are necessary to track these K13 mutants and inform control efforts. Here we apply pooled sequencing to provide a rapid initial assessment of population allele frequency at collection sites. Whole blood samples (n=2,703) from malaria-positive patients were collected from 20 Rwandan health centers from May to December 2022. Samples were pooled at equal volume, stratified by site and month to generate 104 pools. DNA was extracted using magnetic beads and genotyped using molecular inversion probe targeted sequencing of K13 and other resistance genes. Site allele frequencies were calculated weighted by the number of samples in a given pool. From a single round of sequencing, R561H was detected at 13 of 17 sites with an average frequency of 23.5% (0 to 70.3%). The highest site frequency clustered in the center of the country. At sites bordering the DRC (n=2), no R561H was found, suggesting R561H may not have spread west. In Bugaragara, in northeast Rwanda, we found 49.7% average frequency that progressively increased monthly from October to December (0.54% to 94.1%). Notably, A675V, previously seen in Uganda, was found at 6.81% across 11 sites. Other mutations observed to be spreading in Uganda, C469F and C469Y, were not observed at any site. Concerningly, G449A was at 7.11%, a WHO candidate resistance mutation never before reported in Africa but associated with a two-fold prolonged parasite clearance half-life in Asia. It was detected at 2 sites including Tanda (20.8%) where a large outbreak has been occurring. Overall, it appears multiple K13 mutations are rapidly expanding in Rwanda, further endangering control efforts and treatment efficacy with the potential of engendering partner drug resistance.

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PLASMODIUM FALCIPARUM DRUG RESISTANCE MARKERS AND GENETIC STRUCTURE IN MOZAMBIQUE, 2015-2022

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Antimalarial drug resistance is a global threat to malaria control and elimination, and is of particular concern in Mozambique, one of the four African countries which account for over half of all malaria deaths worldwide. Here we aimed to describe antimalarial resistance markers in Mozambique and interrogate parasite population structure using genome-wide microhaplotyes. To achieve this, we performed Plasmodium falciparum amplicon and whole genome sequencing using Next Generation Sequencing in 2251 malaria-infected blood samples collected in 2015 and 2018 in seven provinces of Mozambique. Another batch of samples (1300) from 2021 and 2022 are being tested at the laboratory and the results will be presented at the conference. The preliminary results revealed

a total of 32 non-synonymous mutations in the kelch13 gene, although none of them are currently associated with artemisinin resistance. No mutations or frequencies above 1% were observed for the rest of markers, except for 184F in pfmdr1 (59%), 51I/59R/108N in pfdhfr (>95%) and 437G/540E in pfdhps (>81%). The frequency of pfdhfr/pfdhps quintuple mutants increased from 80% in 2015 to 89% in 2018 (p<0.001), with a lower expected heterozygosity and higher relatedness of microhaplotypes surrounding dhps mutants than wild-type parasites suggestive of recent selection. pfdhfr/pfdhps quintuple mutants also increased from 72% in the north to 95% in the south (2018; p<0.001). This resistance gradient was overlaid with a concentration of mutations in position 436 of pfdhps (17%) in the north, a south-to-north increase in the genetic complexity of P. falciparum infections (p=0.001) and a microhaplotype signature of regional differentiation. The results of this study revealed several public health implications such as, appropriate efficacy of artemisinin-based combination therapy for P. falciparum treatment, chemoprevention with sulphadoxine-pyrimethamine is still recommended in areas with high rates of pfdhfr/pfdhps quintuple mutations, the evidence of a return of chloroquine therapeutic efficacy in Mozambique.

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INADEQUATE ARTEMETHER-LUMEFANTRINE TREATMENT RESPONSE IN A 15-MONTH OLD PATIENT WITH UNCOMPLICATED FALCIPARUM MALARIA IN WESTERN KENYA: A CASE REPORT

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Despite global efforts against malaria, inadequate treatment response and resistance to artemisinin combination therapies (ACTs) are becoming increasingly common, posing a threat to malaria elimination efforts. In endemic zones, ACTs are recommended as first-line treatment of uncomplicated malaria. This case report describes a 15-month old male patient with uncomplicated falciparum malaria who did not respond to artemether-lumefantrine treatment. The patient weighed 9.0 kilograms and presented at Kisumu sub county referral hospital with classical symptoms of uncomplicated falciparum malaria. The first dose of Artemether Lumefantrine (AL) was administered by a health worker who monitored the patient for an additional 30 minutes to confirm drug retention. Subsequent treatment doses were given to the parent for continuation at home. The patient returned on day 7 without symptoms, but was diagnosed with malaria by RDT and microscopy, revealing a Plasmodium falciparum single species infection at 0.2% parasitemia. Molecular diagnosis was done using PCR followed by genotyping for merozoite surface proteins 1 (MSP1), MSP2 and GLURP, which confirmed the presence of P. falciparum and recrudescence from identical alleles between the initial and subsequent samples. No non-synonymous mutations were observed in the Kelch 13 propeller gene of the parasite. Pharmacokinetic analyses, in vitro drug sensitivity tests, and further genotyping of putative drug resistance markers are underway. This case highlights the challenge of inadequate treatment response to artemether-lumefantrine in a young child with uncomplicated falciparum malaria in Western Kenya. The molecular diagnosis and genotyping results confirmed recrudescence of P. falciparum from identical alleles between the initial and subsequent samples. This case report emphasizes the need for close surveillance of antimalarial efficacy and parasite response to current antimalarial drugs in endemic zones. Further research is required to identify the underlying mechanisms of artemether-lumefantrine treatment failure and to develop effective strategies to combat resistance.

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PREVALENCE OF MOLECULAR MARKERS OF RESISTANCE TO SULFADOXINE-PYRIMETHAMINE (SP) BEFORE AND AFTER COMMUNITY DELIVERY OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY: A MULTI-CONTRY EVALUATION IN SUB-SAHARAN AFRICA

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The effectiveness of community delivery of intermittent preventive treatment (C-IPT) of malaria in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) was evaluated in selected areas of the Democratic Republic of Congo (DRC), Madagascar, Mozambique, and Nigeria. We aimed to assess the potential development of Plasmodium falciparum resistance to SP since it could threat C-IPTp effectiveness. Health facility-based, cross-sectional surveys were conducted before and three years after C-IPTp implementation in an area with C-IPTp, and in a neighboring area with no C-IPTp implementation in the four project countries. Dried blood spots from children under five years of age with clinical malaria were collected. SP resistance-associated mutations of the P. falciparum dhfr (N51I/C59R/S108N/I164L) and dhps (I431V/S436A/K437G/K540E/A581G/A613S) genes were analyzed. A total of 4983 children were recruited between June 2018 and November 2021. In DRC, the dhfr/dhps IRNI/ISGEAA haplotype remained lower than 10% in both areas and timepoints. In Mozambique the prevalence of this haplotype was over 60% at baseline and remained stable in both areas after C-IPTp implementation. No P. falciparum isolates harboring the dhps ISGEAA haplotype were found in Nigeria. In Madagascar only five isolates harboring this haplotype were found in both timepoints. No isolates were found to carry the dhps triple mutant ISGEGA haplotype. Community IPTp did not increase the prevalence of molecular markers associated with SP resistance after three years of implementation. These findings reinforce C-IPTp as a strategy to optimize malaria control during pregnancy and support the World Health Organization guidelines for prevention of malaria in pregnancy.

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ESTIMATING THE IMPACT OF PLASMODIUM FALCIPARUM DHFR AND DHPS MUTATIONS ON PROTECTIVE EFFICACY OF SULFADOXINE-PYRIMETHAMINE: EVIDENCE FROM THERAPEUTIC EFFICACY STUDIES AND IMPLICATIONS FOR MALARIA CHEMOPREVENTION

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Sulfadoxine-pyrimethamine (SP) is the recommended treatment for perennial malaria chemoprevention (PMC). The triple mutation in the Plasmodium falciparum dihydrofolate reductase (dhfr) gene (N51I/C59R/S108N) affects tolerance to pyrimethamine and it is largely fixed and saturated across sub-Saharan Africa. Additional mutations in the dihydropteroate synthase (dhps) gene may threaten the protective efficacy of SP, but this relationship has not yet been quantified. Here, we retrospectively analyse PCR-corrected re-infection data from therapeutic efficacy trials to quantify protective efficacy and duration of protection offered by SP (or SP-artesunate [AS]) against parasites with different genetic levels of SP resistance. We use a mathematical model that accounts for site-specific genotype frequencies and incidence rates and fit Weibull survival curves to the duration of drug protection using Bayesian methods. In a study in Benin (2003-2005), where 87.1% of patients had the quadruple mutation (dhfr triple + dhpsA437G), we estimated the mean duration of protection to be 29.9 days (95% Credible Interval [CrI]: 10.4-61.0) for SP and 27.0 days (95%CrI: 11.1-44.9) for SP-AS. The 30-day protective efficacy was 89.7% and 84.9%, respectively. In Malawi in 2005, where 91.6% of participants had the quintuple mutation (quadruple + dhpsK540E), SP-AS provided 14.8 (95%CrI: 10.3-30.3) days protection (30-day protective efficacy: 41.7%). In Tanzania in 2006, SP was estimated to provide 14.8 days (95%CrI: 3.6-39.9) protection against quintuple mutant parasites and 10.7 days (95%CrI: 6.1-30.1) against sextuple mutant parasites (quintuple + dhpsA581G). These findings suggest that accumulation of dhps mutations is associated with a reduced ability of SP to protect against infection. Further data will be added to refine these estimates and to quantify protection against different parasite strains. These findings, along with recent molecular survey data, can help parameterize models quantifying the impact of seasonal or perennial chemoprevention in areas with different genotype frequencies to inform scale-up of these interventions.

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IMPACT OF SEASONAL MALARIA CHEMOPREVENTION (SMC) ON MOLECULAR MARKERS OF PLASMODIUM FALCIPARUM ANTIMALARIAL DRUG RESISTANCE IN KOULIKORO HEALTH DISTRICT, MALI

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With the scale-up of Seasonal Malaria Chemoprevention (SMC), emergence of antimalarial drug resistance may impair the efficacy of the control strategy. This study examined potential changes in Plasmodium falciparum genes related sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ) and dihydroartemisinin-piperaquine (DHA-PQ) resitance. The study was carried out during effectiveness trials using DHA+PQ as an alternative drug treatment to SP+AQ among children under 10s children in Koulikoro region, Mali. DNA was extracted from dried blood spots and P. falciparum PCR positive samples underwent targeted amplicon sequencing (Miseq Illumina) for drug resistance profiling, including SNPs in Pfdhfr, Pfdhps, Pfmdr1, Pfcrt, PfKelch13 and Pfexo. Furthermore, copy number variations (CNVs) in Pfmdr1 and Plasmepsin2 were analyzed by qPCR. In total, 215 and 341 P. falciparum positive samples were successfully genotyped for 2019 and 2020, respectively. High prevalence of the triple mutated Pfdhfr haplotype at 51I-59R-108N (IRN) was observed for both 2019 (95%) and 2020 (93.3%), with no significant difference between two years and the drug arms (p>0.05). For Pfdhps, overall the most prevalent haplotypes observed were the single mutant haplotypes at 431-436-437G-540-581-613 (IAGKAA/ISGKAA), at approx 60% while more mutant haplotypes were observed in low numbers; for 2020 e.g. VAGKAA (0.6%), VAGKGS (1.2%) and ISGEAA (2.4%). No significant differences between the years and between the drug arms were observed (p=1.57). For Pfmdr1 and Pfcrt haplotypes, the most prevalent Pfmdr1 haplotype, NFD (86-184-1246) at >50% did not differ between the years and drug arms while the Pfcrt wildtype CVMNK haplotype increased from 39% to 52% from 2019 to 2020 (p=0.01), no difference between the drug arms were observed (p=0.44). For PfK13 gene, few non-synonymous SNPs were observed, none seemed important. Finally, few CNVs (<2%) in Pfplasmepsin2 and Pfmdr1 were observed for 2019 and 2020. Despite some minor variations from year to year, deploying SMC using either SP+AQ or DHA-PQ does not seem to select for molecular markers of drug resistance in the tested population in Mali.

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SYSTEMATIC REVIEW & GEOSPATIAL MODELLING OF MOLECULAR MARKERS OF RESISTANCE TO ARTEMISININS & SULFADOXINE-PYRIMETHAMINE IN PLASMODIUM FALCIPARUMIN INDIA

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Surveillance for genetic markers of resistance can rapidly provide valuable information on the likely efficacy of antimalarial drugs but needs to be targeted to ensure optimal use of resources. We conducted a systematic review of publications in 7 databases and 5 languages to compile resistance marker prevalence data from studies in malaria endemic states of India published between Jan 2014 and Mar 2022. The earliest identified study was conducted in 1994 and the most recent in 2019 with a median time lag from sample collection to publication of 4 years. Fewer studies were conducted in states with moderate or low malaria endemicity, with no studies conducted in Uttarakhand. In all, pfk13, pfdhfr, and pfdhps genotype data from 2953, 4148, and 4222 samples, respectively, were extracted from these publications. They were combined with data from the WorldWide Antimalarial Resistance Network (WWARN) Molecular Surveyor database and fed into a hierarchical geostatistical model to produce maps of the predicted prevalence of the pfk13 and pfdhps markers and of the associated uncertainty. Zones with a high predicted pfdhps 540E prevalence of >15% were identified in Central, Eastern and Northeastern India. The predicted prevalence of pfk13 mutants was non-zero at only few locations outside the Northeastern states but these were within or adjacent to the zones with high prevalence of pfdhps 540E. The highest uncertainty in the predicted prevalence was from zones where fewer or no studies were conducted but also from locations where conflicting data were collected, possibly reflecting evolving prevalence over time. This study identified regions with high predicted pfdhps 540E prevalence where there may be a higher probability of artesunate-sulfadoxine-pyrimethamine failures due to the predicted co-prevalence of pfk13 mutants. However, the accuracy of these predictions remains to be confirmed as they are based on very sparse data. This work can be applied to conduct systematic, targeted,

and eventually comprehensive molecular surveillance to help identify the treatments most likely to be effective for malaria elimination from India and elsewhere.

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PHARE, A BIOINFORMATICS PIPELINE TO DETECT MINORITY HAPLOTYPES IN MULTICLONAL SAMPLES

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The emergence of drug-resistant clones of Plasmodium falciparum is a major public health concern, and the ability to detect and track the spread of these clones is crucial for effective control and treatment. However, in endemic settings, patients are often infected with more than one clone at the same time making it likely to miss drug resistant clones using traditional molecular screening methods. The PHARE pipeline is a novel method for detecting these minor haplotypes in multiclonal samples sequenced using the Oxford Nanopore MinION platform. The pipeline was validated on three control datasets containing P. falciparum DNA of four laboratory strains at varying mixing ratios, achieving high recall and accuracy rates in all control datasets. Additionally, the pipeline was successfully tested on clinical samples from children in a paediatric hospital in the Central African Republic infected with P. falciparum. The pipeline can be used on any gene and was tested with amplicons of pfdhps, pfdhfr, and pfk13. The PHARE pipeline helps to provide a complete picture of the population structure of the malaria parasite and can be easily adapted to other pathogens and genes.

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MOLECULAR MARKERS OF RESISTANCE TO SULFADOXINE-PYRIMETHAMINE AND AMODIAQUINE IN THE HEALTH DISTRICT OF BOUSSÉ, BURKINA FASO

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Malaria is a major public health problem in Burkina Faso and is the leading cause of hospital visits, hospitalization and death. Malaria transmission is seasonal, with peaks observed during the rainy season. Seasonal malaria chemoprevention (SMC) is a major prevention intervention to reduce malaria burden in children under five, the most vulnerable group. It is recommended that SMC be implemented in areas where Sulfadoxine-Pyrimethamine (SP) and Amodiaquine (AQ) remains effective. Resistance to SP or AQ may reduce the chemopreventive efficacy of SPAQ from clinical malaria in children. To date, there is little data on the prevalence of SP and AQ resistance in Burkina Faso. After more than 7 years of SMC implementation, there are no up to date data on the level of molecular markers of SP and AQ resistance. This study aims to investigate the levels of parasite resistance to SP and AQ in the health district of Boussé in the Central Plateau region. A cross-sectional survey in health facilities was conducted. A total of 150 RDT positives samples were collected prior to the start of the 2022 SMC campaign from 08th to 10th July 2022. After the 4 SMC cycles in the area, 150 other RDT positive samples were collected between 7th to 11th November to 2022. Parasite DNA was extracted using Quiagen Kit at the Molecular Biology laboratory. Parasite genotyping is ongoing and the main outcome measure is the prevalence of molecular markers associated with SP (codons 108, 51 and 59 in dhfr and 437, 540 and 581 in dhps) and amodiaquine (codons 72-76 Pfcrt and 86, 184, 1034 and 1246 pfmdr1) in collected blood samples. This study will provide evidence of the resistance level of AQ and SP in Burkina Faso. Furthermore, this study will inform policy makers about the selective pressure of the SMC intervention on the circulating parasite population in Burkina Faso.

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RESISTANCE HAPLOTYPES DETECTED IN PREGNANT WOMEN IN BURKINA FASO RECEIVING INTERMITTENT PREVENTIVE TREATMENT WITH SULFADOXINE-PYRIMETHAMINE (SP)

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Malaria in pregnancy (MiP) is still a significant public health problem, with effects on both mother and offspring's. The latter includes maternal anaemia, foetal loss, premature delivery and delivery of low birth-weight infants. For the control of MiP, the World Health Organization (WHO) recommends prompt detection and treatment of all malaria cases associated with preventives measures such as of long-lasting insecticide treated nets (LLINs) together with administration of intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP). Resistance to SP is widespread throughout Africa, so IPTp use may be compromised in the near future. As a result, we sought to analyse the genetic profile of Plasmodium falciparum resistant to SP in pregnant women who have received IPTp-SP. This study included 418 samples from pregnant women attending antennal care visit (ANC). In all P. falciparum isolates the presence of SNPs in pfdhfr and pfdhps genes related with SP resistance were studied. Malaria prevalence was 45% (190/418) and 49% (205/418) respectively using microscopy and PCR. The species prevalence was 97.6% for P. falciparum and 2% for P. vivax. The only haplotype detected was the partially resistant (pfdhfr 51-59-108 pfdhps 437); fully and super resistant were not found. Apart from haplotypes, any SNP of importance for resistance has been described. Looking at the result of detected haplotype, partially resistance, indicate the selective pressure exerted by SP is not so high in the country. The use of SP is reserved exclusively for IPTp and nowadays for seasonal malaria chemoprevention (SMC) even if the coverage of 3 IPT-SP doses is not optimal. In addition, these pregnant women included in the study did not have severe malaria in any of the cases indicating the protection of IPTp. Continuous monitoring of genetic profile of malaria parasites infecting pregnant women who are part of IPTp-SP strategy in optimal conditions could give insightful information for the design of effective prevention measures.

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DIAGNOSTIC PERFORMANCE OF NXTEK™ ELIMINATE MALARIA PF TEST FOR THE DETECTION OF PLASMODIUM FALCIPARUM IN SCHOOL CHILDREN WITH ASYMPTOMATIC MALARIA

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Plasmodium falciparum malaria is one of the major roadblocks to the elimination program due to presence of a large number of portions of the population are asymptomatic infection. Targeting such reservoirs is critical to interrupting transmission and enhancing elimination efforts. The NxTekTM Eliminate Malaria Pf test is a highly sensitive rapid diagnostic test (hsRDT) for the detection of HRP-2. However, knowledge gaps exist in Ethiopia on the diagnostic performance of hsRDT in school children with asymptomatic malaria. We collected 994 blood samples between September 2021 and January 2022 to evaluate the diagnostic performance of the hsRDT for the detection of P. falciparum in healthy school children with asymptomatic infection. We compared the performance of hsRDT to the conventional malaria RDT, SD Bioline Pf/Pv (cRDT) in the field and microscopy

examinations of all samples and molecular analysis using QuantStudioTM 3 real-time PCR system (qPCR). We then used both microcopy and qPCR as reference methods. We found that the prevalence of P. falciparum was 1.51%, 2.2%. 2.2% and 4.52%, by microscopy, hsRDT, cRDT and qPCR, respectively. When we used qPCR as reference, the sensitivity of hsRDT was higher (48.89%) than the microscopy (33.3%), and showed 100% specificity and a positive predictive value (PPV). Microscopy showed similar specificity and PPV as hsRDT. Using microscopy as a reference, the sensitivities of both hsRDT and qPCR were similar (100%). Both RDTs demonstrated identical diagnostic performances in both comparison methods.The hsRDT has the same diagnostic performance as cRDT but improved diagnostic characteristics than microscopy for detection of P. falciparum in school children with asymptomatic malaria. These results suggest that the new malaria RDT, NxTek Eliminate Malaria Pf, could be a useful tool for the National Malaria Elimination Plan in Ethiopia to screen for P. falciparum in asymptomatic schoolchildren.

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EVIDENCE OF NON-FALCIPARUM PLASMODIUM CIRCULATION IN WESTERN AND EASTERN SENEGAL AND ITS IMPLICATIONS FOR MALARIA CONTROL

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Malaria elimination in Senegal requires accurate diagnosis of all Plasmodium species. P. falciparum is the most prevalent species in Senegal, although P. malariae, P. ovale, and recently P. vivax have also been reported. Nonetheless, most malaria control tools, such as Histidine Rich Protein 2 Rapid Diagnosis Test (HRP2RDT,) can only diagnose P. falciparum. Thus, HRP2RDT misses non-falciparum species and P. falciparum infections that fall below the limit of detection. These limitations can be addressed using highly-sensitive Next Generation Sequencing (NGS). This study assesses the burden of Plasmodium species in the community using targeting NGS. We collected 3000 samples from symptomatic and asymptomatic individuals in 2021 from three sites in Senegal (Diourbel, Kaolack, and Gabou). All samples were tested using HRP2RDT and photoinduced electron transfer PCR (PET-PCR), which detects all Plasmodium species. Targeted sequencing of the nuclear 18S rRNA and the mitochondrial cytochrome B genes was performed on PET-PCR positive samples. Malaria prevalence by HRP2RDT showed 9.4% (94/1000) and 0.2% (2/1000) in Diourbel and Kaolack, respectively. PET-PCR detected 295 positive samples, of which 29.8 %, 11.6 %, and 17.6 % were in Diourbel, Kaolack, and Gabou, respectively. Successful sequencing of 141/295 samples detected P. falciparum (80.3%), P. malariae (13.4%), and P. vivax (6.3 %). P. vivax was co-identified with P. falciparum in seven samples. Sequencing also detected two HRP2RDT-negative single infections of P. vivax from Gabou and Kaolack. Our findings demonstrate circulating non-falciparum species at the community level, highlighting the need for improved malaria control strategies and accurate diagnostic tools to better understand the prevalence of non-falciparum species countrywide.

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PERFORMANCE EVALUATION OF NOVEL LDH-BASED RAPID DIAGNOSTIC TESTS FOR PLASMODIUM FALCIPARUM AND P. VIVAX MALARIA ON FROZEN SPECIMENS: IMPLICATIONS FOR ACCESS TO RADICAL CURE

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New diagnostics with the potential to improve access to safe radical cure treatment options for Plasmodium vivax (Pv) malaria, such as point-of-care (POC) glucose-6-phosphate dehydrogenase (G6PD) tests and novel malaria rapid diagnostic tests (RDTs), are being deployed. Of particular interest are plasmodium lactate dehydrogenase (pLDH)-based RDTs with improved limits of detection (LODs) that translate into robust clinical performance for Plasmodium falciparum (Pf) infections with histidine-rich protein 2 (HRP2) and HRP3 gene deletions and for Pv clinical infections. In the Brazilian Amazon, where malaria is prevalent, such tools have the potential to optimize malaria case management. Venous blood specimens in K2EDTA were collected in Porto Velho, Rondônia, Brazil, as part of a cross-sectional diagnostic accuracy study to evaluate the performance of the POC STANDARD G6PD Test (SD Biosensor, South Korea) against a reference spectrophotometric G6PD assay. At the time of specimen collection, all participants were tested for malaria by microscopy per the standard of care. Stored frozen specimens from this study were used to evaluate the performance of three novel RDTs with improved LODs for LDH: the BIOCREDIT Malaria Ag Pf/Pv (pLDH/pLDH), Pf (pLDH), and Pf (HRPII/pLDH) (Rapigen Inc., South Korea). A commercially available comparator RDT (Málaria P.f / Pan ECO Teste - TR.003, ECO Diagnóstica, Brazil) was also run. RDT performance was evaluated against a reference assay for Pf and Pv malaria. The study evaluated 981 specimens, including 70 Pf-positives, 262 Pv-positives, 15 positives for both Pf and Pv, and 631 negative specimens by PCR. Diagnostic performance of the RDTs in terms of sensitivity and specificity will be reported. The implications of test performance for malaria case management will also be considered. The proportion of PCR-confirmed Pv malaria cases that would be eligible for radical cure treatment under different testing algorithm scenarios will be presented, considering the BIOCREDIT Ag Pf/Pv (pLDH/pLDH) RDT results, the microscopy results, and the individual's G6PD status.

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LOW PREVALENCE OF PFHRP2 AND PFHRP3 DELETIONS AND NON-FALCIPARUM MALARIA INFECTIONS IN OUTPATIENTS SAMPLED DURING THE 2021 BENIN HEALTH FACILITY SURVEY

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Benin's entire population is at high risk for malaria infection and Benin relies on rapid diagnostic tests (RDTs) detecting the Plasmodium falciparum histidine-rich protein 2 (HRP2) to diagnose malaria. However, no studies to date have systematically investigated the presence of pfhrp2 and pfhrp3 gene deletions in Benin that could affect RDT performance. Estimates of non-falciparum malaria infections, which are undetectable by HRP2-based RDTs, are also lacking in Benin. In this study, a total of 1413 outpatients at a nationally representative sample of 115 health facilities in Benin in 2021 were enrolled. Participants were tested using an HRP2-based RDT (Bioline Malaria Ag P.f Device 05FK50, Abbott) and provided dried blood spot samples for multiplex screening of six Plasmodium antigens and PCR genotyping for pfhrp2 and pfhrp3 deletions. In total, 729 participants (51.6%) tested positive for any Plasmodium antigen, and 673 (47.6%) had high HRP2 antigen levels. 56 Plasmodium antigen-positive isolates with low HRP2 antigen signals had DNA extracted for genotyping. Six non-falciparum single-species infections were identified by PET-PCR among study participants: two were P. ovale (0.3% of 729 Plasmodium-antigen positive), and four were P. malariae (0.5%, 4/729). No P. falciparum isolates lacking the pfhrp2 gene were found. Two infections (0.3%, 2/729) carried

P. falciparum parasites with pfhrp3 gene deletions, but these persons still tested positive by HRP2-based RDT and had received appropriate antimalarial treatment. Using laboratory HRP2-antigen positivity as the comparator assay, the sensitivity of the field HRP2-based RDT was found to be 89.5% (614/686), and the specificity was 86.4% (616/713). Overall, this study identified no pfhrp2 gene deletions in P. falciparum parasites and few non-falciparum Plasmodium infections. In conclusion, these data provide evidence for the continued use of HRP2-based RDTs for malaria case management in Benin.

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PLASMODIUM FALCIPARUM KELCH13 MUTATIONS IN ERITREA AND ASSOCIATIONS WITH PFHRP2 AND PFHRP3 DELETIONS

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Eritrea was the first African country to report a high prevalence of pfhrp2/3-deleted P. falciparum parasites causing high rates of false-negative RDT results and to switch away from exclusive use of HRP2-based RDTs in 2016. While country's high reliance on malaria RDTs was likely the major driving force behind the rapid expansion of pfhrp2/3-deleted parasites, antimalarial (artesunate-amodiaquine) use and host immunity could also exert selection pressures contributing to the spread. We retrospectively examined SNPs in the P. falciparum kelch13 gene from samples collected from the Northern Red Sea (Semenawi Keih Bahri) Zone in 2016 before the RDT switch and from the Gash Barka, Anseba and Debub Zones in 2019 where pfhrp2/3 status had been determined. No non-synonymous changes were identified from the 2016 sample set. However, five different single non-synonymous SNPs were detected in samples collected after 2019. The most prevalent non-synonymous SNP was R622I as it was detected in samples collected from all locations with an overall prevalence of 11.7% (ranging from 2.5% to 28%). Preliminary analysis suggests that the pfk13 R622I variant is twice as likely to occur in single pfhrp3-deleted than dual pfhrp2/3-deleted parasites, and three-times as likely compared to parasites without pfhrp2/3 deletions. Parasites carrying the R622I mutation have diverse microsatellite marker haplotypes, suggesting that they have evolved from different genetic backgrounds. The results suggest that there is an association between pfhrp3 deletion and pfk13 R622I mutation, and indicate an interaction between RDT and artemisinin selection pressure on the parasite population. Continued monitoring of the trend of pfhrp2/3 deletion and pfk13 R622I mutation will help to decipher this interaction. Full analysis will be presented at the meeting.

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SURVEILLANCE OF PLASMODIUM FALCIPARUM HRP23 GENE DELETIONS IN MOZAMBIQUE: A PROSPECTIVE STUDY

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The integration of genomic data into routine surveillance activities has the potential to increase actionable intelligence for making programmatic decisions on the optimal mix of control and elimination measures. With the aim of informing Mozambique's national malaria control and elimination strategies, we are conducting a prospective genomic surveillance study to monitor molecular markers of drug and diagnostic resistance, characterize transmission sources in low transmission settings, and assess the value of genomic data to infer levels of transmission. For the use case of assessing Plasmodium falciparum histidine rich protein 2/3 (pfhrp2/3) deletions, associated with parasite escape from rapid diagnostic test (RDT) detection, sampling took place in 2022 at 40 health facilities from five districts across four provinces of medium/high transmission during both rainy and dry seasons from 2-10 year-old children seeking care for malaria symptoms were tested by both routine HRP2-based rapid diagnostic test (RDT) and P. falciparum lactate dehydrogenase (LDH)-RDT, to identify potential false negative results due to pfhrp2/3 deletions among malaria clinical cases. Dried blood spots (DBS) were collected from those testing positive by one or both RDTs (n=200). Samples were identified according to discrepant results between LDH-RDT and HRP2- RDT, and all DBS from children with a negative HRP2-RDT but positive LDH-RDT will be tested for the presence of deletions by multiplex real time quantitative polymerase chain reaction qPCR. This approach not only detects the pfhrp2 and pfhrp3 genes but also the presence of the human reference genes humtubb (human beta-tubulin) and the pfldh gene.Samples with the following results (humtubb+, pfldh+ and pfhrp2/3-) and (humtubb+, pfldh+ and pfhrp2/3+) will be considered with deletion and no deletion respectively. The results will be incorporated into the Integrated Malaria Information Storage System (iMISS), so that the NMCP has full access to them and can recommend a change in RDTs if the prevalence of pfhrp2/3 gene deletions causing false-negative RDTs among symptomatic patients at national level is above 5%.

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AVAILABILITY OF FREE MALARIA RAPID DIAGNOSTIC TESTS AT THE LEVEL OF PRIVATE PHARMACIES FOR THE CONFIRMATION OF THE DIAGNOSIS OF MALARIA PRIOR TO ANTIMALARIAL TREATMENT: RESULTS OF A PILOT PROJECT IN BENIN: MARCH TO DECEMBER 2022

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World Helth Organisation recommends that all suspected cases of malaria undergo parasitological testing to confirm the diagnosis. Private pharmacies are a reality of the supply of care corresponding to the demand of an increasingly growing urban population. They hold 1/3 of the volume of antimalarial sales in the private sector, which represents 70% of the total volume of antimalarial sales in Benin. Most antimalarials are sold in these pharmacies without confirmation of the parasitological diagnosis. In order to improve the diagnosis of uncomplicated malaria in these private pharmacies in Benin, the National Malaria Control Program initiated the training of pharmacists for the free implementation of rapid diagnostic tests for malaria and artemisinin-based therapeutic combinations subsidized in 44 out of the total of 340 private pharmacies currently operating in Benin. These 44 pharmacies were selected according to well-defined criteria, in particular possession of an authorization to open and operate, adherence to malaria control guidelines, agreement to comply with the rules for the transfer of subsidized ILPs, monthly reporting of consumption data on DHIS2 and the availability of a space to carry out malaria rapid diagnostic tests within the pharmacy. This training of pharmacists, followed by the implementation of the inputs, extended over the period from March to December 2022. Two supervision visits were carried out in July and December 2022 to assess the use rapid diagnostic tests in pharmacies in accordance with relevant directives. Of the 44 pharmacies trained, 35 (80%) started the diagnosis of malaria in accordance with the standards. A total of 2,030 patients suspected of uncomplicated malaria agreed to be tested as a preliminary to treatment for uncomplicated malaria in the 35 pilot pharmacies. Of the 2,030 patients who were tested, 560 tested positive and received antimalarial treatment, representing a positivity rate of 27.58% of rapid

diagnostic tests. Clients who had a negative RDT test result were referred for further assessment. A follow-up will be done for compliance with malaria diagnostic guidelines in the pharmacies.

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MALARIA PARASITEMIA ESTIMATES BASED ON HRP2 AND PLDH ANTIGEN CONCENTRATIONS FROM A LARGE HOUSEHOLD SURVEY IN NIGERIA: HOW MUCH DIFFERENCE DOES RAPID DIAGNOSTIC TESTS (RDTS) PERFORMANCE MAKE?

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Countries increasingly rely on rapid diagnostic tests (RDTs) to estimate malaria prevalence in large surveys. Estimates depend on RDT ability to detect malaria antigens, especially when asymptomatic low-density infections predominate. We assessed how malaria prevalence varies by RDT sensitivity, using antigen data from a large national household survey in Nigeria. Dried blood spots (DBS) prepared during the 2018 Nigeria HIV/AIDS Indicator and Impact Survey were tested for Plasmodium falciparum-specific HRP2 and pan-species pLDH antigens on a multiplex bead assay. Standard antigen concentration curves were also created by testing known concentrations of HRP2 and pLDH on the bead assay. For HRP2, we calculated prevalence that would result from a conventional RDT (cRDT, assumed limit of detection (LoD)=6.7 nanograms HRP2/mL, the median concentration in pre-qualification testing samples) and hypothetical 10-fold more sensitive RDTs (uRDT) and 2-fold less sensitive RDTs (pRDT). For pLDH, we used thresholds for a 'good' RDT (LDHRDT, LoD = 13.6 nanograms/mL) and a 2-fold more sensitive one (sLDHRDT). Estimates account for sampling probability and complex survey design. Our sample comprised all children <15 years (n=31,468), a sample of women of reproductive age (n=9,634), and all respondents 15+ years in 11 of Nigeria's 36 states (n=47,811) with a DBS. Estimated prevalence varied significantly by HRP2 RDT, at 24.3% (95% CI: 23.0, 24.8) by cRDT, 45.1% (95% CI: 44.7, 45.6) by uRDT, and 19.5% (95% CI: 19.1, 19.9) by pRDT. Estimates significantly differed by RDT for all age groups, including children <5 years (CU5), the target for malaria household surveys [cRDT: 28.7% (95% CI: 27.3, 30.1); uRDT: 47.0% (95% CI: 45.3, 48.7); pRDT: 24.4% (95% CI: 23.1, 25.6)]. pLDH RDT differences were smaller but significant for all age groups, including CU5 [LDHRDT: 31.9% (95% CI: 30.3, 33.4); sLDHRDT: 35.8% (95% CI: 34.2, 37.3)]. Malaria prevalence estimates can differ significantly depending on RDT sensitivity. RDT selection is especially important in settings with asymptomatic, low-density infections.

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MALARIA MISDIAGNOSIS IN THE ROUTINE HEALTH SYSTEM IN ARBA MINCH AREA DISTRICT IN SOUTHWEST ETHIOPIA: AN IMPLICATION FOR MALARIA CONTROL AND ELIMINATION

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Accurate diagnosis of malaria is vital for the appropriate treatment of cases and to interrupt its transmission. The objective of this study was to compare microscopy with nested polymerase chain reaction (PCR) to diagnose malaria infections. A cross-sectional survey on health facilities was conducted from November 2019 to January 2020. Two hundred fifty-four microscopically negative and 193 microscopically positive malaria cases were assessed. Of the 193 malaria-positive patients, 46.1% (95% confidence interval (CI): 38.9-53.4) (89/193) were Plasmodium falciparum infections, 52.3% (95% CI: 45.0-59.5) (101/193) were P. vivax infection, and 1.6% (3/193) had mixed infection of P. falciparum and P. vivax. Of the microscopically positive cases of P. falciparum, 84.3% (75/89) were confirmed as P. falciparum, 3.4% (3/89) were P. vivax and 11.2% (10/89) were mixed infections with P. falciparum and P. vivax, and only one case was negative molecularly. Similarly, of the microscopically positive cases of P. vivax cases, 92.1% (93/101) were confirmed as P. vivax, 5.9% (6/101) were P. falciparum and 1% (1/101) was a mixed infection. A single case was negative by molecular technique. Of the 254 microscopically negative cases, 0.8% of patients tested positive for P. falciparum and 2% for P. vivax. Using PCR a reference, the sensitivity of microscopy for detecting P. falciparum was 89%, and for P. vivax, it was 91%. The specificity of microscopy for detecting P. falciparum was 96%, and for P. vivax, it was 98%. However, the sensitivity in detecting mixed infection of P. falciparum and P. vivax was low (8%). Thus, many P. falciparum and P. vivax mixed infections were microscopically overlooked and underreported. In addition, there were cases left untreated or inappropriately treated. Therefore, the gaps in the microscopic-based malaria diagnosis should be identified and regularly monitored to ensure the accuracy of the diagnosis.

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USER PERCEPTIONS OF A SMARTPHONE-BASED MALARIA RAPID DIAGNOSTIC TEST (RDT) AID FOR COMMUNITY AND PRIVATE CLINIC-BASED HEALTH WORKERS IN WESTERN KENYA

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The increased use of malaria rapid diagnostic tests (mRDTs) has helped bridge a quality case management gap since their adoption. This is especially true in remote areas with limited access to malaria microscopy. However, health workers face challenges with proper administration and interpretation of mRDT results. Audere, PS Kenya, and PSI partnered on a study in Busia County, Western Kenya to assess the acceptability and feasibility of using HealthPulse, a smartphone RDT reader app developed by Audere, to aid health workers in mRDT administration, interpretation, and tracking with the aim of improving the mRDT testing process. 203 community health volunteers (CHVs) and 23 private clinic health workers (PCHWs) used their personal mobile devices during the study. Using a pre-and post-quantitative design, the study compared the accuracy of health worker mRDT interpretations before and after HealthPulse was introduced. During the intervention phase, process data, including participant interactions with the app, stock, and medication distribution, were recorded in addition to qualitative baseline and end line surveys. Results indicated that HealthPulse holds potential as a mobile tool that can be scaled up for adoption in low resource settings with possible utility as a supportive supervision, diagnostic, and surveillance tool. Among the 5,278 uploaded encounters, 879 (16.7%) included an image of a previously used mRDT. Process control data showed that most encounters (89.4%) were uploaded within the recommended 30-minute time frame and that 73.4% of uploaded photos passed the app's artificial intelligence (AI) quality check on the first submission. The majority of participants felt that the app was helpful to the diagnostic process and end line survey results showed that 99.6% of participants found the app useful and 90.1% found the app easy to use. Follow-on qualitative work with 25 study participants indicated that HealthPulse provided an opportunity for health workers to submit evidence of their RDT result reporting activities, which enabled them to build credibility and trust with their peers, supervisors, and community members.

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LACK OF MUTANT PLASMODIUM FALCIPARUM PARASITES WITH PFHRP2AND PFHRP3 GENE DELETIONS IN ANLONG VENG AND KRATIE, CAMBODIA

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Malaria transmission remains low in Cambodia after intensive intervention measures aimed towards malaria elimination over a decade ago. HRP2-based RDTs have been widely used as a diagnostic tool to guide antimalarial treatment, in particular to contain artemisinin resistance. Despite these, no RDT failures caused by mutant Plasmodium falciparum parasites with pfhrp2 and pfhrp3 gene deletions have been reported in the country. In this study, we investigated the genes' status in 116 P. falciparum infected blood samples collected between Oct 2018 and Oct 2019 in Anlong Veng and Kratie towns, Cambodia during an antimalarial therapeutic efficacy trial. Plasmodium spp was confirmed by microscopy, RDT and 18S rRNA multiplex PCR. pfhrp2 and pfhrp3 gene status was determined by conventional PCR and probe-based multiplex qPCR. HRP2 expression was also verified by ELISA and samples with negligible levels of HRP2 were tested for pLDH. Microsatellite genotyping was also performed to determine polyclonality, MOI and genetic relatedness. Despite low transmission levels (polyclonality=3.3%, MOI=1.03) and widespread use of HRP2-based RDTs that provide a fertile ground for the emergence of mutant parasites lacking HRP2, no pfhrp2 and/or pfhrp3 deletion was detected in this cohort of samples from northern and western region of Cambodia by both PCR methods. This was confirmed by parasite expression of HRP2. The result suggests a very low population frequency of pfhrp2/3 deletions in the survey location at the time of survey. The continued use of HRP based RDTs is not likely a public health issue at this time. However, continuous surveillance in Cambodia is still required to monitor possible emergence of mutant parasites causing malaria RDT failures.

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PERFORMANCE AND USABILITY EVALUATION OF NOVEL MALARIA RDTS FOR IMPROVED CASE MANAGEMENT IN KÉDOUGOU, SENEGAL

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The emergence of pfhrp2/3-deleted parasites threatens histidine-rich protein 2 (HRP2)-based rapid diagnostic test (RDT) performance. High-performing, heat-stable RDTs that include Plasmodium falciparum (Pf)-lactate dehydrogenase (LDH) targets are needed to address limitations of current products and improve management of malaria patients. From November 2021 to February 2022, a cross-sectional diagnostic accuracy study was conducted in Kédougou, Senegal, to evaluate the clinical performance and usability of three novel RDTs with improved limits of detection for pfLDH. Febrile patients aged ≥6 months were recruited at health facilities. Capillary blood was tested using a standard-of-care RDT (SD Bioline Ag Pf [#05FK50]) and three novel RDTs: the BIOCREDIT Malaria Ag Pf (pLDH), Pf (HRPII/pLDH), and Pf/Pv (pLDH/pLDH) (Rapigen Inc., South Korea). Venous blood was collected to repeat the novel RDTs, and microscopy slides were prepared. Venous samples were frozen and tested with a reference polymerase chain reaction (PCR) assay. Antigen concentration was determined using the Q-Plex™ Human Malaria array (5-Plex) (Quansys Biosciences, USA). A questionnaire was used to evaluate the ability of health workers to comprehend labels and interpret results of the Ag Pf (pLDH) and Pf (HRPII/pLDH) tests. Among 220 febrile patients enrolled in the diagnostic accuracy study, 154 (70%) were Pf-positive by reference PCR. No P. vivax cases were detected on any assay, and one suspected HRP2/3 deletion case was identified by antigen concentration results. Of all RDTs evaluated, the BIOCREDIT Ag Pf (HRPII/pLDH) had the highest performance at 78% sensitivity (70.9%–84.5%) and 89% specificity (79.4%–95.6%). RDTs performed better in terms of sensitivity and specificity when compared to the Quansys antigen than when compared to the PCR reference. All RDTs performed significantly better than microscopy (with a sensitivity of 53%) in this setting. Among 20 health workers, both evaluated tests yielded acceptable usability scores. The BIOCREDIT RDTs show promising usability and performance to address current diagnostic gaps.

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DEVELOPMENT OF A FIELD-DEPLOYABLE RT-PCR DIAGNOSTIC SYSTEM FOR PLASMODIUM DETECTION IN ANOPHELES SPECIES.

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Surveillance of infectious mosquitoes is important for the implementation of appropriate vector control strategies. Diagnostic assays are essential for monitoring the infection prevalence and geographical range of pathogens in mosquito vector populations. We have evaluated a field-deployable Real-Time PCR platform as a molecular diagnosis tool for the detection of Plasmodium species. This surveillance system includes field deployable preparation of mosquito DNA samples and RT-PCR using MGB probe targeting18S rRNA gene and other stage-specific genes using the portable bCUBE RT-PCR machine connected to an automatic data interpretation system. Parasite genomic DNA was detected in individually infected Anopheles mosquitoes and in pools of 5 to 50 mosquitoes. Additionally, emerging drug resistant Plasmodium infection using markers containing K13 SNP mutations, were detected in the field Anopheles population. Conclusively, this surveillance system provides an efficient molecular approach for the detection of Plasmodium in anopheline vectors in the field and therefore has a potential as a practical field-deployable diagnostic test for vector-borne disease surveillance programs.

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EVALUATION OF MALARIA RAPID DIAGNOSTIC TEST SERVICES PERFORMANCE AT HEALTH POSTS IN ETHIOPIA

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The use of RDT by health extension workers at community level in Ethiopia has been a core element of diagnosis since 2005. However, there is limited information regarding malaria RDT use, performance and factors influencing utilization among health extension workers in Ethiopia. Evaluating performance of testing malaria using RDT at health post and addressing the bottlenecks is a vital step to improve community-based malaria treatment and inform decision at local levels is worth addressing. The aim of this study was to evaluate the performance of malaria rapid diagnostic test services at health posts as well as factors influencing malaria rapid diagnostic tests utilization in health posts in Ethiopia. A cross-section survey was conducted in 221 health posts and their 330 staffs found in 72 districts between March and October 2020. The districts were randomly sampled from nine regions and one City Administration. Interview of health extension worker using a structured questionnaire and standardized checklist and panel test was employed to collect data from selected health posts. Open Data Kit software was used to collect and share data with EPHI server. A total of 330 health extension workers from 221 health posts took part in the survey, which implies 1.49 on average. Nine out of ten health posts practice malaria diagnosis using RDT following the SOP, while discrepancies are observed

in the rest particularly in Somali and Gambella Regional States. A moderate agreement, 89.5% (k: 0.46), was observed between the malaria RDT result and the blood film reading using expert microscopist reding. The sensitivity and specificity of the RDTs were 70.2% and 91.1% respectively, referring to expert microcopy. Conclusions, this study demonstrated that most of the health posts practice the standard national guideline and moderate agreement between RDT and expert microscopist reading is obtained. Future capacity building scheme must prioritize on how to improve the use of standard guideline and avoid discrepancy in malaria diagnosis.

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A NOVEL COMPETITIVE ELISA ASSAY TO MEASURE AMODIAQUINE CONCENTRATION IN CHILDREN RECEIVING SULFADOXINE-PYRIMETHAMINE PLUS AMODIAQUINE FOR SEASONAL MALARIA CHEMOPREVENTION IN KOULIKORO, MALI.

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Seasonal malaria chemoprevention (SMC) was recommended by the Word Health Organization in 2012. The strategy involves monthly administration of the antimalarials sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) to all children aged under six years during the malaria season. Monitoring SMC efficacy to protect against clinical malaria requires a detectable concentration of AQ in the blood at least four weeks after treatment. However, rigorous and affordable laboratory methods to quantify AQ are lacking in malaria-endemic countries. This study aimed to validate a new ELISA-based method to reliably measure AQ and its metabolites. We also assessed the kinetic of AQ concentration from day 0 to day 28 after treatment with respect to infection status in Koulikoro, Mali. AQ concentration was measured among 37 children under 10 years who received SP+AQ for SMC and 15 children not treated with SP+AQ as a control group. At enrollment within the treated group, 15 children were parasite-negative by microscopy, 17 parasite-positive with a parasite density of <5000/µL, and 5 parasite-positive with a parasite density of ≥5000. A blood sample (2 mL) was collected from all participants on days 0, 4, 7, 14, 21, and 28 of treatment and used for AQ ELISA. Results show that the AQ concentration peaked on day 4 regardless of the infection status in the treated group. In contrast, AQ was barely detectable in the control group. The median AQ concentration varied between subgroups with 158.75 (9.2-734.16), 138.26 (21.45-224.16), 41.85 (30.71-106.22) ng/mL, respectively, in non-infected children, infected ones with parasite density of <5000, and those with parasite density of ≥5000. Using a mixed linear model, we found that the mean AQ concentration significantly increased by 121.43 ng/mL on day 4 and 64.57 ng/mL on day 7, compared to the AQ level at enrolment (p-values <0.05). A weak but significant negative correlation was found between parasitemia and AQ concentration (r= -0.26, p= 0.01). We demonstrated that a validated ELISA technique could be used to accurately assess compliance with SMC and treatment outcomes in children from malaria-endemic countries.

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USING DEATH AUDITS TO IMPROVE CLINICAL MANAGEMENT OF SEVERE MALARIA AND MAP KEY NEEDS TO REDUCE MORTALITY IN NORTHERN ANGOLA

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Malaria is still the leading cause of death and school and work absenteeism in Angola. Severe forms of malaria can occur if cases are not adequately and on time diagnosed and treated. Several factors concur to negative outcomes including health worker, health system, supply chain issues. The objective of this study was to assess malaria attributed deaths to understand root causes for death occurrence. A 5-year temporal analysis of malaria related lethality was conducted in Uige province. Death audits were undertaken across 12 districts by provincial supervisors using a structured NMCP approved tool. A total of 553 malaria attributed deaths in these districts were registered of which 92 were purposively targeted for audits from HF registering higher number of malaria attributed deaths. The audit included the review of patient files and cross-checking information from diagnosis, treatment and overall provision of care including management of coma, anaemia and other common adverse events. Over the last 5 years, under the implementation of Health for All Project, funded by US President Malaria Initiative, intrahospital lethality in hyperendemic Uige dropped from 0,3% to 0,1%. Death audit results pointed out that of the 92 audits conducted, 7 (16%) could not be attributed to malaria as there was no confirmation test. Of those confirmed for malaria, 82 (96%) died within 24h after admission in the HF. In 82 (96%) cases the national protocol was followed with administration of artesunate as the first line drug. Severe anaemia (Hb<5) was found in 25 cases (29%) of which 15 (60%) received a blood transfusion. 21 (25%) of the patients presented neurological dysfunction. The results indicate a high proportion of cases died within 24h after admission, showing disease presentation was already severe on arrival which may be caused by delayed health care seeking. Severe anaemia and neurologic dysfunction were present in at least a quarter of the deaths, which denotes the need for advance life support care in place to manage severe malaria related consequences. Death audits are an essential tool to understand quality of case management amongst severe cases of malaria.

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MULTIPLEX LOOP-MEDIATED ISOTHERMAL AMPLIFICATION (MLAMP) COUPLED TO CARTRIDGE BASED NUCLEIC ACID LATERAL FLOW IMMUNOASSAY (NALFIA) DEVICE AS A ONE POT DIAGNOSTIC PLATFORM FOR MALARIA

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Asymptomatic malaria carriers contribute significantly to disease transmission especially individuals who remain undiagnosed. Malaria eradication can only be achieved by ultrasensitive detection of both symptomatic and asymptomatic low-level parasitemia. Current malaria diagnosis employs microscopy and rapid diagnostic tests which suffer low limit of detection and quality assurance challenges in endemic countries. Molecular methods like PCR are costly, labor-intensive, and time-consuming. To overcome these problems, we have devised a novel rapid molecular approach by exploiting Multiplex Loop-mediated Isothermal Amplification (MLAMP) and Nucleic Acid Lateral Flow Immunoassay (NALFIA) technologies. Target samples (n=30 positives, 30 negatives) from returning travelers with malaria were chosen for validation of the diagnostic platform. Previous studies have focused only on dual assay Plasmodium genus/P. falciparum (Pf). We used a triplex format Plasmodium genus, Pf, and P.Vivax (Pv) in this study. Briefly, test samples were added to the MLAMP master mix containing six primers of each set that specifically

recognize and amplify different Plasmodium/Pf/Pv in one-pot. Species-specific probes labeled with FAM, Hex, Texas Red, and Cy5 were designed to differentiate between Pan, Pf, Pv, and controls respectively. Following our newly designed "DipQuick" protocol for simple extraction, isothermal amplification occurs inside our engineered "White Lotus" device. Amplification was detected through the excitation of specific fluorescent probes. MLAMP products are then applied to the NALFIA device where the amplicons carrying different fluorophores are captured by specific antibodies coated on the strip. To avoid amplicon contamination, the whole assay occurs in a closed cartridge system, in which multiple bands are formed to visually differentiate among different Plasmodium species. Preliminary data demonstrate that different Plasmodium species were detected ~20 mins. MLAMP-NALFIA is a rapid and ultrasensitive portable low-cost assay for the species-specific detection of malaria to further progress elimination.

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MALARIA RAPID DIAGNOSTIC TESTS (RDTS) INTERPRETATION ACCURACY OF HEALTH WORKERS COMPARED TO ARTIFICIAL INTELLIGENCE (AI) AND PANEL READ IN KANO STATE, NIGERIA

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One strategy found to decrease malaria prevalence and mortality rates is early diagnosis using rapid diagnostic tests (RDTs). Although RDTs are known for their cost effectiveness, speed of result, and ease of use - misadministration and misinterpretation errors remain a concern amongst healthcare workers (HWs). This study investigated whether RDT use could be paired with a mobile application to improve the accuracy of mRDT interpretations amongst Health Care Workers in Kano State, Nigeria. We also investigated future applicability of result digitization and automated interpretation using artificial intelligence (AI) algorithms. The analysis assessed the accuracy of RDT interpretations against a trained group of RDT readers (Panel Read) and artificial intelligence algorithms (AI). Assessments were completed for: (1) AI interpretation compared to a Panel Read interpretation, (2) HW interpretation compared to a Panel Read interpretation, (3) HW interpretation compared to an AI interpretation, and (4) the AI performance for faint positives. The analysis first determined the AI interpretation accuracy by comparing the AI interpretation to the ground truth of the Panel Read for 2,479 RDTs. The AI performed well, correctly interpreting positives 95.54% of the time and negatives 96.90% of the time. The Panel Read was then compared to the HW interpretation, finding agreement 97.54% of the time on positives and 92.28% on negatives. Interpretation accuracy of the HWs was then determined by comparing their interpretations to the AI, providing a real-world use case for AI, with 96.76% agreement on interpretation of positives and 94.50% agreement on negatives. Overall accuracy was determined using a weighted F1 score, yielding 96.4 for the AI compared to 95.3 for experienced, well-trained health workers. The AI performed even better than HWs on faint lines, identifying 14.1% more faint positives than HWs, indicating AI's strengths in elevating performance of humans when evaluating RDT results. Together the HW and AI are a good team to support HW decision making, and ensure accurate reporting.

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EVOLUTION OF PFHRP2 AND PFHRP3 DELETIONS IN EQUATORIAL GUINEE BETWEEN THE PRE AND POST RDT INTRODUCTION AND THE IMPACT OF PUBLIC HEALTH STRATEGIES ON THEIR EXPANSION

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Prompt and accurate diagnosis, mainly based on Rapid Diagnostic Tests (RDT) across Africa, is part of public health strategies for malaria control. However, it has been threatened by false negatives in RDT. The main cause of false negatives are some deletions found in pfhrp2 and pfhrp3 genes, which encode proteins detected by Plasmodium falciparum - specific RDT. Understanding the dynamics of the emergence, selection, and spread of parasites with pfhrp2 and pfhrp3 deletions could give insightful information to predict RDT efficacy in future scenarios for malaria control. This study aims to assess the temporal evolution of deletions considering different epidemiological settings and the impact of RDT use. Samples from two different regions in Equatorial Guinea (West Central Africa), the Island Region, North Bioko Province, (with low prevalence and high use of RDT), and the Litoral Province located in the Continental Region (with high malaria prevalence and low RDT use) were included. In particular, the emergence of deletions has been studied using samples from 1999 - 2001 (pre - RDT period), and two groups from 2016 and 2019, after RDT introduction. Deletions in exon 1 and 2 of pfhrp2 and pfhrp3 and its flaking regions were genotyped, observing an increasing trend in deletion frequencies, especially in the low prevalence region (the Island Region) with high RDT use. Additionally, exon 2 of pfhrp2 and pfhrp3 were sequenced to analyse changes in genetic diversity, aminoacidic composition, and the frequency of major epitopes over time. Finally, population diversity and deletions-expansion characteristics were assessed using 7 neutral microsatellites. Overall, haplotype networks suggest that pfhrp2 and pfhrp3 deletions emerged multiple times in Equatorial Guinea. Our findings highlight the importance of molecular surveillance to assess the efficacy of RDTs in malaria control programs.

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SUPEROXIDE GENERATION AND REDOX CYCLING OF PRIMAQUINE METABOLITES ARE DRIVEN BY BILIVERDIN REDUCTASE B AND N-RIBOSYLDIHYDRONICOTINAMIDE: QUINONE REDUCTASE 2

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Primaquine and tafenoquine are the only approved drugs for radical cure of Plasmodium vivax but can cause severe hemolysis from generation of reactive oxygen species (ROS) in patients with glucose-6-phosphate dehydrogenase deficiency (G6PDd). Primaquine is a prodrug, but small amounts of primaquine metabolites (PMs) generate large amounts of ROS through redox cycling. A PM receives an electron from a donor (e.g., NADH) to form a PM radical, which then transfers the electron to molecular oxygen (O2) to form superoxide (SO, O2• -), and in doing so, regenerates the PM that can undergo another redox cycle. However, many redox toxins do not cycle spontaneously, but require an enzymatic reductase to mediate the electron transfer. We characterized the redox cycling requirements of a major hemolytic PM, 5,6-primaquine-orthoquinone (5,6-POQ). SO

generation was measured by electron paramagnetic resonance (EPR) using a SO-specific spin probe. EPR detected only low levels of SO from 5,6-POQ incubated with common electron donors, NADH, NADPH, or N-ribosyldihydronicotinamide (NRH). However, robust SO generation was observed when either of the two most abundant quinone reductases from RBCs were added in the presence of their cofactors. Biliverdin reductase B (BLVRB) plus NADPH or N-ribosyldihydronicotinamide:quinone reductase 2 (NQO2) plus NRH accelerated SO generation by 6.3- and 13-fold, respectively. Specific inhibitors prevented SO generation for BLVRB (Phloxine B; $p < 0.0001$) or NQO2 (S29434; $p < 0.0001$). These findings identify two RBC reductases that are alone sufficient, in vitro, to reduce 5,6-POQ and promote redox cycling. These findings also have two translational implications. First, adding inhibitors of BLVRB and/or NQO2 to primaquine may mitigate hemolysis in G6PDd patients requiring treatment for relapsing malaria. Because primaquine is redox cycled in hepatocytes by cytochrome P450s, which is not expressed in RBCs, BLVRB and/or NQO2 inhibitors are not predicted to interfere with radical cure. Second, nutritional status may affect primaquine induced hemolysis in G6PDd patients, as NR, the precursor of NRH, is diet derived.

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POTENT ACYL-COA SYNTHETASE TEN INHIBITORS KILL PLASMODIUM FALCIPARUM BY DISRUPTING TRIGLYCERIDE FORMATION

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Identifying how small molecules act to kill malaria parasites can lead to new "chemically validated" targets. By pressuring Plasmodium falciparum asexual blood stage parasites with three novel structurally unrelated antimalarial compounds (MMV665924, MMV019719 and MMV897615), and performing whole-genome sequence analysis on resistant parasite lines, we identify multiple mutations in the P. falciparum acyl-CoA synthetase (ACS) genes ACS10 (PF3D7_0525100) and ACS11 (PF3D7_1238800). Mutations in ACS10 showed either resistance to all compounds (M300I and F427L) or collateral sensitivity to another compound (A268D 10-times more susceptible to MMV019719, A268V 2-times more susceptible to MMV665924). Introduction of M300I mutation into wildtype parasites phenocopied the resistance phenotype of the selected line. ACS genes are highly polymorphic and surprisingly, the ACS10 M300I mutation identified here was present at 78% in a natural Malawi parasite population. A Malawian isolate containing the M300I polymorphism was five-fold more resistant to MMV665924 than a matched ACS10 wild type Malawi isolate. Conditional knock-down lines showed that ACS10 is essential in asexual growth in vitro and reduced ACS10 protein levels rendered parasites more susceptible. Thermal-shift assays followed by Mass-spectrometry identified that MMV897615 indeed shifted the thermal stability curve of ACS10 validating ACS10 as the likely target of these compounds. ACSs are enzymes that activate fatty acids scavenged from the host. Inhibition of ACS10 by MMV665924 or MMV897615 leads to a reduction in triacylglycerols and a buildup of its lipid precursors. On the other hand, while allelic replacement of mutations in ACS11 phenocopies the selected lines, conditional knockdown data demonstrate that ACS11 is not essential for asexual parasite growth, implying that ACS11 may be mediating resistance rather than being a direct target. While ACS10 is an attractive new drug target, natural occurring polymorphisms in field parasite populations might reduce the efficacy of these compounds.

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FIGHTING MALARIA WITH "IRRESISTIBLE" DRUGS

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Malaria is a major global disease which is transmitted to humans through the bites of infected female mosquitoes. According to the last WHO Malaria report there were an estimated of 247 million cases with 619,000 deaths worldwide. Plasmodium falciparum is the species accountable for nearly 90% of these deaths. Children under 5 are particularly susceptible to malaria illness, infection and death. In addition, malaria has severe socioeconomic impact in endemic countries. In fact, approximately 25% of the endemic countries incomes are devoted to treating and minimizing the impact of this disease. With the actual emergence of resistance against all antimalarial treatments including the standard of care artemisinin-based combination therapies (ACTs), first in the Cambodia and Thai-Burmese border region but now spread to certain African regions, there is an urgency to develop novel combination therapies. New compounds with novel modes of action and potent activity against sensitive and resistant Plasmodium parasites, are urgently needed to withstand resistance issues. Among the new opportunities identified as result of GSK whole cell phenotypic screening, a novel pyrazine class of antimalarial with promising potential has been identified. As one of the most outstanding properties, this series has demonstrated an extremely low propensity to select resistant parasites in vitro. The capability of preventing the emergence of malarial resistance renders this molecule an "irresistible" profile and offers a unique opportunity as an additional tool for future novel antimalarial combination. Furthermore, the pyrazine molecule selected as preclinical candidate molecule displays an appropriate pharmacokinetic profile along with a rapid mechanism of action that support potential for single oral dose cure. This profile could increase adherence and improve treatment efficacy whereas contributing to hampering parasite resistance selection.

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LEVERAGING RWANDA'S COMMUNITY HEALTH WORKERS TO CONDUCT A THERAPEUTIC EFFICACY STUDY IN AREAS OF DECLINING MALARIA TRANSMISSION

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Regular monitoring of artemisinin-based combination therapies (ACTs) is important to promptly detect and respond to emerging antimalarial resistance. The last two therapeutic efficacy studies (TESs) in Rwanda conducted in 2013-2015 and 2018, showed an artemether-lumefantrine (AL) efficacy over the 90% WHO benchmark for treatment policy change. However, day 3 parasitemia levels exceeded 10% in two of the three study sites, a criterion for suspected artemisinin resistance. In June 2021, Rwanda began a follow-up TES evaluating AL, the first line treatment, and dihydroartemisinin-piperaquine (DP), the second line treatment, in three health centers (HCs): Masaka, Rukara and Bugarama. Six months into the study, only 9 (1.7%) and 39 (7.4%) participants were enrolled in Masaka and Bugarama, respectively, and none in Rukara. This was due

to a decline in malaria cases (~41% in 2021 compared to 2020), likely a result of the successful malaria control interventions in place. In addition, 55% of all malaria cases in Rwanda are currently diagnosed and treated at the community level with only a small percentage managed in the HCs. To encourage malaria patients to attend the study HCs, Rwanda developed a strategy to engage community health workers (CHWs) to enhance study recruitment. In addition, routine malaria data from 2020 to 2021 were analyzed to replace Rukara HC with Ngoma HC, in a higher burden area. Through meetings with local leaders, partners and the malaria program, and trainings, CHWs were encouraged to refer all malaria RDT positive cases to the study HCs. In total, 92 CHWs from 46 villages in Masaka, 194 from 97 villages in Bugarama, and 64 from 32 villages in Ngoma were trained on the study protocol. From October 2021 to January 2023, 358 of the 528 (68%) required participants were enrolled and 78% of these were referred by CHWs. Innovative enrollment strategies are key to conducting TES in areas of declining malaria transmission. In a country like Rwanda where over 50% of malaria management is at the community level, active involvement and collaboration with CHWs and local leaders is essential.

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NOVEL MULTIPLE-STAGE ANTIMALARIAL PRODIGININES

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Prodiginines are a family of intriguing pyrrolylpyrromethene alkaloid natural products, produced by actinomycetes and other eubacteria. Recently, there has been an increase of interest in natural and synthetic prodiginines because they have shown a broad range of therapeutic applications. While a few natural prodiginines have been evaluated for antimalarial activities, synthetic prodiginines have not been explored until our recent investigations. The modes of action are unknown for these prodiginines and the unique structure along with their pan-sensitivity against a large panel of MDR malaria parasites suggest potential to discover a new drug target to combat malaria parasites. Over the past few years, our research has focused on the discovery and development of novel antimalarials from the natural sources and we have developed prodiginine natural products as novel antimalarials that are effective against multiple life-cycle stages of the malaria parasite. Our prodiginine scaffold is a unique chemotype as compared to existing antimalarials, and potentially operates by a novel mode of action. In this context, we present the detailed optimization and structure-activity relationships of the novel prodiginine chemotype.

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ACRIDONES AS NOVEL LIVER STAGE ACTIVE ANTIMALARIAL

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The global impact of malaria remains staggering despite extensive efforts to eradicate the disease. The challenges for a sustainable elimination include the failing effectiveness of front-line artemisinin-based combination therapy (ACT) due to emerging resistance and safety concerns associated with limited radical cure options for relapsing Plasmodium vivax. There is an urgent need for novel, effective, affordable and safe antimalarial drugs to overcome drug resistance, and ideally, such agents would be efficacious against both blood stage and liver stage malaria infections. We have developed a novel antimalarial acridone chemotype with dual stage efficacy against both liver stage and blood stage malaria, as well as single-dose cure ability and potential to prevent relapsing infection. Our novel acridone chemotype represents a broad-spectrum approach with potential to vanquish many challenges.

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SAFETY AND EFFICACY OF PRIMAQUINE IN PATIENTS WITH PLASMODIUM VIVAX MALARIA FROM SOUTH ASIA: A SYSTEMATIC REVIEW AND INDIVIDUAL PATIENT DATA META-ANALYSIS

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Relapsing malaria caused by Plasmodium vivax causes substantial morbidity. Currently, primaquine is the only available antimalarial to prevent relapses in South Asia, however its optimal regimen remains unclear. A systematic review identified P. vivax clinical efficacy studies published between Jan 1, 2000, and August 23, 2021. Available individual patient data were pooled using standardised methods. The cumulative risks of recurrence between days 7 and 42, and days 7 and 180 were assessed

by Kaplan-Meier methods with the effect of primaquine total mg/kg dose and treatment duration on rate of P. vivax recurrence investigated by Cox regression with random effects for study site. The number of patients with a >25% drop in haemoglobin to <7 g/dL, or an absolute drop of >5 g/dL between day 1-14 were categorised by primaquine daily mg/kg dose. The presence of vomiting, diarrhoea or anorexia following primaquine were assessed as a composite endpoint. Of 17 eligible studies, data were available from 7 studies including 791 patients from 4 countries. The cumulative risk of recurrence at day 180 was 61.1% (95% CI 42.2-80.4; 201 patients followed; 25 recurrences) after treatment without primaquine, 28.8% (95% CI 8.2-74.1; 398 patients; 4 recurrences) following low total dose primaquine (2-<5 mg/kg) and 0% (96 patients; 0 recurrences) following high total dose primaquine (≥5 mg/kg). After controlling for confounders, the rate of first recurrence between days 7 and 42 was reduced following treatment with low total dose primaquine compared to treatment without primaquine (adjusted hazard ratio: 0.4 (95% CI 0.1-2.8); no recurrences were observed following high total dose primaquine. No patients had a >25% drop in haemoglobin to<7g/dL. No data were available to assess gastrointestinal tolerability. Treatment with primaquine led to a marked decrease in the risk of P. vivax recurrences following low (~3.5 mg/kg) and high (~7 mg/kg) total dose primaquine regimens, with no reported severe haemolytic events. However, few data were available to compare efficacy of different primaquine regimen with prolonged follow up.

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EFFICACY OF THREE ARTEMISININ-BASED COMBINATIONS FOR THE TREATMENT OF UNCOMPLICATED MALARIA IN CHILDREN IN BURKINA FASO

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The World Health Organization recommends regularly monitoring the efficacy of artemisinin-based combination therapy (ACT), a critical tool in the fight against malaria. This study evaluated the efficacy of three ACTs recommended to treat uncomplicated P. falciparum malaria in Burkina Faso in three sites across different epidemiological zones of malaria: Niangoloko, Nanoro, and Gourcy. This was a three-arm randomized controlled trial to assess the efficacy of artemether-lumefantrine (AL), dihydroartemisinin-piperaquine (DP), and artesunate-pyronaridine (As-Pyr) in children aged 6 months to 12 years old following supervised treatment. The primary outcomes of the study were uncorrected and PCR-corrected efficacies at day 28 for AL and day 42 for DP and As-Pyr. Day-7 lumefantrine concentrations for the AL arm were measured. We enrolled 1080 children:180 in the AL arm, 90 in the DP arm, and 90 in the As-Pyr arm per site. PCR-uncorrected 28-day efficacy in the AL arm was 64.7% [95% confidence interval (CI) 57.1-71.1], 64.0% [95% CI 56.4-70.6] and 56.7% [95% CI 49.1-63.6] in Gourcy, Niangoloko, and Nanoro. PCR-uncorrected 42-day efficacy in the DP arm was 86.7% [95% CI 77.3-92.4], 88.0% [95% CI 78.8-93.3] and 89.9% [95% CI 81.5-94.6] in Gourcy, Niangoloko and Nanoro. PCR-uncorrected 42-day efficacy in the As-Pyr arm was 64.6% [95% CI 53.0-74.0], 70.9% [95% CI 60.1-79.3] and 54.8% [95% CI 43.5-64.7] in Gourcy, Niangoloko and Nanoro. Median day-7 lumefantrine concentrations were similar across sites and end-point classification. The day-3 positivity rate was null in all arms in Nanoro, in the DP and AS-Pyr arms in Gourcy, and in the DP arm in Niangoloko. The day-3 positivity rate was 1.1% in the AL arm in Niangoloko and Gourcy and 1.2% in the As-Pyr arm in Niangoloko. The study results show evidence of high rates of PCR-uncorrected treatment failures in the AL and ASPY arms. The low uncorrected efficacy in the AL arm is consistent with previous studies. PCR correction is under way. These findings raise concerns about the most appropriate drug policy in Burkina Faso.

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EXPLORING DIMETHYL FUMARATE AS AN ADJUNCTIVE THERAPY FOR CEREBRAL MALARIA IN EXPERIMENTAL CEREBRAL MALARIA MODEL

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Approximately 1% of Plasmodium falciparum infected-children develop cerebral malaria (CM), which presents as a coma and is characterized by cerebral microvascular parasite sequestration. High rates of mortality and long-term neurocognitive impairment can occur in survivors despite potent antimalarial therapy. Adjunctive therapy is needed to improve CM outcomes. Our previous studies demonstrated the association of upregulation of transcription factor, Nrf2 in children with CM who had good clinical outcomes. Nrf2 modulates antioxidant and anti-inflammatory pathways, which may impact the pathophysiology of CM. Dimethyl fumarate (DMF) upregulates the Nrf2 pathway and is used to prevent relapses of multiple sclerosis. We assessed the potential of DMF in the experimental cerebral malaria model (ECM). We examined the effects of DMF on survival, neuro-cognition and blood brain barrier permeability in C57BL6 female mice infected with P. berghei ANKA using state-of-the-art techniques. DMF significantly increased survival in mice during ECM ($p = 0.0002$). No difference was observed in total body or brain parasite sequestration, using in vivo imaging in mice infected with P. berghei ANKA GFP-Luciferase strain, suggesting that the protective property of DMF is not due to an antiparasitic effect. In ECM mice treated with DMF, we also observed improvement of neurocognitive function during the course of infection using the rapid murine coma and behavior scale. Furthermore, DMF reduced the blood-brain barrier disruption in ECM using the Evans blue extravasation assay on day 6 post infection ($p = 0.01$). We also examined the effect of DMF on brain volume in ECM using magnetic resonance imaging. DMF did not impact the increased brain volume which occurs during ECM. Taken together, this data supports DMF, an FDA approved drug, as a potential adjunctive therapy in CM as it increases survival and reduces the neurological decline in ECM.

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METABOLISM OF TAFENOQUINE AND TAFENOQUINE DRUG COMBINATIONS IN LIVER CELL CULTURES

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Antimalarial drugs of the 8-aminoquinoline class (pamaquine, primaquine (PQ), and tafenoquine (TQ)) have been the basis of malaria chemotherapy to prevent relapses and block transmission for nearly a century. Despite their wide-spread use, their metabolism and mechanism of action are still poorly understood. The importance of metabolism was suggested by an extensive 8-aminoquinoline testing program conducted by the US Army which found that 8-aminoquinolines without redox activity were unable to inactivate the latent residual parasites in the liver (hypnozoites) responsible for relapsing malaria. The precise mechanism of action of 8-aminoquinolines has been a subject of interest and conjecture for many years. It is known that monoamine oxidase (MAO) and cytochrome P450 2D6 (CYP2D6) convert PQ to the inactive carboxyprimaquine. Hydroxylated-PQ metabolites (OH-PQm) are responsible for efficacy against liver and sexual transmission stages of Plasmodium falciparum. The major CYP2D6 metabolite, formed by degradation of the unstable 5-hydroxy-PQ was found to be 5,6-OQ (5,6-orthoquinone). We have observed, quantified and partly characterised the hydroxylated metabolite of TQ (5,6-OQTQ) that is a marker of oxidative metabolism. Using high resolution accurate mass spectrometry and sophisticated compound structure elucidation software we have identified

the production of 5,6-OQTQ and other stable TQ metabolites in response to TQ alone and drug combinations of TQ over time. In addition, we have used western blotting to demonstrate CYP1A1 enzyme level modulation by TQ and drug combinations of TQ. The CYP1A1 transcript has previously been shown to be modulated by TQ. Our results may help explain the reduced therapeutic efficacy of TQ when combined with artemisinin combination therapies as well as to identify suitable TQ partner drugs in the treatment and prevention (i.e., post exposure prophylaxis) of P. vivax infections.

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PREDICTION OF ADENYLOSUCCINATE LYASE 3D STRUCTURE A PROMISING THERAPEUTIC TARGET IN PLASMODIUM FALCIPARUM AND ITS POTENTIAL INHIBITORS FROM AFRICAN NATURAL COMPOUND DATABASES

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The emergence and spread of resistant strains of Plasmodium falciparum constitute the main obstacles for the control of malaria. So, the discovery of new drugs is still urgent and requires continuous effort to identify new therapeutic targets. In this study we present P. falciparum AdenyloSuccinate lyase (Pf ADSL) as a highly promising therapeutic target. This important enzyme is involved in de novo purine biosynthetic pathway, unique in P. falciparum, which results to the formation of adenosine monophosphate (AMP). Because of its role in purine metabolism, this enzyme appears as a promising drug target in P. falciparum.We aimed to construct the 3D structure of Pf ADSL and predict its potential inhibitors from three databases of natural products.The 3D structure of Pf ADSL was modeled using ALphafold server, and natural compounds were extracted from AFRODB, SANCDB, ANPDB. ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) predictions were performed using SwissADME, and virtual screening was performed with AutoDock-vina. After virtual screening, the ten (10) compounds with the best binding energies, good ADMET properties and also demonstrated the best results in protein-ligand interactions were selected. The binding energies were ranged between -9.6 and -8. kcal/mol and the selected compounds can provide a basis for invitro studies.The obtained results therefore need to be validated experimentally to confirm their inhibitory activities.

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ARTEMETHER-LUMEFANTRINE VERSUS PYRONARIDINE-ARTESUNATE FOR THE TREATMENT OF MALARIA IN SARS-COV-2 INFECTED PATIENTS IN KENYA AND BURKINA FASO: A RANDOMIZED OPEN-LABEL TRIAL (MALCOV)

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It is unknown whether malaria or malaria treatment affects COVID-19 severity, SARS-CoV-2 viral load or duration of shedding. Several antimalarials exhibit antiviral activity against SARSCoV-2 and have been suggested as potential therapeutic candidates for COVID-19, particularly pyronaridine-artesunate (PA). A previous trial in COVID-19 patients without malaria showed that PA enhanced viral clearance compared to placebo. We conducted an open-label randomised trial comparing standard 3-day treatment with PA and artemether-lumefantrine (AL) in newly diagnosed SARS-CoV-2 infected patients aged >=6 months with rapid diagnostic test or microscopy-confirmed non-severe malaria in Kenya and Burkina Faso. SARS-CoV-2 was assessed by RT-PCR on days 3, 7 (primary endpoint), 14 & 28 and symptom resolution daily for 14 days by FLUPRO+. Complete case analysis was conducted using log-binomial regression for binary outcomes, cox-regression for time-to-event outcomes and Poisson regression for count outcomes, adjusted for age, disease severity and viral load at enrolment. From February 2021 to January 2022, 143 participants were enrolled and 133 (AL:68, PA:65) with confirmed SARS-CoV-2 RT-PCR or positive serology/seroconversion contributed to the mITT analysis; median age 20 yrs (IQR 13-38). The baseline characteristics were comparable. Viral clearance by day 7 was slower with PA (adjusted hazard ratio [aHR]:0.62, 95% confidence interval 0.43-0.89, p=0.010) and median (IQR) SARS-CoV-2 viral load on day-7 was higher (AL:1337 [204-7519] vs PA:12,881 [272-46,624], p=0.080). The proportion SARS-CoV-2 by day 7 was AL:58% (38/66) vs PA:48% (29/61) (RR=0.81, 0.58-1.12, p=0.20), and by day 14 AL:94% (62/66) vs PA:84% (51/61) (RR=0.87, 0.77-0.99, p=0.028). The time to symptoms clearance was similar (HR=1.01, 0.69-1.48, p>0.90). There were 8 serious adverse events (AL:3, PA:5), including 3 hospitalisations (AL:2, PA:1) and 2 deaths (AL:1, PA:1). PA in COVID-19 patients co-infected with malaria was associated with slower viral clearance than standard treatment with AL and with similar symptom resolution.

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LEVERAGING COMMUNITY OWNED RESOURCE PERSONS (CORPS) TO REACH THE UNDERSERVED POPULATION THROUGH INTEGRATED COMMUNITY CASE MANAGEMENT (ICCM) TO FIGHT MALARIA IN TANZANIA

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Malaria modeling in Tanzania demonstrates that case management (CM) should target ≥85% malaria cases appropriately managed in high malaria transmission areas to increase CM effectiveness and decrease transmission. Tanzania's policy against the use of community volunteers for CM creates a gap at the community level, which is addressed through the deployment of Community Owned Resource Persons (CORPs). CORPs are qualified medical personnel at the community who are either retired or unemployed whom the National Malaria Control Program (NMCP) utilizes to promote the early recognition, prompt testing and appropriate treatment of malaria among all age groups in areas with limited access to facility-based health care providers. CORPs were mapped in 10 high malaria councils to establish an equitable and efficient system for delivery of community malaria case management services. The mapped villages had high malaria risk, were hard to reach as well as overstretched health services. The service operates within the routine delivery system by using current logistic and M&E frameworks. Sensitization was done with regional and council health management teams, and CORPs were trained. 104 (33%) CORPs were mapped in 311 villages that also have 434 Community Health Workers (CHWs). Between June and December 2022, CORPs attended to 35,409 patients and tested 33,030 (93.3 %) for malaria. Among them, 10,631 (32%) had confirmed malaria. Community level diagnosis accounts for 5% of national malaria cases and 16% in those Councils during the reporting

period. Community malaria CM promotes the early recognition, prompt testing and appropriate treatment of malaria among all age groups in areas with limited access to facility-based health care providers. Following the experience and lessons learned, the Ministry of Health through the NMCP plans to: 1) review protocol for iCCM implementation to address the challenges (eg. low numbers of CORPS per village); 2) advocate for using CHWs in place of CORPs for the sustainability of the intervention; and 3) review data collection and support supervision tools to address challenges.

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MALARIA AND THE INTERMITTENT PREVENTATIVE TREATMENT FOR FOREST-GOERS IN CAMBODIA: PRELIMINARY RESULTS AND LESSONS LEARNED

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Malaria risk in Cambodia is highest in forest and forest fringe areas and linked to forest-goers. To address this challenge, the National Center for Parasitology, Entomology and Malaria Control (CNM), alongside the World Health Organization (WHO), began implementing "Last Mile Elimination" (LME) in 2021 - an innovative collection of interventions which includes providing intermittent preventative treatment for forest goers (IPTf) to prevent malaria infection. In each of the 117 LME villages, a census was conducted to identify male forest-goers between the ages of 15 and 49 who would be eligible for IPTf. Once identified, village malaria workers (VMWs) went door-to-door weekly to distribute IPTf to those planning to go to the forest in the following 30 days. Based on the preliminary findings of the initial implementation, the rate of this population taking IPTf has not surpassed 50% since the start of the program. Several contributing factors have been identified, including concerns about side effects and their impact on an individual's ability to work and the fact that some forest-goers were engaged in illegal forest activities and were reluctant to disclose their forest-going habits. CNM has responded to these challenges by adapting its approach to IPTf, yielding important lessons learned the application of prophylactic approaches. For example, due to reports of persistent side effects, CNM shifted from artesunate-mefloquine to artesunate-pyronaridine starting in August 2022. CNM has also incentivized treatment completion to ensure forest-goers are fully protected from getting malaria. Despite the low uptake of IPTf, LME villages in Kampong Speu and Kratie implementing the full package of interventions have seen P. falciparum and mixed infections decrease by 82% over the last two years and there are ongoing analyses to ascertain whether this decrease was due, in part, to the distribution of IPTf. As Cambodia approaches elimination, documenting and sharing lessons learned and identifying which programs are truly accelerating elimination will be instrumental in aiding both Cambodia and the region in reaching their elimination targets.

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PLANT-DERIVED ADJUVANTS PROVIDE A PATH TO THWARTING EMERGING DRUG-RESISTANT MALARIA

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Plasmodium falciparum's drug resistance has become a significant issue in recent decades. Humans developed drug resistance to most antimalarial drugs, which caused severe side effects and failed malaria elimination programs. Hence, there is a need to investigate chemotherapeutic agents with low cost and causing minimal toxicity for the treatment of malaria. Combination therapy is a more emerging trend to control drug-resistant malaria. Plant-derived products are highly accessible and available and can be used as partner drugs with recommended ACTs and other clinically used drugs. Considering the above problems, a systematic study was conducted to search for reported plant-based adjuvants and combination therapy. Identifying practical, synergistic/additive drug combinations could improve drug-resistant malaria control. This review critically appraises the available evidence regarding plant-derived adjuvants to combat the problem of drug resistance in malaria. My presentation will highlight my previous work with current drug scenario available in past years for plant-derived adjuvants for combination therapy to combat drug resistance in malaria.

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SPILLOVER EFFECTS OF REACTIVE, FOCAL MALARIA ELIMINATION INTERVENTIONS IN NAMIBIA

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A recent factorial cluster-randomized trial in Zambezi region, Namibia found that interventions targeted within 500m of index cases reduced malaria incidence (NCT02610400). To investigate whether interventions also reduced incidence in nearby areas, we measured spillover effects among untreated individuals within 500m and up to 1km from index cases. The trial randomized 56 clusters to: 1) reactive case detection (RACD) with rapid diagnostic testing and treatment with artemether-lumefantrine (AL) and single-dose primaquine, 2) reactive focal mass drug administration (rfMDA) with presumptive treatment with AL, 3) rfMDA + reactive focal indoor residual spraying (rfIRS) with indoor residual spraying using pirimiphos-methyl, and 4) rfMDA + rfIRS. Our primary outcome was the cumulative incidence of locally acquired Pf malaria in untreated individuals up to 1km from index cases. We defined spillover effects as cumulative incidence ratios (CIRs) for treatment contrasts based on the parasite reservoir targeted: 1) human reservoir (rfMDA vs. RACD); 2) mosquito reservoir (rfIRS vs. no rfIRS); and 3) human & mosquito reservoir (rfMDA + rfIRS vs. RACD). We estimated unadjusted CIRs and adjusted CIRs accounting for statistical interference between outcomes of nearby untreated individuals in different study clusters using hierarchical targeted maximum likelihood estimation. For all treatment contrasts, cumulative incidence in untreated individuals was lower in the treatment vs. comparison arms. Unadjusted CIRs were 0.85 (95% CI 0.75, 0.95) for any rfMDA vs. RACD, was 0.67 (0.60, 0.75) for rfIRS vs. no rfIRS, and 0.57 (0.48, 0.67) for rfMDA + rfIRS vs. RACD. Using TMLE and accounting for interference, CIRs were 0.78 (0.26, 2.37) for rfMDA vs. RACD, 0.93 (0.45, 1.90) for rfIRS vs. no rfIRS, and 0.60 (0.34, 1.05) for rfMDA + rfIRS vs. RACD. Overall, our findings suggest that targeted interventions produced spillover effects and may hold promise for malaria elimination. Measuring spillover effects can inform a precision public health approach using focal interventions to reduce malaria in and near hot spots in low transmission settings.

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EFFECTS OF METEOROLOGICAL FACTORS AND ELEVATION ON MALARIA TRANSMISSION IN ELIMINATION TARGETED DISTRICT OF ETHIOPIA

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Malaria remains a significant public health issue in Ethiopia despite impressive progress made toward the 2030 targets of eliminating the disease. Several factors, most notably climate change, and related environmental factors have been challenging the progress. This study aimed to ascertain the transmission dynamics of malaria and associated factors in the elimination-targeted districts in the country. Malaria morbidity and meteorological data recorded from 2010 to 2017 were obtained from the

district's health facilities and the national meteorology agency, respectively. A community-based asymptomatic malaria survey was also conducted from April to May 2021, using rapid diagnostic test and light microscopy. A total of 135,607 malaria suspects were diagnosed using RDT and microscopy over the last 8 years, of which 29,554 (21.8%) were confirmed positive cases. Plasmodium falciparum, P. vivax, and mixed infection accounting for 56.3 %, 38.4 %, and 5.2 %, respectively. A time series plot showed a marked decline in the disease. In a negative binomial regression, the transmission season, rainfall, temperature, elevation, and the patient's sex and age were predictors of occurrence. The monthly incidence was predicted to oscillate about 88 cases in 2030 by an ARIMA (2, 1, 2), the best-fit model for point prediction. Asymptomatic malaria was prevalent (6.1%), and the use of bed nets, prior travel experiences, and window placement all significantly increased the risk of infection. The prediction models revealed that the elimination target would not be accomplished despite a significant decline in malaria morbidity in the examined years. The rising incidence of asymptomatic malaria in the community supports the model's forecast that the targeted elimination objective would not be achieved. Thus, the intensification of existing interventions by considering community mobility patterns and housing conditions might help in achieving the elimination goal.

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PRESENT STATUS OF THE PRIVATE SECTOR ENGAGEMENT IN MALARIA CASE MANAGEMENT IN BANGLADESH

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Bangladesh has achieved remarkable progress in malaria control and sets a target to become malaria-free by 2030. Currently, private sector involvement is limited to, partner NGOs in the NMEP platform. We conducted this study to understand the role of the for-profit private sector in malaria case management not partnering with NMEP in Bangladesh. Based on the endemicity and strategic priorities, we purposively selected 15 Upazilas for this study. Among them, eight were from high transmission districts (control area), six were from low transmission districts (endemic area) and one from non-endemic districts that have borders with high transmission districts. We have listed and enrolled all the for-profit private sectors in those selected upazilas that have some capacity for malaria case management. A structured questionnaire was developed and used with the advice of the expert panel members. Between August to September 2022, a total of 104 health facilities were enrolled from 15 upazilas. More than half (54.8%) of health facilities were consulted & diagnostic centers followed by private clinics (18.3%) and drug stores with malaria diagnostic facilities (13.5%). Overall, 80.8% of facilities provided malaria testing while only 18.3% provided treatment services. Most of the health facilities in the control areas had facilities for malaria testing by RDT (77.7%), however, it was quite higher (95.0%) in endemic areas than control area. The price of RDT test varies widely from 50-1000 Bangladeshi Taka in different areas. Overall, 42.3% of health facilities reported malaria cases to the health authorities, however, this reporting was much lower in control areas (21.9%) than in the endemic areas (56.1%). Among the providers, 62.9% indicated willingness to work with the NMEP platform. Our study concludes that the for-profit private sector is somehow engaged in malaria case management but their contribution is not recognized. There is interest among the providers to work under the NMEP platform. However, there is an urgent need for a strategy to incorporate them into the nest of the NMEP surveillance systems.

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DETERMINANTS OF HIGH NON-REDUCING MALARIA ADMISSION RATES IN GHANA: AN AUDIT OF MALARIA ADMISSIONS IN 13 HEALTH FACILITIES WITH HIGHEST RATES IN 2021

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Despite reductions in malaria prevalence in Ghana over the years, malaria admissions have remained stagnant, with a recent rise from 120 to 129 per 10,000 population between 2021 and 2022. This study was conducted to identify factors associated with the high unremitting admission rates. A cross-sectional study was conducted in September 2022. January to June 2022 malaria admissions data from the national Health Information Management System (HIMS) for 13 facilities were verified using source data. Also, medical records of 394 clients admitted for malaria (severe malaria) were reviewed, and data abstracted. Data was analyzed using Stata 16.0 into frequencies, proportions and means. Logistic regression was performed to determine association between malaria admission and explanatory variables. P-value <0.05 at 95% confidence interval was judged significant. Nearly half 6/13 (46%) of the facilities were privately owned. Significant data variation was noticed in 33% of the facilities (4/12), with faith-based health facilities and those using only paper-based data management systems more likely to observe significant variations. Fifty-one percent of cases were female, and 42.2% less than 10 years. Over 54% (215/394) of cases did not meet the WHO criteria for severe malaria, and among those meeting the criteria, 54.8% (98/179) had other severe comorbidities warranting admission by themselves. Significant associations were found between facility type, referral status, previous surgery, artemisinin-based combination therapy (ACT)after parenteral antimalarial and timeliness factors; and admission due to severe malaria ($p<0.05$). Eighty-nine percentof cases were tested for malaria, 18.0 % triaged, 96.7% received parenteral antimalarial for at least 24 hours, 86.4% prescribed full-course ACT after parenteral treatment and 54.5% scheduled for follow-up visit. Improvements are needed in quality of data validation meetings, application of WHO criteria for severe malaria, documentation, patient triaging and follow-up scheduling. Admission reporting forms need revision to distinguish severe from uncomplicated malaria.

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FORMULATION OF G6PD HEMOGLOBIN CONTROL FOR POINT-OF-CARE G6PD DIAGNOSTICS

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Radical cure of Plasmodium vivax malaria requires glucose-6-phosphate dehydrogenase (G6PD) testing. A significant gap for the implementation of point-of-care (POC) G6PD testing is the availability of reagents to support quality control (QC) of G6PD products along the supply chain from the manufacturer to the end user. Key attributes to the utility of these reagents are stability and unitized packaging. Although reagents and systems exist to support QC of laboratory screening tests for G6PD, they are not formulated or packaged adequately to support programmatic quality assurance (QA) programs for POC G6PD tests. PATH has developed a G6PD-hemoglobin combined control reagent that can be used in POC settings. To represent high or normal G6PD concentration, human recombinant G6PD was used for spiking whole blood in K2EDTA, whereas low or deficient G6PD was created with contrived whole blood sample. Prior to lyophilization, a protective formulation was mixed in the blood sample to protect the G6PD enzyme activity against degradation from denaturation. Formulated blood samples were aliquoted into individual single-use tubes for lyophilization. Post lyophilization, the freeze-dried reagents were placed in individual packs with desiccants and stored at different temperatures for a one-year stability

study. Reference assays for G6PD activity and hemoglobin concentration were used to determine the stability of the G6PD-hemoglobin controls. Lyophilized G6PD-hemoglobin controls in both normal and deficient levels are stable for at least 365 days when stored at 2°C-8°C. The reconstituted control in the liquid format is stable for 3 hours at ambient temperature. The formulation of combined G6PD-hemoglobin controls with high and low G6PD enzyme activity with yearlong stability will support a framework for a sustainable QC/QA system at country level to support robust point-of-care G6PD testing for P. vivax radical cure.

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INVESTIGATING THE IMPACT OF LARVICIDING AS A SUPPLEMENTARY MALARIA VECTOR CONTROL TOOL IN RURAL SOUTH EASTERN TANZANIA: A SIMULATION STUDY

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Despite tremendous gains in reducing the malaria burden due to the massive use of insecticide-treated nets (ITNs) and indoor residual spraying (IRS), transmission continues in most of sub-Saharan Africa. Rufiji district located in rural southeastern Tanzania, still has malaria transmission occurring despite high ITN coverage (80 -85%), which may be explained by the evolution of insecticide resistance and behavioral changes in malaria vectors. Therefore, there is an urgent need for additional interventions to complement ITN use. To investigate the potential impact of larviciding in different scenarios and coverage levels, a mathematical model, Vector Control Optimization Model was adapted and simulated with 80% ITN coverage as a baseline. To evaluate the effect of the application of larviciding on the mortality rate of An. gambiae, matured and immature mosquitoes were collected in two phases, before (2016-2017) and after (2019-2021) larviciding application. The entomological inoculation rates (EIR), reproduction number (R0) and biting rate were used as the primary outcome measures during the simulation. For the period of 1 year, larviciding was predicted to reduce EIR by 76.43% more than when only ITN was used, took over from 42 down to 9.9, Additionally, deploying larviciding together with ITNs was predicted to have a large impact, as it was estimated to reduce mosquito biting rate (approximately 60%) relative to the scenario without larviciding. Sensitivity analysis over a range of likely values for the biting rate, mosquito lifespan, and mosquito carrying capacity shows comparable the estimated impact between scenarios. This indicates that the predicted impact of larviciding is robust to uncertainty in model parameters and assumptions. The application of larviciding has practical challenges such as hardship in attaining high coverage but gives an assurance to vector control especially targeting the spreading An. Stephensi. This study supports larviciding as a successful strategy that policymakers and public health professionals, like the NMCP, may use to control malaria vectors based on WHO application recommendations.

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IMPACT OF MASS DRUG ADMINISTRATION AND INDOOR RESIDUAL SPRAYING ON MALARIA BURDEN IN A HIGH TRANSMISSION SETTING: A QUASI-EXPERIMENTAL STUDY DESIGN

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Mass drug administration (MDA) is likely to accelerate vector control impact. Yet exists little evidence on its impact on the malaria burden. We test the hypothesis that MDA plus indoor residual spraying (IRS) accelerates malaria burden reduction as compared to IRS.The study used a quasi-experimental design in three sub-counties of high malaria transmission endemicity where all received the standard of care. Toroma and Kapujan sub-counties received four rounds of IRS using primiphos-methyl (Acttellic SC300) six to eight months apart from December 2016 till December 2018. Kapujan sub-county received simultaneously with IRS, MDA using dihydroartemisinin-piperaquine (DHA-PQ). Patient data were collected routinely from health facilities and aggregated in the health management information system (HMIS), at the facility level, and into the District Health Information Software (DHIS2). Data were analyzed using interrupted time series (ITS) and difference-in-difference (DID) to estimate the differences in changes in malaria case incidence rate and test positivity rate and the value of MDA on IRS. Safety was recorded through passive surveillance and patients managed following the standard of care. This study was registered with the Pan African Clinical Trial Registry under PACTR 201807166695568. Malaria cases dropped by 83% (IRR: 0·17 (0·16- 0·18); p=0·001) while in the IRS arm, these drops were 47% (IRR: 0·53 (0·51, 0·56); p=0·001) in children under 5 years. A total of 6·85 (CI 95: 2·53, 11·19) cases per 1000 persons per month were prevented in the IRS+MDA arm compared to the IRS arm in under 5 years. TPR dropped at a rate of 21 positives per 1000 persons (p=0·003) and a month-to-month decline of 0·09 positives per 1000 persons (p=0·90) in children under 5 years. An additional decrease of 60 (p-value, 0·040) mean malaria cases among children under five years and a mean decrease in TPR of 16·16 (p-value, 0·001) was observed. MDA reduces malaria burden among children under 5 years suggesting it's a potential key strategy for malaria control and elimination in high transmission settings.

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ASSESSMENT ON THE RATIONAL USE OF ANTIMALARIA DRUGS IN HEALTH FACILITIES OF ETHIOPIA, CROSS SECTIONAL STUDY

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Malaria is one of the major causes of morbidity and mortality in in Ethiopia. Appropriate use of antimalarial drugs is vital in the effective management of malaria. This study helps to assess antimalarial drug use and level of adherence to national malaria treatment guideline and identify improvement areas at health facilities. To assess the rational use of anti-malarial drugs on the management of malaria cases in selected six health facilities in Ethiopia. Indicator based cross-sectional study was conducted by reviewing medical records of malaria patients who were treated from August 1, 2021, to June 30, 2022. Medical records of 540 patients were selected using systematic random sampling for data collection by standard questionnaire, exported to SPSS and descriptive analysis was done. 540 malaria patient medical records were reviewed. Most of the patients were male (55.7%), mean age of the patients was 22.9 years (SD=15.3) and 162 (30%) were children under 15 years. Only 136 (25%) of the patients were treated based on weight. Laboratory test was done for 463 (85.7%) of the patients, and 14.3% were treated without laboratory confirmation. Plasmodium falciparum species was the predominant species (54.9%), and most (39.1%) of the patients were diagnosed with severe malaria followed by uncomplicated malaria (23.3%). Primaquine co-administration was provided to only 124 (24.5%) of the patients, which is a small proportion compared to the need to provide it to all the patients. Parenteral IV of AR was shifted to PO within the recommended period for only 64.7% of the patients. Even though Primaquine is contraindicated during any trimester of pregnancy 3 pregnant women were given. In conclusion, there is low compliance to the national malaria treatment guideline and irrational use of antimalarial drugs. Prescription pattern of antimalarial drugs for most indicators was inappropriate. Health facilities should strengthen Drug Therapeutics Committees to continuously assess drug use at health facilities, design and implement interventions.

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ASYMPTOMATIC MALARIA AND ITS TREATMENT EFFECTIVENESS IN GIA LAI AND PHU YEN PROVINCES OF VIETNAM FOR THE MALARIA ELIMINATION ROADMAP GIA LAI AND PHU YEN PROVINCES OF VIETNAM FOR THE MALARIA ELIMINATION ROADMAP

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A significant challenge for malaria elimination in Vietnam is the detection and elimination of asymptomatic malaria infections, which presents a hidden reservoir for malaria transmission contributing to the spread of drug-resistant malaria parasites. Gaining an understanding of the prevalence, distribution and persistence of asymptomatic malaria will help design intervention strategies to accelerate malaria elimination. Between 11 June 2022 and 17 February 2023, we screened 1,200 asymptomatic people (adults and children ≥ 5 years old) residing in Krong Pa district, Gia Lai province (n=1,045 people) and Song Hinh district, Phu Yen province (n=155) in Central Vietnam. Of these, 400 people (cohort 1) were living in close proximity to the previous year's symptomatic malaria cases and 800 people (cohort 2) were close contacts of the "index" symptomatic malaria cases associated with a concurrently run therapeutic efficacy study of pyronaridine-artesunate (Pyramax®). Finger prick blood samples were collected. All subjects were malaria negative by rapid diagnostic tests and blood film microscopy. RNA was extracted from 150 µL of blood and malaria parasites were detected by one-step RT-qPCR targeting 18S ribosomal RNA transcripts of Plasmodium falciparum, P. vivax, P. ovale and P. malariae. Of the 1,200 subjects, 77 (6.4%, CI 95%: 5.2-7.9%) were positive for malaria parasites by RT-qPCR, with 73 (94.8%) cases infected with P. falciparum and four cases of unknown speciation. The prevalence of asymptomatic malaria in cohort 1 of 1.8% (CI 95% 0.9%-3.6%) was significantly lower (P<0.0001), than that in cohort 2 amongst close contacts of the current symptomatic malaria cases of 8.8% (CI 95% 7.0%-10.9%). A total of 54 malaria positive subjects elected to be treated with Pyramax® (3-day course) and a single dose of primaquine. The study is ongoing with 25.9% (14/54) of treated subjects still being followed up to day 90 after starting treatment. The efficacy findings will be presented at the meeting. This information will inform the National Malaria Control and Elimination Program of Vietnam on strategies to accelerate malaria elimination in Vietnam.

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EVALUATION OF THE PERFORMANCE OF THE EXTENSION OF INVESTIGATIONS - RESPONSE OF MALARIA CASES IN THE REGION OF FATICK (SÉNÉGAL) FOR THE YEAR 2021

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In order to eliminate malaria in Senegal, investigations - responses to malaria cases started in 2013 initially in the northern zone of the country to interrupt local transmission. The Fatick Region is the first in the central zone to be enrolled in the extension phase in 2020 due to its low incidence. Evaluating the first year of activity is important to ensure proper implementation. The performance evaluation concerns the year 2021 and the entire Fatick region. The population of the eight districts is included. Data were obtained from registers, documentation forms, case listing, supervision reports, Tracker and DHIS2 platforms. Analyses were done with Excel software and the Tracker and DHIS2 analysis modules. 90% of the skilled workers and 20% of the community health workers were trained on the investigations. The completeness of the reports was 98% with 1333 malaria cases reported; 94% were documented within 24 hours and 94% investigated within 72 hours. The sex ratio was 3:1 in favor of females, and the age group 15 to 30 years represented 55% of the cases [1 month to 83 years]. There were 1299 uncomplicated cases, 34 severe cases and 1 death. The analysis of the travel history of the patients shows that a stay in the regions of Dakar and Diourbel was the most frequent, respectively 34% and 17%. The positive rate of RDTs during investigations with the FTAT approach was 0.38% (177 cases/45424 tests); there was a 0.1% refusal from the population and a need for 10733 LLINs in the concessions visited was identified. On the other hand, 55 cases of outbreaks were detected with 6557 people treated. The results of the first year of investigations show a successful implementation in the Fatick region. It is necessary to work for a change in the behavior of the 15-30 year old age group, which bears the main burden. The distribution of LLINs through investigations must be strengthened given the gaps observed. Also, the weakness of the trained community actors must be corrected for the appropriation of the populations and the sustainability of the approach.

5405

EXPOSURE TO A MULTI-CHANNEL MALARIA SBC PROGRAM AMONG GOLD MINERS IN GUYANA

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Early diagnosis and prompt treatment is critical for malaria elimination. Guyana's Ministry of Health has implemented a program to increase access to testing and treatment in remote gold mining communities where malaria is endemic. The program interventions cut across the social ecological model, including distribution of insecticide-treated nets and training community members as volunteer malaria testers (VMT) who can administer rapid diagnostic tests, provide treatment for individuals with uncomplicated cases of malaria, and conduct ongoing monitoring. In partnership with the USAID-funded Breakthrough ACTION project, the VMT program is complemented by a National Malaria Social and Behavior Change (SBC) strategy and a multi-channel SBC intervention, Little Mosquito Big Problem (LMBP), that utilizes culturally relevant activities and messaging to increase miners' perceptions of malaria risk and self-efficacy to sleep under LLINs, test for malaria, and complete treatment. A robust mixed methods evaluation of this program examined pre-and post-intervention changes in malaria knowledge, attitudes, and practices among gold miners in the study areas. The evaluation included cross-sectional surveys with approximately 1,200 adult miners in 2019 and 2022. At post-test 77% of miners recalled at least one LMBP campaign component and a third of the miners knew about the VMT program. Multivariable logistic regression analysis controlling for miner's sociodemographic characteristics and mining context found that exposure was associated with higher knowledge, progressive attitudes towards malaria prevention and treatment, self-efficacy for malaria-related behaviors, positive self-image, and availability of social support. The results highlight gains made in Guyana to address malaria in remote areas. Care-seeking behaviors were reported by slightly more than half of all miners, and as such, there continues to be the need for multi-level programs for malaria elimination and expanded reach of the program.

5406

CONSIDERATIONS FOR MEDICATION SAFETY FOR MASS DRUG ADMINISTRATION FOR PLASMODIUM FALCIPARUM MALARIA ELIMINATION

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The use of mass drug administration (MDA) for malaria can have a large impact - ranging from rapidly decreasing morbidity and mortality during malaria outbreaks to potentially contributing to malaria elimination with multiple rounds. These two scenarios may carry different risk-benefit outcomes because of their differing levels of malaria transmission, yet there are few published reports on the implementation of safety measures in MDA campaigns notably for malaria elimination. A medication delivered to a large population should be both operationally appropriate and safe to justify its use in MDA. The ideal medication for MDA would meet the following criteria: efficacious in clearing all stages of the parasite, long prophylactic effect against new infections, a single dose regimen per round, safe in pregnancy, safe in common chronic medical conditions, minimal risk of drug-drug and drug-food interactions, low potential for drug hypersensitivity reactions, and associated with only minimal reports of adverse drug reactions (ADRs). In addition, rigorous screening algorithms to assess an individual's eligibility to participate may be implemented during the MDA campaign to further minimize the risk of adverse events. In 2020, the National Malaria Control Program in Haiti administered sulfadoxine-pyrimethamine (SP) and a single low dose of primaquine (PQ) to 42,249 people. We implemented a medical eligibility screening algorithm that found self-reported rates (preliminary data) of kidney or liver failure (1.92%), SP allergy (0.28%), PQ allergy (0.39%), currently taking other medications that required additional review before administering SP or PQ (4.58%); and among women 15-49 years old, known or possible pregnancy (9.44%), currently breastfeeding (19.92%). Additional screening questions or testing were administered as needed. For ADR monitoring, passive pharmacovigilance was implemented that detected four cases of Stevens-Johnson syndrome. A review of MDA screening procedures identified no errors. An analysis of our campaign procedures and experience will provide lessons learned to increase the safety of MDA campaigns.

5407

ELUCIDATING INTERSEASON RESIDUAL PLASMODIUM INFECTION IN HUMANS AND WILD MOSQUITOES TO GUIDE THE SUCCESSFUL IMPLEMENTATION OF INTERVENTIONS FOR MALARIA ELIMINATION

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In the efforts of malaria control, multiple interactive strategies need to be deployed in the field. Because of specific mechanisms and action of each strategy, it is critically important to assess the main epidemiological parameters of malaria transmission in natural setting. The responsibility of human and vector as the main Plasmodium reservoirs in the parasite transition between two malaria seasons is unclear. Here, we aim to investigate the seasonal variations of Plasmodium infection during the dry season emphasizing on the potential role of human and vector in Burkina Faso. A longitudinal survey was performed during an entire dry season of 6 months for P. falciparum infection combining molecular and microscopy analysis in school age-group of children who were classified into 4 cohorts. The first group consisted of confirmed-uninfected individuals, the second, malaria submicroscopic infections, the third, asymptomatic infected-children with low P.f densities (to monitor parasitemia progress), and the fourth group included malaria asymptomatic cases which were treated with antimalaria drug. In parallel, we examined the spatial and temporal distribution of the mosquito vectors and their Plasmodium infection status. Following approximately 1000 children revealed that humans remain the main parasite reservoir between malaria seasons: with more than 50% of P.f-asymptomatic carriers remain infected all dry season during which the vector was quasi-absent. Advanced molecular analysis using Plasmodium in blood samples will provide more information about the parasite genotypes. Interestingly, 95% of negative individuals for P. falciparum infection (naturally or by antimalarial treatment) remains uninfected until the start of the transmission season, implying that intervention such as mass drug administration in the absence of the vector could be more beneficial for malaria control.

5408

KNOWLEDGE AND PERCEPTIONS OF NATIONAL GUIDELINES FOR THE CASE MANAGEMENT OF MALARIA IN PREGNANCY AMONG HEALTHCARE PROVIDERS AND DRUG DISPENSERS IN THE CONTEXT OF MULTIPLE FIRST-LINE THERAPIES IN WESTERN KENYA: A MIXED METHODS STUDY

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Emerging resistance to artemether-lumefantrine (AL) in Africa prompted the pilot introduction of multiple first-line therapies against malaria in the general population in western Kenya, potentially exposing women of childbearing age to antimalarials with unknown safety profiles in the first trimester. We undertook a mixed-methods study to explore the knowledge and perceptions of malaria treatment guidelines for pregnant women among healthcare providers and drug dispensers. Structured questionnaires were administered to 174 providers across 50 health facilities and 40 drug outlets. In-depth interviews (IDIs) were conducted with 33 purposively selected healthcare providers, drug dispensers, and health managers. Transcripts were coded by content analysis using the WHO health system building blocks framework. Descriptive analyses and Chi-square tests were used to report differences in proportions. There was a greater awareness of guidelines in health facilities (83/134 [62%]) versus drug outlets (16/40 [40%]) (p=0.023), and more staff in health facilities had been trained on malaria in pregnancy in the last year (49% vs 20%, p=0.002). Lack of training on malaria case management was also evident from the IDIs with drug outlet providers, who did not know the national malaria treatment guidelines and reported a lack of pregnancy tests. Knowledge of recommended antimalarials for treatment in the first trimester (72% vs 90%, p=0.02), second /third trimesters (70% vs 84%, p=0.07), and for severe malaria (50% vs 71%, p=0.02) was less common in drug outlets than health facilities. Providers reported using AL instead of quinine in the first trimester due to the side effects and unavailability. Patient preference was a major factor in the antimalarials prescribed. Health managers reported a lack of supervision of drug outlets due to insufficient funds. Almost all providers reported drug stock-outs, with quinine most affected. Improved training, regulation, and monitoring of drug outlet providers is warranted, in addition to regular supply of malaria commodities and pregnancy test kits to ensure adequate management of malaria in pregnancy.

5409

WHY DID BLACK SOLDIERS HISTORICALLY HAVE MORE PNEUMONIA THAN WHITE SOLDIERS IN THE US ARMY?

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Black US Army soldiers had four times as much bacterial pneumonia as White US Army soldiers during both the US Civil War and World War 1 (WW1). Pneumonia case fatality rates were a third higher in Black soldiers during the US Civil War but were the same between the racial groups by WW1. During WW2 the use of antibiotics decreased bacterial pneumonia mortality rates 100-fold and apparently erased racial differences. Similar differences in bacterial pneumonia rates by racial group were observed in African colonial soldiers of the French and British Armies during WW1. Pneumonia rates in Indian, Pilipino and Puerto Rican soldiers suggested that genetic polymorphisms were not a decisive factor determining Black pneumonia mortality. Post-measles pneumonias did not suggest an immune deficit in Black soldiers. Geographic focus of pneumonia in Black soldiers from the southern USA States and other tropical regions raises the possibility that increased bacterial pneumonia rates were indirectly related to malaria infections. Malaria remains a difficult to measure but potentially important mortality risk factor in pneumonia.

5410

ONE OUT OF TWO CHILDREN CARRIES MALARIA PARASITES: HIGH PREVALENCE OF ASYMPTOMATIC MALARIA AMONG CHILDREN IN THE AHANTA WEST DISTRICT, GHANA

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Malaria is a persistent problem in sub-Saharan Africa, particularly among children. The World Health Organisation (WHO) has set a goal to reduce cases by 50% and mortality by 90% by 2025. However, the asymptomatic carriage of parasites continues to pose a challenge. Rapid diagnostic tests (RDTs) are recommended for surveillance due to their ease of use and low technical requirements. In this study, we evaluate the performance of three RDTs for detecting Plasmodium falciparum and Pan Plasmodium in asymptomatic children in the Ahanta West Municipality of Ghana in December 2022. We collected demographic and medical information using a structured questionnaire and performed venepuncture to obtain peripheral blood for the malaria RDTs. The study included 113 participants with a mean age of 12.10±2.3; 70 (61.9%) were girls, and 25 (22.1%) reported receiving malaria treatment in the three months prior to data collection. Malaria positivity rates were 44.2% for Bioline, 49.6% for NxTek, and 52.2% for First Response, with an overall prevalence of 53.1%. No significant associations were found between asymptomatic malaria positivity and study variables. Our findings suggest a high prevalence of asymptomatic malaria even during the dry season, which may hinder current elimination strategies and contribute to the transmission of malaria. Additionally, individuals with asymptomatic malaria may act as reservoirs for malaria parasites, underscoring the need for continued surveillance and treatment.

5411

VIVAX MALARIA IN DUFFY NEGATIVE ETHIOPIAN PATIENTS SHOWS INVARIABLY LOW ASEXUAL PARASITAEMIA

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The detection of Plasmodium vivax infection among Duffy negative individuals in Africa has challenged the established dogma of the associations between Duffy antigen and P.vivax invasion of reticulocytes. The human host P.vivax relationship has brought new insights in the impact of Duffy polymorphisms on the epidemiology of malaria. The objective of this study was to determine the prevalence of P.vivax among Duffy negative and Duffy positive individuals; and to compare parasite density in those patients. Identification of Plasmodium species was performed by microscopic examination on field sites and by real time PCR in the laboratory. Genotyping of Duffy antigens was followed by DNA sequencing to determine its polymorphisms in a total of 138 P.vivax infected samples. The proportion of Duffy negative among P. vivax infected patients was 2.9% (4/138) with FYB/FYBES and FYA/FYBES genotypes being the common variants. However, FYBES/FYX genotype was only seen in two P. vivax infected patients. Low P. vivax parasitemia was counted in individuals with FYBES/FYBESand FYBES/FYX genotypes. In conclusion, although P. vivax infects Duffy negative individuals, polymorphisms of Duffy antigens have effect on asexual parasitemia. Patients with Duffy negative had low density parasitaemia as compared to those with Duffy positives. Infection in Duffy negatives, remain undetected by the commonly used malaria diagnostic tools (microscopy and Rapid diagnostic tests) putting them as the silent reservoirs in fueling onward malaria transmission. This unquestionably affects the elimination efforts.

5412

EPIDEMIOLOGICAL STUDY TO ESTIMATE MALARIA PREVALENCE AND USE OF CONTROL MEASURES IN AN AREA WITH PERSISTENT TRANSMISSION IN SENEGAL

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While there is evidence of malaria burden among under-five, limited data on malaria prevalence and use of control measures are available across all age groups in Senegal. As the country is shifting from control to elimination, there is a need to better understand malaria distribution across all age groups in order to guide future interventions. A cross-sectional survey was conducted in four health posts in the Saraya health district, an area with persistent malaria transmission during the 2021 transmission season. A multistage random sampling technique was used to select households and individuals over 6 months of age who consented were invited to participate. Socio-demographic data, household assets, and use of preventive measures were collected using an electronic questionnaire. Malaria parasites were screened by microscopic examination of blood smears, and hemoglobin levels were measured using a portable hemoglobinometer (Hemocue 301TM). Logistic regression was used to identify factors associated with malaria infection. Overall, 1759 participants were enrolled and P. falciparum prevalence was 20.5%. There is no statistically significant difference between the prevalence of under-five children (20.5%) and adolescents (26.6%), (p=0.52), nor between 5-10 years old children (26.6%) and adolescents (24.7%), (p=0.76). P falciparum accounted for 99.2% of the malaria infection, and 69% were asymptomatic. The odds of malaria was associated with the location of Khossanto (aOR=1.97, 95% CI: 1.35-2.88) and the primary education level (aOR=1.64, 95% CI: 1.08-

2.50). Around 33% of the study participants were anemic (hb<11g/dl), with under five children bearing the highest prevalence (67.3%). P. falciparum positive individuals (aOR=1.33, p=0.037), females (aOR=2.10, p=0.000), and under-five children (aOR=11.90, p=0.000) were more at risk of anemia. Bed net usage was lower among adolescents (31,1%) compared to 48.0% for under five and 41.2% for 5-9 years old children. Malaria prevalence was higher among adolescents. Interventions tailored to this specific population group are needed to better control the disease and reduce its burden.

5413

MALARIA TRENDS DURING THE COVID-19 PANDEMIC IN THE CITY PROVINCE OF KINSHASA / DR CONGO

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Malaria Trends During The COVID-19 Pandemicin The City Province Of Kinshasa / Dr Congo. Laishe B1, Musema B2, Mukomena E1,3, Likwela J4 National Malaria Control Program, RD Congo 2. University of Kinshasa, 3 . University of Lubumbashi, 4 University of Kisangani, I.

Malaria is one of the scourges that concern the world with high morbidity and mortality In 2019, 212 million cases of malaria were recorded worldwide with 429,000 deaths. The African region is the most affected and accounts for 89% of all cases and 91% of deaths recorded worldwide (WHO 2019). In DR Congo, malaria is the leading cause of hospitalization among children under 5 and pregnant women. Added to this is the occurrence of the COVID-19 pandemic with the highest lethality (2.6%) (Epidemiological Bulletin 2020). We want to know if the COVID-19 pandemic has an impact on the proportions of malaria in the city of Kinshasa. II. We carried out a cross-sectional study using data from the annual reports of the PNLP / DR Congo edition 2019 and 2020. In 2019, about 2,249,789 suspected cases of malaria were registered, 1,270,497 confirmed cases (56%, 119,009 serious cases and 973 deaths. In 2020, 2,148,169 suspected cases, 1169,841 (54.5%) confirmed cases, death.The results of this study revealed no significant difference. The increase in deaths during the pandemic period is justified by the fact that at the start of this pandemic, the population had deserted the health structures. In conclusion, COVID-19 appears to have no impact on the proportions of malaria cases. Large-scale studies across the country need to be conducted to confirm these findings.

5414

FACTORS ASSOCIATED WITH ACTIVE PRIVATE HEALTH PROVIDER FOLLOW-UP OF PLASMODIUM VIVAX PATIENTS TREATED WITH PRIMAQUINE IN MYANMAR

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Recorded cases of Plasmodium vivax have risen in Myanmar since 2019, with 39342 cases reported in 2022, almost double that of 2021. Myanmar aims to eliminate P. vivax by 2030. Elimination will require patient adherence to radical cure with primaquine (PQ), which has hitherto proven difficult due to the 14-day dosing regimen. Adherence can be supported by active provider follow-up. We developed a suite of tools to support malaria care providers, including an NMCP-approved direct observation treatment form, patient counseling form and case management guide. A cross sectional mixed-method study was conducted with private general practitioners (GPs) and trained informal private outlet (PO) providers to investigate knowledge, attitudes, and practices related to P. vivax treatment and explore opinions of the new tools. A total of 216 GP and 204 PO providers completed a quantitative survey, which was followed by qualitative in-depth interviews (IDIs) with 10 GP and 6 PO. Descriptive and logistic regression analyses were conducted for survey data and deductive content analysis performed on qualitative data. Providers had excellent knowledge of P. vivax treatment, with 99.1% of GPs and 94.1% of POs correctly citing the national guidelines. However, only 25.5% of GP and 79.4% of PO reported that they usually followed-up patients who were treated with PQ. Multivariate regression identified the following significant determinants of patient follow-up: providers aged above 60 yrs (aOR=0.39, p=0.016), provider education above high school (aOR=0.15, p<0.001) and providers in rural areas (aOR=1.9, p=0.019). IDIs revealed transportation and connectivity at patients' location and poor patient awareness of the importance of adherence as challenges to patient follow-up. Providers valued the new tools and believed that they would help improve treatment adherence and monitoring PQ side effects. However, providers could not complete the counseling form for every patient when their case load was high. The study highlighted additional customized program support is needed to support providers with active patient follow up per treatment guidelines.

5415

DISTRIBUTION OF ANOPHELINES AND MALARIA PREVALENCE ACCORDING TO HOUSE STRUCTURE AND COMMUNITY PRACTICES DURING A LARVICIDING PROGRAM IN THE CITY OF YAOUNDÉ, CAMEROON

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The most efficient malaria vectors bite and rest inside houses, hence houses play a determinant role in malaria transmission. During the implementation of additional vector control tools such as larviciding, individual disease risk perception could be affected. We carried out this study to evaluate the influence of house structures, community knowledge and practices on anophelines diversity and malaria prevalence, before and during a larviciding program. The study was conducted before and during larviciding intervention in 26 districts. Indoor CDC light traps were used to collect mosquitoes. Questionnaires were administered to collect data on house characteristics and to assess the impact of larviciding on population knowledge and behaviour. After morphological identification, anophelines were tested by ELISA to detect infection to Plasmodium parasites. RDT was used to test the blood samples of participants. Binary analyses were used to assess the correlation between different variables. The majority of houses were made with cement walls. The most abundant anophelines was Anopheles coluzzii, followed by An. gambiae s.s, with the highest densities in traditional houses before the treatment and in control sites, whereas, they were most abundant in modern houses in treated sites. Opened eaves and the absence of a ceiling exposed people to anopheline bites. Possession of LLINs before the treatment and in control sites exposed people to anopheline bites while they were protected in treated sites. Infection to Plasmodium and malaria prevalence were highest in modern houses found in control sites; while in treated sites, infection to Plasmodium was high in modern houses, but malaria prevalence was the same in both house types. People who lived in treated sites knew more about malaria prevalence and mosquito breeding sites, and the latter used fewer LLINs. Well-built houses protect people against anophelines species. The implementation of larvicide control improved the knowledge of people and decrease their personal protection against mosquito bites.

5416

BREAKING THE MALARIA CYCLE; ASSESSMENT OF REPEAT MALARIA INFECTIONS IN LAKE ENDEMIC REGION OF WESTERN KENYA, JUNE 2021-MAY 2022

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The burden of malaria in Kenya is not uniformly distributed, with the Lake-endemic region in Western Kenya having a prevalence of 19% compared to the national average of 6%. There's limited data on repeat malaria infections in this region. We sought to characterize repeat malaria infections epidemiologically and identify associated factors among outpatients.We reviewed medical records from 1st June 2021 through 31st May 2022 in nine public health facilities in three counties in the Lake-endemic region. The study population was patients diagnosed with confirmed malaria. Temporal, demographic and diagnostic data were abstracted using a standardized template from outpatient and laboratory registers. A repeat malaria infection was defined as confirmed parasitemia in a patient fourteen days after treatment initiation. The outcome variable was >1 confirmed malaria episode in the same patient. Analysis was performed using Epi Info v7.2.5. We calculated means and medians for continuous variables, frequencies and proportions for categorical variables. Chi-square test was used to measure the association between repeat infections and independent variables and factors with p<0.05 were considered statistically significant. We analyzed 26,133 records; 12% (3,132/26,133) were repeat malaria cases, 64% (1,993/3,132) were aged <15 years and 27% (844/3,132) < 5 years. The majority, 87% (2,728/3,132), had one repeat infection, and 15.2% (476/3,132) had more than one episode. The median duration to repeat episodes was 146 days (IQR:51-341). Overall, diagnosis by microscopy was 57% (1,783/3,132) and 43% (1,335/3,132) by RDT. Healthcare workers adhered to national treatment guidelines in 88.2% (1,683/1,909) cases representing 90.6% (727/802) among <5 years and 86.4% (956/1,107) among 5-14 years. We found an association between diagnosis and patients <5 years (cOR 1.5, 95%CI 1.1-2.1).Persons aged <15 years had the highest burden of repeat infections. The malaria lake-endemic counties should enhance laboratory surveillance and treatment for repeat malaria infections in children.

5417

INSIGHTS INTO THE IMPLEMENTATION OF A LIFE-SAVING INTERVENTION: A PROCESS EVALUATION OF PRE-REFERRAL RECTAL ARTESUNATE SUPPOSITORIES ADMINISTRATION IN CHILDREN FROM RURAL ZAMBIA FOR SEVERE MALARIA

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Children with severe malaria in remote rural areas have the highest risk of malaria mortality. Appropriate malaria treatment may be delayed due to travel costs, geographical barriers, and travel distances. Rectal artesunate suppositories (RAS) administered by community health workers as a pre-referral treatment for severe malaria (SM) have been shown to help save the lives of children with SM by greatly reducing their parasite load. These children must still be taken to referral hospitals for case management and completion of antimalarial treatment, or risk parasite resurgence. Recent observational studies found that children with SM in regions where RAS was being implemented had an increased risk of dying compared to regions without RAS. This surprising result led to the WHO revising its recommendations on RAS implementation and encouraged process evaluation of ongoing in-country implementations. The National Malaria Elimination Centre (NMEC) of Zambia along with its partners, successfully piloted the RAS intervention package in 2017 and has since scaled it up to 10 districts in Zambia. This mixed-methods study assesses real-world implementation of the RAS intervention package across three districts in Zambia with varying implementation experience. The primary objectives are to ascertain service availability and readiness of service providers across the cascade of care for severe malaria, enumerate what proportion of severe malaria cases complete each step along the cascade, describe where children with severe malaria are dying and why, and identify perceptions, facilitators, and barriers to referral care for caregivers and other community members. Data collection is being conducted during peak malaria transmission season and preliminary results will be presented. These results will provide critical information for the NMEC and its partners. In addition, it will provide a more holistic understanding of the RAS intervention package, which may help improve RAS implementation in other countries and reduce mortality among children in remote rural areas with severe malaria.

5418

HELMINTH AND MALARIA CO-INFECTION AMONG PREGNANT WOMEN IN TWO DISTRICTS OF THE VOLTA REGION OF GHANA

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In sub-Saharan Africa, approximately 40 million pregnant women are exposed to parasitic diseases such as malaria caused by Plasmodium falciparum, Schistosome parasites, and soil-transmitted helminth (STH). When parasitic diseases share the same habitat and overlap in distribution then high rates of co-infection occur. The co-infection can lead to consequences for the child, such as intrauterine growth retardation, low birth weight, pre-term delivery, and neonatal mortality. The objective of the study was to determine the nature and extent of coinfection from 100 samples collected from the Battor (50) and Adidome (50) districts of Ghana in collaboration with Noguchi Memorial Institute for Medical Research, University of Ghana. Out of 50 for the Adidome district determined for P. falciparum by RDT, Malaria PAN, and Malaria Pf kit, 39 were true positive (TP), 8 were true negative (TN), and 30 were false negative (FN). For Battor, 19 were TP, 12 TN, and 20 FN. For S. mansoni in Adidome via polymerase chain reaction (PCR) and loop-mediated isothermal amplification (LAMP), 21 tested positive, and 29 negatives with 52.5% sensitivity and 100% specificity. For S. haematobium, 28 were positive and 22 negatives using PCR with 70% sensitivity and 100% specificity. In LAMP, 28 were positive, and 22 negatives with 70% sensitivity and 100% specificity. In Battor PCR for S. mansoni, 28 positives and 22 negatives with 68.3% sensitivity and 100% specificity. In LAMP, 32 were positive, and 18 were negative with 80% sensitivity and 100% specificity. For S. haematobium, PCR showed 30 positive and 20 negative with 73.2% sensitivity and 100% specificity. With LAMP, 21 were positive, and 29 negatives with 51% sensitivity and 100% specificity. In both district age groups, B (20-30 years) had the highest infection prevalence for P. falciparum, S. mansoni, S. haematobium, and Strongyloides stercoralis. The results will be utilized as a part of the continuous surveillance for future research aiming at gathering nationally representative data in Ghana on the prevalence of coinfection and proposing interventions based on that for the vulnerable pregnant women population.

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TARGETING MALARIA CONTROL EFFORTS IN MALAWI: OUTPUTS AND RECOMMENDATIONS FROM A WORKSHOP ON BURDEN STRATIFICATION FOR THE 2023-2030 STRATEGIC PLAN

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Malawi's National Malaria Control Programme (NMCP) is developing a new strategic plan for 2023-2030 to combat malaria and recognizes that a blanket approach to malaria interventions is no longer feasible. To inform this new strategy, the NMCP set up a task force comprising 18 members from various sectors, which convened a meeting to stratify the malaria burden in Malawi and recommend interventions for each stratum. The burden stratification workshop took place from November 29 to December 2, 2022, in Blantyre, Malawi, and collated essential data on malaria burden indicators, such as incidence, prevalence, and mortality. Workshop participants reviewed the malaria burden and intervention coverage data to describe the current status and identified the districts as a appropriate administrative level for stratification and action. Two scenarios were developed for the stratification, based on composites of three variables. Scenario 1 included incidence, prevalence, and under-five all-cause mortality, while Scenario 2 included total malaria cases, prevalence, and all-cause mortality counts in children under five. The task force developed four burden strata (highest, high, moderate, and low) for each scenario, resulting in a final list of districts assigned to each stratum. The task force concluded with 10 districts in the highest-burden stratum (Nkhotakota, Salima, Mchinji, Dowa, Ntchisi, Mwanza, Likoma, Lilongwe, Kasungu and Mangochi) 11 districts in the high burden stratum (Chitipa, Rumphi, Nkhata Bay, Dedza, Ntcheu, Neno, Thyolo, Nsanje, Zomba, Mzimba and Mulanje) and seven districts in the moderate burden stratum (Karonga, Chikwawa, Balaka, Machinga, Phalombe, Blantyre, and Chiradzulu). There were no districts in the low-burden stratum. The next steps for the NMCP are to review context-specific issues driving malaria transmission and recommend interventions for each stratum. Overall, this burden stratification workshop provides a critical foundation for developing a successful malaria strategic plan for Malawi.

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COMMUNITY HEALTH VOLUNTEER CONTRIBUTION TO MALARIA SURVEILLANCE IN SIAYA COUNTY, WESTERN KENYA

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Significant efforts have been undertaken to improve malaria surveillance data in Africa. These efforts are geared towards transforming surveillance into a core intervention. Despite these, there has been little emphasis on granular analysis of community case management of malaria (CCM) data. We reviewed 3 scannable registers routinely completed by community health volunteers (CHV) in Siaya County, western Kenya: household and service delivery registers and daily activity log. We analyzed line-listed data from 416 CHVs covering 443 villages in 73 community units (CU) in 2021-2022. The household registration in 2022 documented 250,707 people (128,926 Rarieda, 118,372 Alego Usonga). Over the year, 47% were offered CCM services by CHVs. Vitamin A, family planning, and routine check-ups were the most frequent referrals constituting 19% (n=16,454) of total referrals by CHVs to health facilities. In 2022, CCM evaluations rose from 12,513 to 21,044; CHVs performed 17% of total tests and identified 20% of all malaria cases in both sub-counties. Mean monthly rapid diagnostic tests (RDTs) performed per CHV increased from 2.1 to 5.2 in the same period. During this period, 33,197 RDT tests were done by CHVs, 75.0% (n=24,729) among febrile patients. 83.5%(n=20661) of febrile and 79.6% (n=6715) of afebrile cases tested positive for malaria. 95% (n=26015) of RDT positive cases were treated with artemisinin combination therapy, spotlighting. Overall, test positivity rate (TPR) was high: 82.5%, with mean CU TPR of 87.3% (95% CI:85.2-89.4) in Alego Usonga and 82.4% (95% CI:80.8-83.9) in Rarieda. Interestingly, village level TPR was over 80% in 247 villages, substantially higher than health facility TPRs: 56.4% overall, 64.9% (95% CI;63.3-66.7) Alego Usonga, 54.6% (95% CI;51.5-57.7) Rarieda. The discrepancy between CU and facility TPR suggests a community bias towards CHV care for people who think they have malaria while those suspecting another illness go to the facility. Further investigation is needed to better understand care-seeking behaviors and whether these TPR differences are real.

5421

MALARIA TEST POSITIVITY RATES IN COMMUNITY SURVEILLANCE AS COMPARED TO HEALTH FACILITY SURVEILLANCE IN MALARIA ENDEMIC AREA RARIEDA SUB-COUNTY, WESTERN KENYA

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In malaria endemic western Kenya, community case management (CCM) for malaria is a key strategy to increase access to care and provide prompt diagnosis and treatment. However, there are few data assessing the proportion of malaria cases identified by community health volunteers (CHV) compared to facility out-patient departments (OPD) in our setting. In Kenya, CHVs are organized in community units (CUs), which consists of a number of villages and the health facilities that they are linked to. CHVs visit households with reported malaria symptoms, and test and treat them

for malaria and other health conditions. These data are recorded in CHV Activity Registers (CHV-AR) which was digitized using ocular character recognition technology (ScanForm) to enhance quality, timeliness, and data use of information collected in this register.We analyzed data collected between January 2021–December 2022 from 35 health facility OPD ScanForm registers (stratified by age to <5yrs, 5–14yrs and 15+yrs) and CHV-ARs from the corresponding 39 CUs covering 397 villages with a total population of about 128,926 people in Rarieda sub-county, western Kenya. We reviewed the number of persons tested for malaria and calculated test positivity rates (TPR). Overall, 229,511 malaria tests were performed, including 203,208 at OPD (5yrs=40,326, 5–14yrs=63,321, 15+yrs=99,435) and 26,598 in the community (<5yrs=7,770, 5–14yrs= 9,453, and 15+yrs=9,080)The overall TPR was 56.4% at OPD (<5yrs=51.9%, 5–14yrs=69.3%, 15+yrs=48.1%) and 81.1% in the community (<5yrs=85.3%, 5–14yrs=82.5%, 15+yrs=76.0%). Community cases accounted for 11.5% of all malaria tests but 16.1% of all positive cases, highlighting the high TPR in the community. Appropriate provision of artemisinin-based combination therapy for test positive cases was 92.4% at OPD and 95.1% at the community. Despite significant utilization of health facilities, the burden of symptomatic malaria in the community remains high. Our data suggest that CHVs appropriately follow testing and treatment guidelines and reach a population in need. Further support for the CCM should be considered to increase the reach of CHVs.

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IMPLEMENTING HIGH QUALITY COMMUNITY CASE MANAGEMENT AND DATA REPORTING: LESSONS FROM THE FIELD IN SIAYA, WESTERN KENYA

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Malaria is still a major cause of mortality and morbidity in western Kenya, despite implementation of recommended malaria control interventions. Community case management of malaria (CCM), implemented by Community Health Volunteers (CHVs), is a key strategy for timely identification of fever cases and management. However, inadequate data capture tools, training and supervision affect the quality of data. We aimed to track access to diagnostics, treatment, and referral services offered by CHVs using scannable registers to enhance accurate data capture and reporting. In 2021, we deployed scannable registers in 2 sub-counties, in Siaya County, western Kenya. 914 CHVs covering 975 villages in 89 community units (CU) attached to 95 health facilities were trained on the use of scannable registers and senior MoH staff trained on supervision and data quality review, including summary dashboards.34 CUs up from 22 CUs in Alego Usonga began reporting during the implementation period (out of 50). In Rarieda, which has received support since 2021, all CUs are reporting (n= 39). There was an increase in the number of malaria positive cases reported by CHVs, from 8653 in 2021 to 12955 in 2022. While cases seen at the health facility decreased (from 61370 to 51842), the proportion of overall cases seen by a CHV increased from 12.4% in 2021 to 20%. More frequent (Monthly) data reviews at CU level as opposed to quarterly at sub-county level improved reporting timeliness. We uncovered gaps in data collection, review, tallying and reporting. Delayed reports prevented action on critical interventions e.g., restocking malaria testing and treatment commodities. Multiple registers collecting similar indicators presented challenges for CHVs. Therefore, streamlining existing data tools and ensuring partner coordination could reduce CHV workload and improve efficiency. Routine data reviews provide opportunities for supportive supervision and could improve quality of care and data. Integrating and automating tallies from CHV line-listed data into DHIS2 could enhance data quality and facilitate analyses for more targeted malaria control interventions.

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NON-RANDOM DISTRIBUTION OF PLASMODIUM SPECIES INFECTIONS AND ASSOCIATED CLINICAL OUTCOMES IN CHILDREN 3-17 YEARS OF AGE IN THE LAKE VICTORIA REGION, KENYA, 2012-2020

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Plasmodium falciparum (Pf), P. malariae (Pm), and P. ovale (Po) infections are endemic in Kenya. However, plasmodium species mixed infections (co-infections) have not been well documented. We assessed the distribution of co-infections and associated clinical features in the Lake Victoria region of Kenya. Twelve school-based cross-sectional surveys were conducted in Mfangano island and Ungoye village between 2012-2020. Peripheral blood was collected on filter paper for dried blood spots from children aged 3 to 17 years. Plasmodium infection was determined by microscopy and nested polymerase chain reaction (nPCR). The multiple-kind lottery (MKL) model calculated the expected distribution of plasmodium infections in the population and compared it to observed values using a chi-squared test ($\chi 2$); a p-value of 0.05 was considered statistically significant. Multivariate logistic regression model generated adjusted odds ratios (aOR) adjusting for age, sex, school, and survey year and 95% confidence intervals (CI) to assess any association between co-infections, and fever (axillary temperature above 37.5°C), splenomegaly (clinically palpable spleen), and anemia (hemoglobin below 11 g/dl) all measured on the day of the survey. The plasmodium prevalence by nPCR was 41.3% (6849/16563). Among all infections (6849), Pf, Pm, and Po mono-infections were 60.1%, 4.1%, and 2.4%, respectively. Pf-Pm, Pf-Po, Pm-Po, and Pf-Pm-Po co-infections were 21.5%, 3.4%, 0.2%, and 6.9%, respectively. MKL modeling revealed non-random distributions with frequencies of Pf-Pm and Pf-Pm-Po co-infections higher than expected ($\chi 2$=2130, p<0.001). Pf co-infections with Pm and or Po were associated with a decreased risk of fever (aOR 0.70, 95% CI 0.56-0.87; p=0.03). Co-infections with Pf were associated with splenomegaly (aOR 2.79, 95% CI 2.13-3.64; p<0.001) and anemia (AOR 1.23, 95% CI 1.00-1.50; p=0.04) compared to single-species infections. Plasmodium co-infections were common and non-randomly distributed. Prompt diagnosis and adequate treatment of plasmodium co-infections are urgently needed for malaria elimination to be realized in Kenya.

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DYMANICS OF SUBMICROSCOPIC MALARIA INFECTION IN SOUTHERN BENIN

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Since 2016, malaria cases have increased; the largest annual increase of 13 million cases was observed between 2019 and 2020 during the first year of the COVID-19 pandemic according to WHO. In Benin, malaria transmission occurs throughout the year with a peak during the rainy season. Since 2000, there has been a progressive increase in the number of new cases of malaria in Benin, despite the various control strategies in place. According to Health Statistical Yearbook 2021, malaria is the first cause (44.6%) of outpatient consultations in public health facilities. Malaria remains a major public health problem in Benin, which is struggling to control morbidity and mortality. Benin, has set a target of malaria elimination.This study was conducted in urban areas of Adjrako in south of Benin, located in the Atlantic department in the south of Benin; All 1064 inhabitants of Adjrako village were screened for malaria in 2021. Then the following year, 436 individuals from the same village were also screened. Factors influencing submicroscopy and microscopy were studied, using an ordered polytomous logistic regression model.Of the total number of infections,

86.49% were asymptomatic in the dry season and 82.95% in the rainy season. The proportion of individuals with asymptomatic infections was 34.30% and 49.88% in the dry and rainy seasons respectively. Whether in the dry or rainy season, individuals between 5 and 15 years of age have the largest infectious reservoir (50.8% in the dry season and 70.1% in the rainy season) followed by those over 15 years of age (41.1% in the dry season and 60.3% in the rainy season) and then by those under 5 years of age (21.6% and 42.5%) In univariate polytomous logistic regressions, the effect size for age was high in both years and significant ($p < 0.001$). During the rainy season, the risk was greater for 5-15 year olds (OR: 3.43 [95% CI: 2.44- 4.81]) than for those over 15 years old (OR: 2.00 [95% CI: 1.42 - 2.81].Our results confirm the ubiquity of the asymptomatic reservoir in the dry and rainy seasons. Age, sex, season and the use of preventive measures played a role in explaining the asymptomatic infections..

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HIGH PROPORTION OF LOW PARASITAEMIA AND SUBMICROSCOPIC MALARIA INFECTIONS IN HONDURAN MOSKITIA

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Efforts towards malaria elimination in Honduras have achieved substantial progress and reductions in the incidence of cases in the country. La Moskitia, a region with the highest concentration of malaria infections in the country, reported less than 800 cases in 2020. However, achieving and sustaining malaria elimination requires the implementation of highly sensitive tests that can detect low-density parasitemia to identify asymptomatic and submicroscopic carriers. In this study, we implemented photoinduced electron transfer polymerase chain reaction (PET-PCR) and assessed its performance versus light microscopy and conventional nested PCR (nPCR) on 309 whole blood samples collected from febrile subjects using a passive surveillance approach at the Puerto Lempira hospital in Gracias a Dios, Honduras. Different diagnostic performance metrics were calculated including sensitivity, specificity, negative and positive predictive values, kappa index, accuracy, and ROC. Malaria prevalence was estimated at 19.1% by Light Microscopy (LM), 27.8% by nPCR, and 31.1% by PET-PCR with 40 and 13 cases missed by LM and nPCR, respectively. The sensitivity of LM and nPCR was 59.6% and 80.8% using PET-PCR as the reference test. LM showed a kappa index of 0.67, with a moderate level of agreement. This study identified a prevalence of 12% submicroscopic malaria among febrile cases in the Honduran Moskitia. Potential asymptomatic malaria cases are not routinely tested, and, therefore, the actual prevalence in this population could be even higher. Asymptomatic malaria represents a major challenge to malaria elimination in Honduras. Therefore, highly sensitive molecular surveillance tools such as PET-PCR that maximize malaria diagnosis are needed to reduce overall malaria burden, and to secure the progress that Honduras has achieved in the fight against malaria

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A PRELIMINARY ANALYSIS OF HEALTH BEHAVIORS AND ACCESS TO CARE FOR SEVERE MALARIA DISEASE AT SUSSUNDENGA-SEDE HEALTH CENTER

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Severe malaria disease prevention is influenced by access to care, individual health behaviors, and navigation of care at health centers. Severe malaria case management rarely considers the complexity of factors and environments that cause increased morbidity and mortality associated with severe malaria disease. There is limited research about severe malaria case management in Western Mozambique, especially in rural, high transmission settings. Our aim was to quantify access to care and use of malaria prevention behaviors among individuals seeking care at the Sussundenga-Sede health center in Sussundenga, Mozambique, a rural village bordering Zimbabwe in Manica Province. We conducted a time-matched case control study from April 2022-2023. We used systematic sequential sampling to enroll 120 individuals with severe malaria disease and 120 individuals with non-malaria disease who are hospitalized at the Sussundenga-Sede health center. Cases were defined as a hospitalization with malaria tested by blood smear or positive malaria rapid diagnostic test (RDT) and one or more severe malaria symptoms. Controls were defined as a hospitalization without malaria tested by a negative blood smear or negative malaria RDT and not seeking care for conditions related to an accident. Eligible participants were: 1) older than 3 months; 2) full time residents in Manica Province; 3) had the capacity to provide consent; and 4) presented to Sussundenga-Sede health center within 72 hours of enrollment. The study excluded military members, children younger than 3 months, and pregnant women. All consenting participants completed a survey about their neighborhood level access to care, malaria prevention behaviors, and process to seek care at Sussundenga-Sede health center. The survey included a medical records abstraction tool to record severity of disease and treatment. The findings of this preliminary analysis will provide additional insight into community access to care and identify malaria health behaviors that impact seeking care for severe malarial disease.

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HEAVY SCHISTOSOMA MANSONI INFECTION IS ASSOCIATED WITH REDUCED RISK OF PLASMODIUM INFECTION IN SCHOOLCHILDREN IN LEMFU, DEMOCRATIC REPUBLIC OF THE CONGO

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Schistosoma mansoni and Plasmodium spp. coinfection is common in the tropics. Studies on the interactions between these parasites have yielded conflicting results in the sense that S. mansoni infection is associated either with reduced or increased concurrent Plasmodium spp. infection intensity. The lack of data on the interaction between these two diseases in the Democratic Republic of the Congo (DR Congo) motivated the undertaking of the present study. An analytical cross-sectional study was conducted in two elementary schools in Lemfu. The diagnosis of S. mansoni and Plasmodium infections was made by Kato-Katz and Giemsa-stained blood drop smears techniques, respectively. The association between both infections was determined by the Chi-square test of independence. Out of 216 schoolchildren involved in the study, 93 (43.1%) were concurrently infected with both S. mansoni and Plasmodium spp., of whom 52 (56.52%) and 23 (24.7%) had light malaria parasite burden and heavy S. mansoni infection, respectively. Half (13) of those with heavy schistosomiasis had light malaria infection. Forty-two (45.16%), 35 (37.63%), and 16 (17.2%) schoolchildren had S. mansoni-P. falciparum, S. mansoni-P. malariae and S. mansoni-P. falciparum-P. malariae, respectively. Twelve-years old subjects with heavy schistosomiasis had about 6 times less risk of having concurrent malaria infection than those with light S. mansoni infection, especially with P. malariae. S. mansoni-Plasmodium spp. coinfection is common in tropics, including DR Congo where it constitutes a public health problem. Effects of S. mansoni on Plasmodium spp. seems to be dependent on the S. mansoni parasite burden and the age of the human hosts. Further studies are needed to exclude possible influence of the endemicity and transmission levels for both schistosomiasis and malaria.

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ASYMPTOMATIC AND SUBMICROSCOPIC MALARIA INFECTIONS IN SUGAR CANE AND RICE DEVELOPMENT AREAS OF ETHIOPIA

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Water resource development projects such as dams and irrigation schemes have a positive impact on food security and poverty reduction but might result in an increased prevalence of malaria. Therefore, we assessed asymptomatic and sub-microscopic malaria in sugarcane and rice development areas of Ethiopia. We conducted two cross-sectional surveys in dry and wet seasons in irrigated and non-irrigated clusters of Arjo sugarcane and Gambella rice development areas of Ethiopia in 2019. A total of 4464 and 2176 blood samples were collected from Arjo and Gambella. A subset of 2244 microscopy-negative blood samples was analyzed by polymerase chain reaction (PCR). Multivariate logistic regression was used to estimate the association between risk factors and malaria infection. The prevalence of malaria infection by microscopy was 2.0% (88/4464) in Arjo and 6.1% (133/2176) in Gambella. In Gambella, the prevalence was significantly higher in rice-irrigated clusters (10.4% vs 3.6%) than in non-irrigated clusters, but no difference was found in Arjo (2.0% vs 2.0%). Educational level was a risk factor associated with infection in Arjo [adjusted odds ratio (aOR): 3.2; 95% confidence interval (CI) (1.27-8.16)] and in Gambella [aOR: 1.7; 95%CI (1.06-2.82)]. While the duration of stay in the area for < 6 months [aOR: 4.7; 95%CI (1.84-12.15)] and being a migrant worker [aOR: 4.7; 95%CI (3.01-7.17)] were risk factors in Gambella. Season [aOR: 15.9; 95%CI (6.01-42.04)], no ITN utilization [aOR: 22.3; 95%CI (7.74-64.34)] were risk factors in Arjo, while irrigation [aOR: 2.4; 95%CI (1.45-4.07)] and family size [aOR: 2.3; 95%CI (1.30-4.09)] were risk factors in Gambella. Of the 1713 and 531 randomly selected smear-negative samples from Arjo and Gambella analyzed by PCR the presence of Plasmodium infection was 1.2% and 12.8%, respectively. P. falciparum, P. vivax, and P. ovale were identified by PCR in both sites. In conclusion, strengthening malaria surveillance and control in project development areas and proper health education for at-risk groups residing or working in such development corridors is needed.

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ANTENATAL CARE SURVEILLANCE OF PLASMODIUM FALCIPARUM IN MOZAMBIQUE: FROM MALARIA TRENDS TO GENOMICS

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Pregnant women at first antenatal care (ANC) visit may provide accessible routine information of malaria trends in the community. With the purpose of testing the viability of an ANC-based surveillance approach in Mozambique, we are recruiting pregnant women at first ANC visit (from January 2022 to December 2023) at sixty-five health facilities, in eight provinces, with low and medium-to-high intensity of malaria transmission. At this first ANC visit, clinical and demographic information are being collected together with malaria rapid diagnostic test (RDT) results. Finger-prick blood samples onto filter papers are being collected for detection and quantification of Plasmodium falciparum by real-time quantitative PCR (qPCR) and amplicon-based next generation sequencing. From January to December 2022, a total of 3.764 pregnant women were recruited. The preliminary results showed that P. falciparum positivity rate by rapid diagnostic test (PfPRRDT) was 0.8% (10/1253) in the low transmission area (Magude district) and 31.7% (796/2511) in medium-to-high transmission areas (highest in the provinces of Sofala [49.7%], followed by Nampula [44.4%] and Zambézia [42.3%] and lowest in the provinces of Gaza [7.6%], Manica [14.7%], Inhambane [15.4%]; and Niassa [33.3%] p<0.001). We are currently comparing the PfPRRDT in pregnant women with data obtained from 2-10 year-old children at health facilities and assessing the impact of antimalarial interventions in reducing parasite rates at ANC clinics. Those samples that are positive by RDT will be quantified for P. falciparum and analysed using amplicon-based next generation sequencing to identify molecular markers of resistance against artemisinin , sulfadoxine-pyrimethamine, chloroquine, P. falciparum multidrug resistance gene 1 copy number variation (pfmdr1 CNV), amodiaquine, Plasmepsin II-III CNV and markers of genetic diversity. This study will provide epidemiological and genomic information for the validation of an ANC surveillance approach to improve the programmatic performance of malaria control and elimination activities in Mozambique.

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SPATIO-TEMPORAL DISTRIBUTION OF MALARIA CASES IN MUTASA DISTRICT FOLLOWING MALARIA CONTROL INTERVENTION BETWEEN 2017 AND 2023

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Over the last decade, the incidence of confirmed malaria has declined significantly in Mutasa District. Despite a relatively good national case reporting system, detailed maps of malaria distribution have not been publicly available. In this study, monthly surveillance records over the period 2017 - 2023 of malaria burden data by PfHRP2 based rapid diagnostic tests confirmed malaria parasite positive blood specimen, were used to produce maps of malaria distribution across the District. The maps show that Plasmodium falciparum malaria incidence has a marked variation in distribution over the District. The incidence of P. falciparum malaria follows a spatial heterogeneity pattern. In the north of the district, malaria shows one seasonal peak in the period April- May of the year, whereas towards the south, the malaria cases are sporadic. This paper provides maps of

P. falciparum malaria incidence distribution in Mutasa district resolution, which may be useful to health professionals, travelers in their assessment of malaria risk in Mutasa. As incidence of malaria changes over time, regular updates of these maps are necessary.

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SPATIAL DYNAMICS OF MALARIA TRANSMISSION

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Malaria transmission dynamics are complex due to variations in space, time, heterogeneity, stochasticity, and other exogenous forces like the weather. These variations affect mosquito ecology and malaria transmission dynamics through blood feeding. From the Ross-Macdonald model, several individual-based models have been developed and analyzed but with little emphasis on the analysis of spatial dynamics and uncertainty. Modeling and analyzing real systems can become computationally overwhelming with parametric challenges and increasing factors from dimension, interactions, and system processes. This always leads to the development of simple but unrealistic models that give limited room for robustness. This study aims at providing a modular framework as an alternative approach to dealing with complexity that is analytically tractable. It also provides algorithms to understand mosquito ecology, parasite dispersal, mosquito dispersal on a spatial landscape, and human stratification by behavior, travel, age, sex, bed net usage, and care-seeking among others. The framework further provides a platform for quantifying and synthesizing transmission that occurs at a particular time and place by keeping track of the mosquito and human position. As a case study, we provide a three-habitat, two patches, and two human stratified model describing mosquito ecology and malaria dynamics in the modular framework. This is analyzed with steady states and reproductive numbers to prove mathematical consistency and biologically meaningful output. From this study, it is noted that the modular framework makes it easy to develop and extend this existing model to incorporate other factors including exogenous forcing, drug resistance, and vector control among others. It is also easy to modify the functional response and some basic parameters that may affect the outcome while maintaining robustness. We intend to show a model of malaria transmission in Uganda at the district level built using this framework

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EPIDEMIOLOGICAL PROFILE OF PLASMODIAL SPECIES IN SYMPTOMATIC SUBJECTS IN THE CITIES OF BANDUNDU AND KIKWIT, KWILU PROVINCE, DEMOCRATIC REPUBLIC CONGO OF THE

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Malaria is a parasitosis transmitted to humans by the bite of theinfected female Anopheles. In 2020, approximately 220 million cases were reportedby WHO country members. The Democratic Republic of Congo (DRC) is the secondmost affected African country, with 15,272,767 cases reported. Three of theseplasmodial species, Plasmodium falciparum, P. malariae and P. ovale are reported but theirdistribution in the cities of Bandundu and Kikwit is poorly known. This study aims toprovide reliable and updated date on frequency and distribution of the plasmodialspecies in the study cities to improve management of malaria. To determine the frequency and distribution of the plasmodial speciescirculating in the towns of Bandundu and Kikwit. A cross-sectional study was conducted. We collected thick and thinblood smears from patients admitted in the health facilities to determine parasite loadand identify the plasmodial species involved. Measures of central tendency anddispersion of study variables were determined. The association between test positivityand study variables was tested by logistic regression and the non-parametric Kruskall-Wallis test. The parasite prevalence was of 33.1% in both cities. The study revealed 2 plasmodial species circulating in the region; P. falciparum 94.3% of cases and P. malariae 5.7% of cases. We found a statistically significant association betweengender, overnight stay under mosquito nets and malaria positive test of respectivelyOR=0.668, p=0.009 and OR=0.59, p=0.023. In conclusion, the study identified two plasmodial species, P. falciparum and P. malariathat circulate in Bandundu and Kikwit. P. falciparum being the most frequent.

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METHODOLOGY TO ESTIMATE DISTRIBUTION OF MALARIA CASES AMONG CHILDREN IN SUB-SAHARAN AFRICA BY SPECIFIED AGE CATEGORIES

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Children in Sub-Saharan Africa (SSA) remain the most vulnerable to malaria infections and death, thus a better understanding of distribution of malaria within this subpopulation is important for the enrolment of representative populations into clinical trials. To estimate the distribution of Plasmodium falciparum (Pf) malaria among children by specified age categories (0 to <2 years, 2 to < 6 years, 6 to <12 years, ≥12 years) in SSA. We employed data on the number of cases and incidence rates of PF malaria by age group from the Institute of Health Metrics and Evaluation (GBD 2019) for 11 countries located in SSA. Different statistical distributions were fitted to observed data. The best fitting statistical distribution was used to estimate the percentage of individuals within the age bands of interest. We found that the best-fitting distribution of Plasmodium falciparum (Pf) malaria cases by prespecified age categories was derived using a combination of a log-Normal and Weibull distribution. According to this distribution of Pf malaria was 15.4% for ages 0 to <2 years, 30.5% for 2 to < 6 years, 17.6% for 6 to <12 years, and 36.5% for ≥12 years based on data from selected countries in SSA. In conclusion, our results have important implications for the current drive by regulators to ensure the representativeness of real-world populations in clinical trials evaluating the safety and efficacy of medication exposure. The theoretical distributions of Pf malaria reported in this study will help guide researchers in ensuring that children are appropriately represented in clinical trials and other interventions aiming to address the current burden of malaria in SSA.

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PREVALENCE OF ASYMPTOMATIC AND SUBMICROSCOPIC MALARIA INFECTIONS AMONG HIV PATIENTS IN YAOUNDE, CAMEROON

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Malaria remains a major public health problem in Cameroon despite the scale-up of interventions. Asymptomatic carriers are important reservoirs

for transmitting malaria parasites to susceptible human hosts. Malaria and HIV infections are known to interact bi-directionally and synergistically with each other. Hence, this study aimed to determine the prevalence of asymptomatic and submicroscopic malaria infections among HIV patients in Yaounde, Cameroon. A cross-sectional hospital-based study was conducted among HIV patients attending the antiretroviral clinic at the District Hospital Cité Verte, Yaounde, in 2018. Malaria parasite detection was done using microscopy and rapid diagnostic test (RDT). Parasite DNA was extracted from the Whatman 903 filter papers spotted with whole blood. Molecular detection was done by nested PCR (n-PCR) targeting the 18S rRNA. A total of 240 asymptomatic samples were successfully genotyped. The prevalence of asymptomatic malaria infections by microscopy, RDT and n-PCR was 23.8% (57/240), 10.8% (26/240), and 16.3% (39/240), respectively. Submicroscopic malaria infections were identified in 14.5% (26/179) of the study participants. Moreover, the sensitivities, specificities and overall diagnostic accuracies using n-PCR as the standard method were: microscopy (35.90%, 78.61%and 71.67%) and RDT (33.33%, 93.53%and 83.75%). The Cohen's Kappa value for microscopy, rapid diagnostic test, and n-PCR was 0.448 (P<0.0001). The performance of RDT was higher (AUC=0.634, P=0.008) when compared with microscopy (AUC=0.573, P=0.152). Among the Plasmodium species identified, Plasmodium falciparum accounted for 50.0% (17/34) of asymptomatic infections, followed by P. malariae and P. ovale with 26.5% (9/34) and 23.5% (8/34), respectively. This study reported a moderate prevalence of asymptomatic and submicroscopic malaria infections among HIV patients. It was observed that RDTs performed better than microscopy in the identification of asymptomatic malaria infections. There is a need to reinforce training in microscopy due to the high number of false positives registered.

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EXPLORING THE COST EFFECTIVENESS OF PROACTIVE CASE DETECTION IN HARD-TO-REACH, HIGH INCIDENCE COMMUNITIES FROM A COHORT STUDY IN SOUTHEAST MADAGASCAR

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Passive, untargeted malaria control strategies may fail to reach and manage cases in hard-to-reach communities. Investments in proactive approaches targeted at these communities may enable progress towards malaria elimination goals. However, questions remain as to cost-effectiveness and scalability. We studied a cohort of 500 households (2485 individuals) from a high-incidence district (Mananjary) in southeast Madagascar. Households were defined as hard-to-reach if they had low access to treatment at healthcare facilities, community case management, and prevention coverage. Beginning in July 2021, bimonthly testing and treatment were provided to enrolled households via mobile clinic. At baseline, less than 3% of infected individuals received treatment from a healthcare facility or community health worker, and prevalence varied from 15.3% to 60.4% among communities. From the monthly screening data (23,632 total observations to date), we estimate cost-effectiveness in terms of the cost per individual screened, cost per infection treated, and explore potential savings from cases averted. During follow-up, we observed a mean decline in prevalence of 58.6% among enrolled households to date. We leverage this empirical data and mathematical modeling to explore scalability from two perspectives. First, we model susceptibility of proactive case detection approaches to disruptions, such as extreme weather events. Second, we model the extent and sustainability of declines in incidence achievable at varying levels of coverage at the community level. The optimal screening frequency and coverage to maximize cost-effectiveness will be presented. Results demonstrate the need to invest in more proactive case management in hard-to-reach areas to achieve basic control goals and set foundations for elimination efforts.

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GENETIC DIVERSITY AND GENOTYPE MULTIPLICITY OF PLASMODIUM FALCIPARUM INFECTION IN PATIENTS WITH UNCOMPLICATED MALARIA IN CHEWAKA DISTRICT, ETHIOPIA

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Genetic diversity in Plasmodium falciparum poses a major threat to malaria control and elimination interventions. Characterization of the genetic diversity of P. falciparum strains can be used to assess intensity of parasite transmission and identify potential deficiencies in malaria control programmes, which provides vital information to evaluating malaria elimination efforts. In this study, we investigated the P. falciparum genetic diversity and genotype multiplicity of infection in parasite isolates from cases with uncomplicated P. falciparum malaria in Southwest Ethiopia. A total of 80 P. falciparum microscopy and qPCR positive blood samples were collected from study participants aged six months to sixty years, who visited the health facilities during the evaluation of a therapeutic efficacy study of arthemeter-lumefantrine from September-December, 2017. Polymorphic regions of the msp-1 and msp-2 were genotyped by nested polymerase chain reactions (nPCR) followed by gel electrophoresis for fragment analysis. Of 80 qPCR-positive samples analyzed for polymorphisms on msp-1 and msp-2 genes, the efficiency of msp-1 and msp-2 gene amplification reactions with family-specific primers were 95 % and 98.8%, respectively. A total of 29 msp alleles (10 for msp-1and 19 for msp-2) were detected. In msp-1, K1 was the predominant allelic family detected in 47.7% (42/88) of the samples followed by Mad20 and RO33. For msp-2, the frequency of FC27 and IC/3D7 were 77% (57/74) and 76% (56/74), respectively. Eighty percent (80%) of isolates had multiple genotypes and the overall mean multiplicity of infection was 3.2 (95% CI: 2.87- 3.46). The heterozygosity index was 0.43, and 0.85 for msp-1 and msp-2, respectively. There was no significant association between multiplicity of infection and age or parasite density. The study revealed high levels of genetic diversity and mixed-strain infections of P. falciparum populations in Chewaka district, Ethiopia; reflecting both the endemicity level and malaria transmission remained high and more strengthened control efforts are needed in Ethiopia.

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ULTRA-DEEP AMPLICON SEQUENCING OF HIGHLY POLYMORPHIC NOBLE MARKERS OF PLASMODIUM FALCIPARUM SHOWS DECLINING OF MALARIA TRANSMISSION IN ETHIOPIA

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Plasmodium falciparum is the most serious, genetically complex, and fastest-evolving malaria parasite. This study was initiated to explore the population structure, to generate relatedness networks, multiple infections, and heterozygosis of the P. falciparum population in three malaria-endemic sites northern, eastern, and southern Ethiopia. The participants of the study were patients who were recruited for uncomplicated falciparum malaria therapeutic efficacy tests from October 2015 to December 2015 and November 2019 to December 2019. Quantitative real-time polymerase chain reaction (QRT-PCR)-confirmed Dry blood spot samples were analyzed by ultra-deep amplicon sequencing to detect P. falciparum amp-1, csp, cpp, cpmp, and msp7 genes. Population structure was analyzed using STRUCTURE software. Identity-by-state (IBS) was calculated as a measure

of parasite relatedness and used to generate relatedness networks. 183 were successfully sequenced by deep amplicon sequence. Five genes, ama 1, csp, cpp, cpmp and msp7 genes were successfully sequenced and respectively detected in 179(97.8%), 181(98.9%) and 179 (97.8%),178 (97.3%) and 160.(87.4%) of the samples from the three sites. Multiple of infection (MOI) of each marker was 1.2, 1.06, 1.16, 1.14, and 0.99, respectively. The overall MOI was 1.38. The expected heterozygosity index (He) of each marker was 0.25, 0.15, 0.26, 0.24, and 0.36, respectively. No population structure was evident for suggesting high transmission and gene flow among the three sites (P > 0.05). In conclusion, low genetic diversity in the P. falciparum population and the overall declining trend were observed as demonstrated by the lower Multiple of infection and heterozygosis suggesting better progress in malaria control in the regions.

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GENETIC DIVERSITY OF PLASMODIUM FALCIPARUM AND TRANSMISSION PATTERNS IN FOREST-GOING POPULATIONS IN SOUTHERN LAO PDR

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The Lao People's Democratic Republic (PDR) is approaching malaria elimination and the remaining cases are increasingly clustered in forest areas in the southern provinces. To assess parasite transmission patterns in this area, 53 Plasmodium falciparum (Pf) positive cases detected through test and treat campaigns between December 2017 and November 2018 were sequenced, targeting 180 diverse microhaplotypes. Two R packages, Moire and Dcifer, were applied to assess the complexity of infections (COI), within-host parasite relatedness, and inter-sample relatedness. Genomic data were integrated with survey data to investigate the associations between parasite genetic diversity and case characteristics. Parasite genomic analysis showed that 32% of the cases (17/53) were polyclonal infections (COI = 2-3), and 68% (36/53) of cases were infected by a single parasite clone (COI = 1). Most of the polyclonal samples showed evidence of strong within-host relatedness (mean $\hat{r}$ = 0.7), suggesting that cotransmission rather than superinfection was primarily responsible for maintaining polyclonality in this low transmission setting. We identified five genomic clusters with high pairwise relatedness ($\hat{r}$ = 0.7-0.9) in forest fringe villages in Pathoomphone (PT) district; this area had the highest test positivity and forest activity. There were four smaller clusters of 2-3 cases linking Moonlapamok (MP) and PT districts, with a lower degree of genetic relatedness (mean $\hat{r}$ = 0.58) or greater sampling time difference (> two months), suggesting cross-district transmission, possibly on a longer time scale. Among 53 positive cases, 81.1% (43/53) were infected by genetically linked parasites, and they were primarily male adults (median aged 27) detected through a focal test and treat intervention specifically targeting forest-goers. Transmission clusters identified in this study provide useful information for understanding malaria parasite transmission dynamics in this highly mobile forest-going population and targeting of remaining foci, where there is stronger evidence of ongoing local transmission.

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GENETIC DIVERSITY OF PLASMODIUM FALCIPARUM AND GENETIC PROFILE IN CHILDREN WITH ACUTE UNCOMPLICATED MALARIA IN CAMEROON

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Malaria is a major public health problem in Cameroon. Genotyping of malaria parasite population is essential for understanding the mechanism underlying malaria pathology and to determine parasite clones profile in an infection, for proper malaria control strategies. The objective of this study was to perform a molecular characterization of Plasmodium falciparum genetic markers and to determine allelic distribution with their influencing factors valuable to investigate malaria transmission dynamics in Cameroon. Merozoite Surface Protein-1 (MSP-1) and Merozoite Surface Protein-2(MSP-2) revealed greater parasite diversity than Glutamate-Rich Protein (GLURP). Of 350 isolates analysed, a total of 16 different MSP-1 genotypes were identified, including K1, MAD20 and RO33 allelic families. A peculiarity of this study is that RO33 revealed a monomorphic pattern among the Pfmsp-1 allelic type. A total of 27 different Pfmsp-2 genotypes, were recorded of which 15 belonged to the 3D7-type and 12 to the FC27 allelic families. The analysis of the MSP-1 and MSP-2 peptides reveals that the region of the alignment corresponding K1 polymorphism had the highest similarity in the MSP1and MSP2 clade followed by MAD20 with 93% to 100% homology. Therefore, population structure of P. falciparum isolates from Cameroon is identical to that of other areas in Africa, suggesting that vaccine developed with k1 and MAD20 of Pfmsp1 allelic variant could be protective for Africa children. The MOI was significantly higher ($P<0.05$) for Pfmsp-2 loci (3.82), as compared to Pfmsp-1 (2.51) and heterozygotes ranged from 0.55 for Pfmsp-1 to 0.96 for Pfmsp-2. High genetic diversity and allelic frequencies in P. falciparum isolates indicate a persisting high level of transmission. This study advocate for an intensification of the malaria control strategies in Cameroon

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CYP3A4 GENE VARIANTS AMONG RESIDENTS OF LAKE VICTORIA REGION, KENYA, 2013

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Precision medicine approaches in Africa need to be driven by native population data. Cytochrome P450 enzymes, the main drug-metabolizing enzymes in humans, therefore, must be better characterized in the African population. Cytochrome P450 3A4 (CYP3A4) significantly contribute to inter-individual variation in drug metabolism and is involved in the metabolism of about 30% of clinically used drugs, including the antimalarials lumefantrine and halofantrine. We explored CYP3A4 polymorphisms in residents of the Lake Victoria basin where malaria is highly endemic. We used 136 archived DNA samples collected in 2013 during malaria cross-sectional surveys from adults resident in the four islands (Takawiri, Mfangano, Ngodhe, Kibuogi, and Ngodhe) in the Lake Victoria region and a coastal mainland (Ungoye). We used polymerase chain reaction

(PCR) amplification and sequencing to explore the genetic variation in the ~800bp of the 5-upstream region and all thirteen exons, including flanking introgenic regions of the CYP3A4 gene. Human Cytochrome P450 Allele Nomenclature Database and dbSNP were utilized to identify variants. Analysis of molecular variance (AMOVA) within and among the population was carried out using GeneAlex version 6.5 and a p-value of <0.05 was considered statistically significant. We identified 14 single nucleotide polymorphisms (SNPs), including rs4986907 (1.5%) and rs2740574 (81) promoter polymorphism. Most SNPs were introgenic at varying frequencies, lowest in Mfangano (2.0%) and highest in Ungoye (77.8%). Based on AMOVA, a lower proportion of variation among populations (8%) was observed as compared to variation within the population (92%, p<.001). In addition, we mapped an introgenic SNP, rs3735451, involved in hydroxychloroquine metabolism. To our knowledge this is the first study in Kenya to genotype the entire CYP3A4 variation which provides a foundation for future pharmacogenetic studies. Our work contributes to the data needed to improve precision medicine approaches in Africa.

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PLASMODIUM FALCIPARUM WITH PFHRP2 AND PFHRP3 GENE DELETIONS IN ASYMPTOMATIC MALARIA INFECTIONS IN THE LAKE VICTORIA REGION, KENYA

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As an important component in early diagnosis and treatment of malaria, rapid diagnostic tests (RDTs) are easy to use and can provide results in as few as 15 minutes. For diagnosis of Plasmodium falciparum, RDTs targeting the P. falciparum histidine rich protein 2 (PfHRP2) are widely used. Recently, reports of P. falciparum strains lacking PfHRP2 and structurally similar PfHRP3 have led to concern about the usefulness and reliability of PfHRP2-based RDTs. The aim of this study was to detect the presence of P. falciparum with pfhrp2/3 gene deletions in the area around Lake Victoria, Homa Bay County, Kenya. Dried blood spot samples were collected during four cross-sectional malaria surveys of school children between September 2018 and January 2020. RDT negative but PCR positive (n=445) samples were selected for analysis. PCR amplifications of two different single-copy genes (msp1 and msp2) indicated that 125 (28.1%) samples had sufficient P. falciparum DNA for detection of pfhrp2/3 gene deletions. PCR amplifications of the region between exons 1 and 2 of pfhrp2 and pfhrp3 showed that 11.2% (n=14), 7.2% (n=9), and 12.8% (n=16) of the examined samples harbored pfhrp2, pfhrp3, and pfhrp2/3 double deletions, respectively. P. falciparum with pfhrp2/3 double deletions were found in all surveys. While the presence of P. falciparum with pfhrp2 deletions in the study area was identified in 2014, this study reveals for the first time the presence of both parasites with pfhrp3 and parasites with pfhrp2/3 double deletions in Kenya. Although the study was not designed to determine the prevalence of P. falciparum with pfhrp2/3 deletions, the presence and persistence of these parasites highlight the need to monitor and evaluate the performance of PfHRP2-based RDTs currently in use.

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POPULATION AND EVOLUTIONARY GENETICS OF AMA1 GENE IN CAMEROONIAN PLASMODIUM FALCIPARUM ISOLATES

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Antigenic variation associated to genetic diversity in global Plasmodium falciparum apical membrane antigen-1 (PfAMA-1) is a major impediment to broadly effective malaria vaccine design. Here, we report the first study on genetic diversity and natural selection of PfAMA-1 in P. falciparum isolates from Cameroon. A total of 328 P. falciparum PCR-positive samples collected in 2016 and 2019 from five localities of Cameroon were analysed. Ectodomain coding fragment of PfAMA-1 gene was amplified and sequenced. Polymorphic profile and natural selection were analysed using MEGA 11.0 and DnaSP6 software, PAML package and Datamonkey sever. A total of 108 distinct haplotypes were found in 208 P. falciparum isolates with considerable nucleotides (π = 0.0161) and haplotype (Hd = 0.976). diversity Most amino acid substitution detected were scattered in the ectodomain domain I and few specific mutations viz P145L, K148Q, K462I, L463F, N471K, S482L, E537G, K546R and I547F were seen only in Cameroonian PfAMA-1 isolates. Five statistically reliable positively selected codon sites (P145L, S283L, Q308E/K, P330S and I547F) were identified which overlapped with predicted B-cell epitopes and red blood cell (RBC) binding sites suggesting their potential implication in host immune pressure and parasite-RBC binding complex modulation. Evidence of departure from neutrality towards positive diversifying selection was observed (Taj D =2.05824, P < 0.05). The Cameroonian P. falciparum population indicated a moderate level of genetic differentiation compared with global sequences with exception from Vietnam and Venezuela. Our findings provide baseline data on existing PfAMA1-1 gene polymorphisms in Cameroonian field isolates which will be useful information on malaria vaccine design.

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GENETIC DIVERSITY AND MOLECULAR EVOLUTION OF PLASMODIUM VIVAX DUFFY BINDING PROTEIN AND MEROZOITE SURFACE PROTEIN I IN NORTHWESTERN THAILAND

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The local diversity and population structure of malaria parasites vary across different regions of the world, reflecting variations in transmission intensity, host immunity, and vector species. This study aimed to use amplicon sequencing to investigate the genotypic patterns and population structure of P. vivax isolates from a highly endemic province in Thailand during 2015-2021. Amplicon deep sequencing was done on 70 samples for the 42-kDa region of PvMSP1 and domain II of PvDBP. Unique haplotypes were identified and a network constructed to illustrate genetic relatedness in northwestern Thailand. Overall, 16 and 40 unique haplotypes were identified in PvDBPII and PvMSP142kDa, respectively. Nucleotide diversity was higher in PvMSP142kDa than in PvDBPII (π = 0.027 and 0.012) as well as haplotype diversity (Hd = 0.962 and 0.849). Significant positive values of neutrality tests were observed in both PvMSP142kDa (dN-dS = 2.87, p < 0.05) and PvDBPII (Fu and Li's D* and F* = 1.6421 and 1.7078, p < 0.05). A lower recombination rate was found in PvDBPII, while the PvMSP142kDa showed strikingly higher levels of genetic differentiation (Fst) in northwestern Thailand versus other regions (0.2761-0.4881). Based on the two gene markers, the genetic diversity of P. vivax in northwestern Thailand was influenced by host immunity and evolved under the balancing selection. The PvMSP142kDa exhibited higher variation and showed genetically specific signatures in a certain area, while PvDBPII is more likely to be a candidate for strain-transcending vaccines due to its fewer genetic polymorphisms. Findings from this study provide an understanding of P. vivax population structure and the evolutionary force on vaccine candidates. They also established a new baseline for tracking future changes in P. vivax diversity in the most malarious area of Thailand.

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PREDICTING THE GENETIC SIGNATURES OF DRY SEASON AESTIVATION AMONG MALARIA TRANSMITTING MOSQUITOES

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Direct evidence suggests that aestivation, a form of dormancy, contributes to Anopheles coluzzii's dry season (DS) survival and its re-establishment

at the next rainy season (RS), but finding a handful of such mosquitoes precluded any opportunities for quantitative essay or parameter estimation. This work uses an indirect (i.e., genetic) approach as a means to estimate the two seasons' breeding sizes as well as the aestivating sizes, in particular, utilising signals from temporal allele frequency dynamics. We mathematically make derivations that the magnitude of drift is dampened at early RS when previously aestivating individuals reappear. This has a severe impact on temporal effective population size () estimates, that the DS breeding size is overestimated by a factor of , where is the aestivating proportion when two samples are from consecutive RS. In fact, sampling the breeding individuals at three consecutive seasons starting from RS is sufficient to estimate the three sizes. This method does not require sampling aestivating individuals, which is the biggest challenge in most experiments. We apply the method to a published An. coluzzii dataset collected from Thierola, Mali between 2008 and 2010. The estimated breeding sizes are 658 and 61 for the first year, with an aestivating size of 580 (. While information is lacking for the second year, precise estimates are obtained for the DS size (59) and the composite parameter (51%). Further, the DS breeding sizes for both years are significantly larger than 0, suggesting the coexistence of reproducing and aestivating populations in the DS. Extensive simulations are run to verify our derivations.

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TRANSCRIPTOME ANALYSIS REVEAL MOLECULAR TARGETS OF INVASION PHENOTYPE DIVERSITY IN NATURAL PLASMODIUM FALCIPARUM ISOLATES FROM MALARIA ENDEMIC REGIONS OF CAMEROON

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Better understanding of the diversity of molecular interactions and mechanisms underlying RBC invasion phenotypes in natural endemic malaria parasites will facilitate target identification and prioritization for vaccine or drug development against blood stage infection in malaria. Current understanding of invasion ligands is limited to the well characterized erythrocyte binding (EBAs) and reticulocyte homolog (Rhs) gene families. To uncover the wider and complex repertoire of genes associated with invasion phenotype diversity, RBC invasion phenotypes and transcriptome profiles were simultaneously investigated in schizont-stage preparations of Plasmodium falciparum isolates from uncomplicated malaria cases from endemic sites in Cameroon. RBC invasion phenotypes were determined for 63 samples using two-color flow cytometry-based invasion assays against RBCs treated with standard proteases: Neuraminidase (Nm), Trypsin (Tp) and Chymotrypsin (Ch). The transcriptome profiles of a random set of 16 samples were determined by deep RNA sequencing on Illumina NextSeq550. The Cameroonian isolates showed a wide diversity of RBC invasion phenotypes. More than 75% were able to invade Ch treated RBCs but not Nm treated RBCs, representing alternative or sialic acid (SA)-independent pathways of RBC invasion and corroborating previous endemic reports. Genome-wide transcript levels were determined for 5746 genes, of which ~78% were from schizont stages. Two distinct clusters belonging to SA-dependent and SA-independent parasite populations was obtained by data reduction with principal component analysis, mirroring the invasion phenotypes data. Differential analysis of gene expression between the two clusters revealed multiple merozoite-surface, export, and virulent proteins to be up-regulated in the SA-independent parasite isolates, in addition to the EBAs and Rhs. Most of the upregulated genes have been described to have structural and physiological relevance to immune interactions against parasites in endemic settings. These proteins can be further explored as priority targets for next generation vaccine development.

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NANOPORE SEQUENCING FOR REAL-TIME GENOMIC SURVEILLANCE OF PLASMODIUM FALCIPARUM

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Malaria is a global public health priority causing over 600,000 deaths annually, mostly young children living in Sub-Saharan Africa. Molecular surveillance can provide key information for malaria control, such as the prevalence and distribution of antimalarial drug resistance. However, genome sequencing capacity in endemic countries can be limited. Here, we have implemented an end-to-end workflow for Plasmodium falciparum genomic surveillance in Ghana using the Oxford Nanopore Technologies (ONT) handheld MinION device, targeting antimalarial resistance markers and the leading vaccine antigen, circumsporozoite protein (csp), in a multiplex PCR amplicon sequencing approach. Sample collection, sequencing and analysis was undertaken in Accra and the Upper East Region, using the latest ONT chemistry and a commercial gaming laptop computer. An open-access Nextflow informatics pipeline was developed for real-time genetic variant calling, called nano-rave (the nanopore rapid analysis and variant explorer). The workflow was rapid, robust, accurate, affordable and straightforward to implement. We found that P. falciparum parasites in Ghana had become largely susceptible to chloroquine, with persistent sulfadoxine-pyrimethamine (SP) resistance, and no evidence of resistance to the current front-line antimalarial, artemisinin. Multiple single nucleotide polymorphism differences from the vaccine csp sequence were identified at high frequencies, though their clinical significance is uncertain. These results agreed closely with Illumina sequence data from the same regions. We will present further development and expansion of this ONT amplicon sequencing platform, including the addition of a new variant calling software that can detect minor variants in mixed infections, and extension of the method to dried blood spot samples. Overall, this ongoing study demonstrates the potential utility and feasibility of malaria genomic surveillance using nanopore sequencing, and provides methodological and analytical tools for its establishment in endemic settings.

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GYPB DELETION VARIANTS (DEL1 AND DEL2) DISTRIBUTION AMONG GHANAIAN POPULATIONS AND RELATIONSHIP WITH MALARIA SUSCEPTIBILITY

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Glycophorins play an important role in the mediating the invasion of erythrocytes by Plasmodium falciparum, and thus variation in the glycophorin gene locus has implications for malaria susceptibility. In West Africa, the most common variants are deletions of the whole GYPB gene.

The allele frequencies of these GYPB large deletions have been previously estimated to be between 0.05-15% for GYPB DEL1 and DEL2 respectively in populations in Africa but the effect of these deletions on malaria susceptibility is still unknown. To understand this, we genotyped for GYPB DEL1 and DEL2 alleles to facilitate the identification of phenotypes for functional characterization of these variants and malaria disease outcomes. In this study, the distribution and the allele frequency of GYPB DEL1 and DEL2 among Ghanaian populations were determined using a high throughput assay for the identification of these deletions. We genotyped over 2000 samples from different ethnicities in Ghana. Overall, the allele frequency of GYPB deletions was observed to be 0.072% and 0.032% for GYPB DEL1 and DEL2 respectively. The highest allele frequencies for GYPB DEL1 and DEL2 were in the Zambrama (41.67%) and Mo (20.59%). In addition, we observed that GYPB DEL1 or DEL2 allele was associated with absence of malaria parasites and self-reported absence of malaria re-infections. This is the first comprehensive large survey on the distribution of the Glycophorin B deletion variants using a high-throughput assay to genotype different populations. This allows for further experimental work to be done using these ethnic groups with relatively high GYPB DEL1 or DEL2 variants within the Ghanaian population, and for stratification of genetic association studies to understand the role of this region in malarial disease. This study also will pave the way for GYPB DEL1 and DEL2 surveys in other malaria endemic populations in relation to malaria susceptibility.

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INCREASED FREQUENCY OF PFHRP2-DELETED PLASMODIUM FALCIPARUM IN THE PERUVIAN AMAZON IS NOT EXPLAINED BY SELECTION OF THE GENE DELETION

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Since the first report of the pfhrp2 gene deletion (pfhrp2-) in Plasmodium falciparum parasites from the Peruvian Amazon, the deletion has become more frequent. Recently, this deletion has been reported in other countries within and outside of South America, threatening malaria control efforts. In regions where the deletion surpass 5% prevalence, WHO recommends using alternative diagnostic tools to hrp2-based RDTs. The use of RDTs has been suggested as a main factor driving the increase of pfhrp2- parasites in Ethiopia. However, those findings cannot be extrapolated to countries like Peru, where malaria diagnosis is mainly performed by microscopy. In this regard, using PCR, we evaluated if the frequency of the deletion has increased in samples collected between 2013-2017 (n=172). Subsequently, we performed the genomic analysis of P.f with time, for what we added to our genomic data (n=41), available genomes from additional years (n total=100, 2006-2018). Thus, we characterized the population structure and analyzed the genomes looking for signatures of selection. Our findings showed that pfhrp2- parasites increased to >76%. In addition, pfhrp2- and pfhrp2+ parasites are two different clonal populations that would have expanded after a bottleneck around 2010, when PAMAFRO interventions ceased. We could not detect any signature of selection in the genomic region close to the deletion with Tajima's D test neither with LD-based methods. However, parasites with and without pfhrp2 deletions share common regions with signals of be under balancing selection in genes of the var family, which are involved in parasite interaction with immune system of the human host. Furthermore, pfhrp2-deleted parasites presented unique candidate regions to be under selection that include a transcription factor involved in the gametocyte differentiation (AP2-G) and a gene suggested to be associated with artemisinin resistance (FP2A). These findings suggest that the pfhrp2 deletion has not been under selective pressure in Peru, and its increase in frequency could be consequence of this parasite's drug sensitivity profile and/or increased transmission success.

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HYBRID CAPTURE SEQUENCING OF PLASMODIUM MALARIAE FROM TANZANIA

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Plasmodium malariae (Pm) is already prevalent in certain African regions and expected to become more prevalent as P. falciparum (Pf) is eliminated. Like other non-falciparum malaria species, Pm usually causes less clinically severe infections than Pf, but it can cause chronic infections. To better understand this neglected but widespread malaria pathogen, we performed hybrid capture sequencing of 42 Tanzanian Pm isolates collected as part of the Molecular Surveillance of Malaria in Tanzania (MSMT) project in 2021 and Transmission from Submicroscopic Malaria in Tanzania (TranSMIT) project 2018-2021. These isolates span fourteen different regions representing malaria transmission strata ranging from very low (e.g. Kilimanjaro) to very high (e.g. Tabora), with regional Pm positivity rates ranging from 0.2% to 4.5%. Fourteen isolates (33%) are Pm mono-infections, while the others are mixed with Pf. Positive isolates were identified using a semi-quantitative Pm-specific 18S qPCR, with a CT of 35 as the upper limit for sequencing. Library preparation and hybrid capture were performed using a custom Twist Bioscience kit prior to sequencing on an Illumina NovaSeq 6000. This method enables us to generate high coverage sequences spanning the entire Pm genome. Initial experiments in six isolates showed enrichment, with an average of 78% of reads mapping to Pm (range 64% - 88%). Using this method, we are able to generate high-quality Pm sequences even in lower-density isolates and Pm/Pf mixed infections. Using these genome sequences, we will present the first in-depth, country-wide population genomic analysis of this understudied and poorly understood malaria species.

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EXPLORING HOW TRANSMISSION INTENSITY, SAMPLING, AND HUMAN MOBILITY IMPACT OUR ABILITY TO MEASURE GENETIC RELATEDNESS ACROSS PLASMODIUM FALCIPARUM POPULATIONS

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Malaria parasite genomic data are increasingly used to identify highly related infections which can illuminate epidemiological, spatial, or temporal factors associated with patterns of transmission. However, in settings with moderate to high transmission, measuring relatedness between infections is inhibited by complex infections, overall high forces of infection, and diverse parasite populations. It is not clear how these factors impact the ability to measure between-infection relatedness under various conditions including different sampling schemes, patterns of missing data, and levels of human mobility. Further investigation is required to determine which patterns of relatedness we expect to be able to reliably detect with high quality, densely sampled genomic data in a high transmission setting. We evaluated two identity-by-state measures of relatedness and applied them to amplicon

deep sequencing data collected as part of a longitudinal cohort from an area of high transmission in Western Kenya. We observed evidence of temporal structure, but not of fine-scale spatial structure in the cohort data. To explore factors associated with the lack of spatial structure in these data, we constructed a series of simplified simulation scenarios using an agent-based model calibrated to entomological, epidemiological, and genomic data from this cohort study to investigate whether the lack of spatial structure observed in the cohort could be due to inherent power limitations of this analytical method. We further investigated how our hypothesis testing behaves under different sampling schemes, levels and mechanisms of missingness, transmission intensity, and patterns of human mobility. In high transmission settings, we found that identity-by-state measures of relatedness, even using frequently sampled, longitudinal infection data were likely underpowered to detect moderate levels of spatial structure in parasite populations. This has important implications for the use of parasite genomic data in illuminating patterns of transmission in areas of high endemicity.

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AMPLICON DEEP SEQUENCING REVEALS MULTIPLE GENETIC EVENTS LEAD TO TREATMENT FAILURE WITH ATOVAQUONE-PROGUANIL IN PLASMODIUM FALCIPARUM

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Atovaquone-Proguanil (AP) is used as treatment for uncomplicated malaria, and as a chemoprophylactic agent against Plasmodium falciparum. Imported malaria remains one of the top causes of fever in Canadian returning travellers. In this study, twelve sequential whole-blood samples before and after AP treatment failure were isolated from a patient diagnosed with P. falciparum malaria upon their return from Uganda and Sudan after partial compliance with AP as a chemoprophylactic agent. Targeted ultra-deep sequencing was performed on the cytb, dhfr, and dhps markers of treatment resistance before and during the episode of recrudescence. Haplotyping profiles were generated using three different approaches: msp2-3D7 agarose and capillary electrophoresis, and cpmp using amplicon deep sequencing (ADS). A complexity of infection (COI) analysis and haplotyping profiles were included. De-novo cytb Y268C mutants were observed during an episode of recrudescence 17 days and 16 hours after the initial malaria diagnosis and AP treatment, indicating treatment failure. No Y268C mutant reads were observed in any of the samples prior to the recrudescence,, suggesting no preselected mutants within the limits of detection of electrophoresis and ADS haplotyping. SNPs in the dhfr and dhps genes were observed upon initial presentation. The haplotyping profiles suggest multiple clones mutating under AP selection pressure (COI>3) with a soft selective sweep. Significant differences in COI were observed by capillary electrophoresis and ADS compared to the agarose gel results. ADS using cpmp revealed the lowest haplotype variation across the longitudinal analysis compared to the msp2 length-polymorphic marker. Our findings highlight the power of ultra-deep sequencing to provide a higher resolution to reveal the natural selection of a mutation as well as haplotyping profiles to understand P. falciparum infection dynamics. Longitudinal samples should be analyzed in haplotyping studies to increase the precision, sensitivity, and specificity in haplotyping calls. This is the first study to report multiclonal (COI>3) cytb de novo mutation.

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A CANDIDATE GENE ANALYSIS OF SEVERE MALARIA VARIANTS IN A COHORT OF MALIAN CHILDREN IDENTIFIES A NOVEL SUSCEPTIBILITY LOCUS IN CSMD1 GENE

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Plasmodium falciparum malaria is still a leading cause of child mortality in sub-Saharan Africa. Malaria infection can be asymptomatic or symptomatic, with sequelae ranging from no clinical signs to severe disease. Variations in malaria clinical outcomes are partly attributed to host genetic factors with estimated narrow-sense heritability of 23%. Here, we investigated associations of human candidate gene polymorphisms and risk of severe malaria (SM) in a cohort of Malian children. Based on our previous Genome-wide Association (GWAS) analysis, specific candidate genes (N=11) were selected for in-depth analysis. Selection criteria included gene-level GWAS scores, functional overlap with malaria pathogenesis, and evidence of association with protection or susceptibility to other infectious and inflammatory diseases. Twenty-two representative single nucleotide polymorphisms (SNPs) residing within these genes were selected primarily based on p-values in our previous GWAS studies as well as allele frequency in West African populations. The selected SNPs were genotyped using KASP technology in 477 DNA samples (87 children that had experienced SM and 390 that did not). Logistic regression analysis revealed that a common intron variant, rs13340578 in Cub and Sushi Multi Domain (CSMD1) gene, is associated with increased susceptibility to severe malaria in a recessive mode of inheritance (MAF = 0.42, OR=1.8, 95% CI = [1.78, 1.84], P= 0.029). The SNP is in linkage disequilibrium (LD) (r2=0.75) with a regulatory variant, rs59961277, located 888bp up-stream in the complement control (Sushi) domain of CSMD1. This finding suggests that modified regulation of complement may contribute to malaria disease severity. Further studies are needed to identify causal variants in this locus and the underpinning molecular mechanisms mediating SM.

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PROTECTIVE HUMORAL RESPONSE TO PLASMODIUM FALCIPARUM PF27 AND ITS ORTHOLOG P. VIVAX PV27 ANTIGENS IN SERA FROM DANGASSA AND KOILA, TWO MALARIA ENDEMIC AREAS IN MALI

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We identified new Plasmodium falciparum (Pf) and P. vivax (Pv) proteins using Bioinformatic tools. Preliminary results showed that individuals sera from Malian donors reacted well with the couple Pf27/Pv27 antigens (42.7% vs 29.2%) about antigens tested, suggesting existence of crossreactivity between Pf and its ortholog Pv proteins and their potential as malaria vaccine candidates. This study aimed to assess the protective immunity (antibody responses) associated with Pf27/Pv27 proteins in sera from a cohort study in Mali. Samples and data on malaria episodes were collected during cross-sectional survey in December 2021 amongst 209 participants from Dangassa and Koila, two malaria endemic areas located approximately at 82 km south-west and 385 km northeast of Bamako, the capital city of Mali, respectively. Antigenic peptides covering orthologs Pf and Pv protein were tested on sera using ELISA assay. Overall prevalence of antibodies anti-Pf27 vs Pv27 was 55.9% vs 64,7% in Dangassa and 54.2% vs 63.6% in Koila. In Dangassa, Pf27 seroprevalence (87.5% vs 42.4%, p = 0.02) and antibody levels (p = 0.010) were significantly higher in children healthy during malaria transmission season, while they were similar in adults. No significant variation in antibody levels against both proteins was observed in Koila. High level of antibodies against Pf27 in children and its association with protection against clinical malaria in Dangassa may warrant further investigation of Pf27 as a potential malaria vaccine candidate.

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BROADLY REACTIVE ANTIBODIES TARGET SEVERE MALARIAL ANTIGEN TO NEUTRALISE PARASITE SEQUESTRATION

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Severe childhood malaria caused by Plasmodium falciparum is associated with the accumulation of parasite-infected erythrocytes in blood vessels and tissues. Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) family expressed on the surface of infected erythrocyte binds to the endothelial protein C receptor (EPCR), is associated with development of severe symptoms. Naturally acquired antibodies which block this interaction are found in people from malaria endemic regions and are expected to confer protection to severe malaria. Individuals developing protein against severe malaria harbour broadly reactive antibodies against EPCR binding PfEMP1s. In this study, through the characterisation of PfEMP1 specific B cell receptor and serum repertoire, we have isolated antibodies capable of neutralising PfEMP1 - EPCR interaction. The structural and sequence analyses have revealed unique epitopes of these antibodies capable of recognising high sequence diverse PfEMP1s and neutralise EPCR interaction.

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THE CHEMOKINE RECEPTOR CXCR3 PLAYS A CRITICAL ROLE IN T CELL-MEDIATED PROTECTION FROM LIVER-STAGE PLASMODIUM INFECTION

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Plasmodium infection involves an asymptomatic liver stage that occurs in hepatocytes and a symptomatic blood stage that occurs in red blood cells. Immunization with whole sporozoite vaccines including genetically attenuated parasites (GAPs) that arrest in the liver can completely prevent the symptomatic blood stage. However, improving these GAPs requires a better understanding of anti-Plasmodium hepatic immunity. Activated T cells increase surface expression of CXCR3 and CXCR3+ liver-resident memory CD8 T cells (TRMs) are critical mediators of protection against infection following GAP vaccination. Hepatocytes also upregulate the CXCR3-binding chemokines CXCL9 and CXCL10 during liver-stage Plasmodium infection, indicating a role for CXCR3 in T cell-mediated protection. We find that GAP-immunized CXCR3-/- mice exhibit impaired ability to control liver-stage infection at 40 days post-immunization. While flow cytometry analysis shows impaired recruitment of activated CD8 T cells into the livers of CXCR3-/- mice early after GAP immunization, by day 40 GAP-immunized CXCR3-/- and wildtype mice exhibit similar numbers of TRMs. This indicates that while CXCR3 is critical early after immunization, other factors may recruit T cells to the liver at later timepoints. However, given that CXCR3-/- mice have impaired protection from challenge at 40 days post-immunization, CXCR3 must play other roles in TRM reactivation, recruitment, and/or function. Hepatic immunity is unique in that hepatocytes and resident immune cells are asymmetrically positioned across the tissue. Recent studies indicate that parasite development in the liver is not uniformly distributed. Thus, we hypothesize that CXCR3 modulates TRM positioning in the liver such that these cells are optimally placed to respond to future infections. Ongoing spatiotemporal studies will characterize parasite development, chemokine production, and TRM positioning to determine how chemokines impact GAP-induced immunity. These findings about the role of CXCR3 in T cell-mediated protection from liver-stage Plasmodium could assist in the development of improved GAP vaccines.

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IMMUNOLOGICAL PROFILING OF MALARIA PHENOTYPES IN ENDEMIC AREAS OF KENYA: A LONGITUDINAL COHORT STUDY

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Malaria is a life-threatening disease caused by Plasmodium parasites and transmitted via infected Anopheles mosquitoes. In 2021, an estimated 247 million cases and 619,000 deaths were registered worldwide, with Sub-Saharan Africa bearing the major burden. Clinical manifestations of malaria can vary and depend on a dynamic interplay between host, parasite, and environmental factors. Distinct "malaria phenotypes" can be categorized as asymptomatic, uncomplicated, or severe. The course of the infection is shaped by the host immune response. Within the adaptive immune system, Plasmodium-specific T and B cells play a crucial role in determining the progression from asymptomatic to severe malaria and the development of immunological memory. However, the dynamics and interactions between distinct immune populations in response to malaria remain poorly understood. To define the immunoprofile driving individual reactions, a heterogeneous population with a full spectrum of clinical phenotypes needs to be interrogated. To this purpose, we designed a longitudinal cohort study involving 300 individuals aged 5 to 65 years old from a highly malaria-endemic area of western Kenya. Our baseline surveys indicated a prevalence by RDT of 40.7% and the presence of both symptomatic and asymptomatic cases. 46.3% of these showed repeated infection at the following monthly visit. By analyzing field-transmission samples throughout a broad range of age groups, we aim to profile antimalarial immunity and stratify the cohort into distinct infection groups. Moreover, while cross-sectional studies do not allow to distinguish between asymptomatic or pre-symptomatic states, in longitudinal cohorts disease progression is tracked overtime, allowing asymptomatic cases to be defined more clearly and individuals categorized into a gradient of clinical phenotypes. By analyzing peripheral blood mononuclear cells (PBMCs) from the cohort via high-throughput mass cytometry (CyTOF), we will gain insights into distinct immunological signatures of the host antimalarial response, eventually leading to new vaccination and immunotherapeutic strategies.

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OPSONICPHAGOCYTOSIS IGGS TO ICAM1BINDING PLASMODIUM FALCIPARUM ERYTHROCYTE MEMBRANE PROTEIN 1 ARE ASSOCIATED WITH THE CLINICAL PRESENTATION OF MALARIA IN BENINESE CHILDREN

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The pathogenicity of severe malaria (SM) caused by Plasmodium falciparum is supported by the adhesion of P. falciparum-infected erythrocytes (IEs) to the microvasculature of infected individuals. This adhesion is mediated

by PfEMP-1, which binds one of the most common receptors of the human host, intracellular adhesion molecule-1 (ICAM-1). Knowledge on the quantity and quality of IgG to such PfEMP-1 is limited. The acquisition of IgG specific for IEs, selected for expressing ICAM-1 binding PfEMP-1 and the IgG-mediated opsonic-phagocytosis of such IEs are unknown and the objective of this study was to provide such data.Plasma samples collected from Beninese children under the age of five years with either SM or uncomplicated malaria (UM) were used to measure antibody levels to two recombinant PfEMP-1 domains and their corresponding native proteins expressed on the surface of IEs. ELISA was used to measure PfEMP-1-specific antibodies to the domains, flow cytometric based assay was employed for IE surface reactivity and antibody-mediated opsonic phagocytosis to measure the functional properties of antibodies with respect to the selected PfEMP-1 expressing IEs.Levels of PfEMP-1-specific IgG to the domains and their corresponding IEs were similar in the two groups, SM and UM, suggesting similar exposure to P. falciparum parasites expressing those PfEMP-1 variants. Also, no differences in the reactivity to native IT4VAR13 were observed between all plasma at hospitalization and at convalescence. However, in qualitative assessment, the ability of antibodies to promote opsonic phagocytosis of IEs by monocytes (THP-1 cells) was significantly higher in children with UM at hospitalization on PFD1235w expressing parasite. The findings indicate similar P. falciparum malaria exposure in children with either SM or UM and supports the presence of antibody dependent phagocytosis as a measure of antibody effector function and its association with protection against SM in children.

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COMPOSITION OF PRE-TRANSMISSION SEASON STOOL MICROBIOTA IS ASSOCIATED WITH RESISTANCE TO MALARIA IN OLDER MALIAN CHILDREN

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Gut microbiota composition is known to alter the susceptibility of mice to Plasmodium infection; however, the impact of gut microbiota on the severity of malaria in humans is less well defined. We collected stool samples from a cohort of 180 Malian children aged six to ten years at multiple time points before, during, and after a Plasmodium transmission season, analyzed them using 16S rRNA gene sequencing, and examined the relationship between fecal microbiota composition and the prospective susceptibility of the children to symptomatic Plasmodium infection. We found that microbiota composition of the pre-transmission season sample from ten-year-old children was significantly associated with whether the children were resistant or susceptible to the development of malaria during the study period. No relationship was observed in younger children, who overwhelmingly developed febrile symptoms when infected, or in samples taken during or shortly after the transmission season, possibly due to obfuscation by additional season-dependent factors. In order to examine the potential causal role of gut microbiota, germ-free mice were colonized with the fecal samples from either resistant or susceptible children and then infected with Plasmodium. Mice that received fecal samples from resistant children displayed significantly better control of their parasitemia compared to mice that received fecal samples from susceptible children, demonstrating that gut microbiota play a causal role in malaria severity in Malian children. The specific mechanisms and bacteria associated with susceptibility to malaria are currently being investigated.

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EVALUATING THE IMPACT OF NATURAL KILLER CELL PHENOTYPE, MALARIA DIVERSITY AND TRANSMISSION, AND ERYTHROCYTE POLYMORPHISMS ON ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY

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In recent years, the ability of natural killer (NK) cells to mediate antimalarial immunity through antibody-dependent cellular cytotoxicity (ADCC) has become increasingly appreciated. Our group recently reported that an atypical population of NK cells prevalent in malaria-exposed children has enhanced ADCC activity against opsonized infected erythrocytes superior to that of conventional NK cells. However, ADCC was only evaluated in wild-type erythrocytes infected with laboratory-adapted P. falciparum, despite the high prevalence of hemoglobin polymorphisms in endemic areas and antigenic diversity of field isolates. Furthermore, extensive cellular phenotyping to find features associated with enhanced cytotoxicity and malaria exposure have not been conducted. This work aims to characterize the impact of parasite diversity, erythrocyte polymorphism, NK cell phenotypes, and malaria exposure on the ability to mediate ADCC against infected erythrocytes. We have already found that HbAS erythrocytes and plasma from high-transmission areas enhance ADCC in comparison to HbAA erythrocytes and low-transmission plasma. Experiments in progress are characterizing NK cell phenotypic traits associated with ADCC capacity in malaria-exposed Ugandans in comparison to malaria-naive North Americans. Peripheral blood mononuclear cell (PBMC) samples from the PRISM (Program for Resistance, Immunology, Surveillance, and Modelling of Malaria) observational study cohort in Nagongera, Uganda and malaria-naive North Americans are stimulated with infected erythrocytes or pro-inflammatory cytokines analyzed for phenotypic markers and activation using multiparameter flow cytometry. Killing of infected erythrocytes by NK cells is assessed using a colorimetric assay that quantifies released hemoglobin in cell supernatant. These results will help improve the translatability of future research by creating experimental conditions that better reflect malaria-endemic settings.

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BIOCHEMICAL AND BIOINFORMATIC CHARACTERIZATION OF SURFACE EXPRESSED HYPERVARIABLE PROTEIN FAMILIES (RIFIN AND STEVOR) ASSOCIATED WITH PATHOGENESIS AND ACQUIRED IMMUNITY TO PLASMODIUM FALCIPARUM INFECTION

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Malaria, caused by the infectious parasite Plasmodium falciparum (Pf), is a vector borne disease, responsible for approximately 619 thousand deaths and 247 million cases worldwide in 2021, with 94% cases in sub-Saharan Africa. Pathogenesis of malaria infection is dependent on parasite and host factors, and geographic and social factors, causing different clinical outcome and disease severity. Parasite virulence is partly caused by evasion of the human host immune system during the blood stage of infection. Sequestration and cytoadherence are characteristic Pf virulence factors, enabled by parasite-derived proteins expressed on the surface of infected erythrocytes (IEs). These proteins are antigenic and are associated with acquired immunity to Pf. IE surface-expressed antigens are associated with antigenic variability, called Variant Surface Antigens (VSA). VSA are

translocated from blood stage Pf to the IE surface via protein trafficking through Maurer's cleft, a parasite-derived membranous structure, and are expressed on the IE membrane. RIFIN and STEVOR are VSA protein families encoded respectively by 180 rif and 40 stevor gene copies per parasite. Members of each family differ mostly in their hypervariable region, exposed to the circulation and possessing antigenic epitopes. Both variable domains are associated with Pf exposure and potentially clinical outcome. Seroreactivity and recognition to both protein families are age and exposure dependent, with higher reactivity in adults and higher domain recognition in individuals with clinical malaria than in subpatent infections. This study is the first to successfully express isolated domains of RIFIN and STEVOR proteins as recombinants, characterize their antigenicity, expand understanding of the Pf proteome, by investigating novel markers for exposure to Pf and develop a library of variants to explore the breath of antibody responses in participants following mass drug administrations (MDA) in clinical trials (MATAMAL NCT04844905; MASSIV NCT03576313) to explore the impact of the trial interventions on naturally acquired immunity to Pf.

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CRYO-EM REVEALS THE STRUCTURAL BASIS OF EPITOPE SELECTIVITY AND PROTECTION FROM MALARIA INFECTION IN A FAMILY OF POTENT ANTI-PFCSP ANTIBODIES

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The generation of high-quality antibody responses to PfCSP, the primary surface antigen of Plasmodium falciparum sporozoites, is paramount to the development of an effective malaria vaccine. Here we present an in-depth structural and functional analysis of a panel of potent antibodies targeting the PfCSP major repeat region (NPNA) and the highly potent mAb L9, which targets the PfCSP minor repeats (NPNV). Each of these mAbs is encoded by the IGHV3-33 heavy chain germline gene, which belongs to one of the most prevalent and potent antibody families induced in the anti-CSP immune response in humans. Cryo-EM reveals a remarkable spectrum of higher-order Fab-CSP structures stabilized by homotypic interactions, many of which correlate with somatic hypermutation. Notably, the homotypic interface in the L9-CSP complex is distinct from the panel of NPNA-specific mAbs; this is the first observation of homotypic interactions in a PfCSP epitope outside of the NPNA region. In vitro and in vivo data demonstrate the key role of these mutated homotypic contacts for high PfCSP avidity and in protection from P. falciparum malaria infection. Importantly, correlation analyses of mAb binding kinetics with in vivo protective efficacy indicates high PfCSP affinity is insufficient to confer potency, highlighting a potential structural determinant of protection. Overall, these data emphasize the importance of anti-homotypic affinity maturation in the frequent selection of IGHV3-33 antibodies and inform next-generation PfCSP vaccine design.

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ANTIBODY PROFILES AGAINST NON-MALARIA PATHOGENS DISPLAYED IN PLASMODIUM VIVAX-INFECTED INDIVIDUALS FROM THE PERUVIAN AMAZON

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In this study, we screened IgG antibody responses to serological markers (seromarkers) from malaria and other non-malaria pathogens endemic in tropical areas, in Plasmodium vivax (Pv)-infected individuals from the Peruvian Amazon. Between 2018 - 2021, a nested case-control study was conducted in the Peruvian Amazon, for a comparison of immune responses between Asymptomatic (Asym, n=28) and Symptomatic (Sym, n=30) Pv-infected individuals vs control endemic individuals (n=30). Asym individuals had no common malaria symptoms but remained infected with Pv during a 3-week follow-up (qPCR). Control endemic individuals had no history related to malaria during the last three years and no history of comorbidities or chronic infections. Serum samples from all individuals were processed to measure exposure (IgG antibodies responses) against 24 antigens from a validated panel of seromarkers for neglected tropical diseases, using Multiplex Bead Assay (Luminex).Results: Pv-infected individuals showed significantly high IgG antibody responses against PvMSP119 protein and seromarkers for Chikungunya and Filariasis ($p < 0.0001$); Strongyloidiasis, Taeniasis, and Neurocysticercosis ($p \leq 0.01$); and Giardiasis and Trachoma diseases ($p < 0.05$) compared to endemic controls. Interestingly, IgG antibody levels against seromarkers for DENGUE serotype 1, 2, 3, and 4 were lower than endemic controls ($p < 0.0001$). No significant difference was found for IgG responses between Asym and Sym Pv-infected individuals. Furthermore, using a classical cut-off, we were able to determine a higher proportion of Pv-infected individuals exposed to Chikungunya (98% vs 67%), Filariasis (76 vs 37%), Strongyloidiasis (69% vs 30%), Neurocysticercosis (66% vs 23%), and Taeniasis (47% vs 17%) in comparison to endemic controls respectively. In conclusion, his study demonstrates that Pv-infected individuals in the Peruvian Amazon are more exposed to other tropical infectious diseases than endemic control individuals.

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PLACENTAL MALARIA MODULATES NEONATAL DENDRITIC CELLS' PHENOTYPE AND FUNCTION: A CROSS SECTIONAL STUDY IN BENIN

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Malaria in Pregnancy (MiP) is characterized by the accumulation of Plasmodium falciparum (Pf)-infected red blood cells in the placenta and leads to adverse outcomes in infant. They have a shorter delay to first malaria infection and a higher number of malaria and non-malaria infections in infancy. This indicates that not only infant's adaptive but also innate immunity is modulated by maternal infection. Several studies demonstrated that immune responses were modulated at birth depending on the timing of infection during pregnancy (recent-active, chronic-active or past MiP). There are strong in vitro and ex vivo evidences that Pf is also able to modulate Dendritic Cells (DCs). In that sense, our team showed that neonatal DCs are partially activated in case of MiP. The mechanisms responsible for this modulation and the capability of those DCs to induce (or not) a strong T cell response have not been established. In our cross sectional study, we have purified DCs from cord bloods of 50 naturally-exposed individuals and phenotyped the DC subtypes (cDC1, cDC2 and pDC). We confirmed the partial activation of neonatal DCs with a lower expression of CD80 in

cDC2 when the mothers are Pf-infected (2.77 [CI:2.01; 3.13]) compare to not infected (3.25 [CI:2.56;5.55], p=0.05). Then, we have explored the functionality of neonatal DCs by ex vivo stimulation and co-culture with naïve and hyper-immune T cells (from healthy donors). Compare to chronic MiP, DCs from neonates born from mother with active MiP induced a lower T cell proliferation (1.28 [sd:0.65] vs 1.66 [sd:0.54], p=0.02), a lower Th2 frequency (3.78 [sd:8.38] vs 4.27 [sd:2.64], p=0.005) and a higher Treg frequency (11.53 [sd:9.0] vs 3.98 [sd:6.3]). In parallel, we have characterized the T cells from those same neonates. We observed a high level and frequency of CD28 in newborns' CD4+CXCR3+ and CD8+CXCR3+ T cells in case of active MiP, suggesting that neonatal T cells are fully capable of being activated. Overall, our results demonstrate that the modulation of neonatal DCs differs depending on the timing of infection during pregnancy and may impact the efficacy of the crosstalk between the DCs and the T cells.

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THE ROLE OF PFEMP1 IN SICKLE-CELL RESISTANCE TO PLASMODIUM FALCIPARUM MALARIA

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Heterologous carriers (HbAS) of the sickle-cell mutation (HbS) enjoy clinical protection from severe Plasmodium falciparum malaria relative to individuals with either normal hemoglobin (HbAA) or homozygous mutation (HbSS; sickle-cell disease). However, all three genotypes are equally susceptible to infection with these parasites. The reason for the clinical resistance to severe malaria in HbAS is not fully understood. The ability of P. falciparum-infected erythrocytes (IEs) to adhere to host vascular receptors is a central component of the pathogenesis of the disease in general, and of severe malaria in particular. This adhesion is mediated by PfEMP1, parasite-encoded adhesins displayed on the IE surface on characteristic structures called knobs. It is well-documented that knob formation is compromised in HbAS, and it is therefore often assumed that the clinical resistance against severe malaria in HbAS is a consequence of impaired adhesion and increased splenic destruction of IEs. However, little direct evidence is available. An alternative - or additional - possibility is that parasites in HbAS IEs are able to modulate the expression of PfEMP1 variants associated with severe malaria. We studied the expression of PfEMP1 by parasites grown in vitro in HbAA and HbAS erythrocytes under different oxygen tensions. We also assessed the immune response to PfEMP1 variants associated with uncomplicated and severe malaria in Ghanaian children with and without sickle-cell trait. Finally, we determined the proportion of circulating and sequestered IEs in these children. Our results provide direct evidence of impaired cytoadhesion of HbAS IEs in vivo, whereas we did not find convincing in vitro or serological evidence in favor of the hypothesis that resistance to severe malaria in children with sickle-cell trait reflects a qualitative modulation of PfEMP1 expression on HbAS IEs.

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ASSESSMENT OF HOST CLINICAL PARAMETERS AND PARASITE DETERMINANTS RESPONSIBLE FOR DISEASE SEVERITY

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Plasmodium falciparum is known to cause severe malaria but since the last decade, P. vivax is also seen to be causing severe malaria in clinical isolates. There are no reported studies for P.vivax immunopathogenesis in clinical patients. In the present study clinical parameters, cytokine profile (SOD-1, TNF-α, IL-10, IL-6, and IFN-γ), integrin gene, and parasite molecular marker (vir genes, drug resistance genes, and msp3 genes) were analyzed in P.vivax clinical infections. A total of 169 P. vivax samples were collected and categorized into severe vivax malaria (n=106) and non-severe vivax malaria (n=63) according to WHO severity criteria. Samples were diagnosed with microscopy, RMAT, and 18S PCR. We measured host biomarker levels of interferon (IFN-γ), superoxide dismutase (SOD-1), interleukins viz. (IL-6, IL-10), and tumor necrosis factor (TNF-α) in patient plasma samples by ELISA for pro- and anti-inflammatory cytokines in severe malaria. Severity was assessed and correlated with the integrin, drug resistance, Pvmsp3, and vir gene using PCR, RT-PCR and sequencing analysis. In our study, thrombocytopenia and anemia were major symptoms in severe P. vivax patients. The levels of cytokines (IL-10, IL-6, and TNF-α) and the anti-oxidant enzyme SOD-1 were significantly higher in severe vivax patients. Molecular genotyping of Pvmsp3α gene has four major genotypes out of which Type B (1.5kb) was predominant in severe and Type C (2kb) was predominant in non-severe samples. For drug resistance genes severe isolates had more mutation than non-severe isolates. Vir-14 gene indicates a significantly higher expression level in the severe samples and Vir-10 related gene showed a higher level of expression in non-severe vivax samples. In conclusion, higher levels of inflammatory cytokine can serve as baseline data for evaluating severe P. vivax infections which will be helpful in developing an effective diagnostic biomarker for understanding the immunopathology of P. vivax malaria.

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THE DIRECT BINDING OF PLASMODIUM VIVAX AMA1 TO ERYTHROCYTES DEFINES A RON2-INDEPENDENT INVASION PATHWAY

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Plasmodium vivax is a major human malaria species and is the most geographically widespread disease accounting for approximately 2.5 billion people living under threat of infection. Nonetheless, the study of P. vivax has been greatly impeded due to the absence of an in vitro cultivation system, with only two host proteins, Duffy blood group antigen and Transferrin receptor 1, identified as binding partners for P. vivax Duffy Binding Protein (PvDBP) and Reticulocyte Binding Protein 2b (PvRBP2b), respectively. The increase, thus, in Duffy-negative infections and lack of P. vivax-specific vaccine candidates make the discovery of more ligand/receptor combinations an important task. In this study, we used a transgenic parasite in which Plasmodium falciparum parasites were genetically modified to express P. vivax apical membrane antigen 1 (PvAMA1) protein in place of PfAMA1 to study PvAMA1-mediated invasion. In P. falciparum, AMA1 interaction with rhoptry neck protein 2 (RON2) is known to be crucial for invasion, and PfRON2 peptides (PfRON2p) blocked the invasion of PfAMA1 wild-type parasites. However, PfRON2p has no effect on the invasion of transgenic parasites expressing PvAMA1 indicating that PfRON2 had no role in the invasion of PvAMA1 transgenic parasites. Interestingly, PvRON2p blocked the invasion of PvAMA1 transgenic parasites in a dose-dependent manner. We found that recombinant PvAMA1 domains 1 and 2 (rPvAMA1) bound to reticulocytes and normocytes indicating that PvAMA1 directly interacts with erythrocytes during the invasion, and invasion blocking of PvRON2p may result from it interfering with PvAMA1 binding to erythrocytes. It was previously shown that the peptide containing Loop1a of PvAMA1 (PvAMA1 Loop1a) is also bound to reticulocytes. We found that the Loop1a peptide blocked the binding of PvAMA1 to erythrocytes. PvAMA1 Loop1a has no polymorphisms in contrast to other PvAMA1 loops and may be an attractive vaccine target. We thus present the evidence that PvAMA1 binds to erythrocytes in addition to interacting with PvRON2 suggesting that the P. vivax merozoites may exploit complex pathways during the invasion process.

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ELEVATED FERRITIN, SEVERE MALARIA, AND ACUTE KIDNEY INJURY

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Ferritin is a multimeric iron-storage protein expressed by different tissues to either efficiently bind and sequester iron (spleen and liver) or respond to free iron associated oxidative stress (kidney). Ferritin levels are increased in severe malaria but the clinical implication and importance of this pathway in severe malaria pathogenesis is poorly understood. Children <5 years of age with severe malaria (n=594) and community children (n=120) were enrolled at two sites in Uganda and followed for one year. Ferritin was measured at enrolment in all children and one month follow-up in severe malaria survivors. A ferritin threshold of ≥ 5000ng/mL was considered elevated. At enrolment, 22.4% of children with severe malaria had elevated ferritin levels and clinical risk for elevated ferritin included acute kidney injury and signs of hemolysis (severe anemia, jaundice, blackwater fever). Elevated ferritin was associated with increased mortality with 11.3% of children with elevated ferritin dying compared to 6.1% of children with normal ferritin levels (p=0.04). However, ferritin was no longer related to mortality when adjusted for acute kidney injury. At one month follow-up, none of the severe malaria survivors had elevated ferritin but the median ferritin levels remained higher compared to community children (p<0.0001). The presence of elevated ferritin on admission was associated with increased post-discharge mortality OR 3.32 (95% CI 1.89 to 5.81), p<0.0001 independent of acute kidney injury or persistent kidney disease. We further explored the relationship between elevated ferritin and pathways of host response on admission. Elevated ferritin was strongly associated with increases in markers of hemolysis and depleted heme-hemoglobin scavengers (p<0.001 for all) but was not associated with the acute phase response. These findings suggest that ferritin increases in the context of acute kidney injury in response to free iron from hemolysis. Further, ferritin may be a useful biomarker to identify children with severe malaria who have higher risk of post discharge mortality.

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IMPACT OF SEASONAL MALARIA CHEMOPREVENTION ON MALARIA PREVALENCE AND IMMUNITY AMONG CHILDREN IN NORTHERN BENIN

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Malaria is still a major cause of morbidity and mortality despite all efforts to control the disease. The burden of death is still particularly marked in young children in sub-Saharan Africa. A new preventive strategy was recently developed to strengthen the fight against pediatric malaria in areas of seasonal transmission called Seasonal Malaria Chemoprevention (SMC). The Ministry of Health in Benin, as in other countries with this epidemiological facies, initiated the implementation of this strategy in 2019. However, and as often, the countries have not provided the means to assess the impact of this program. This study aims to evaluate the effects of SMC with Sulfadoxine-Pyrimethamine (SP) and Amodiaquine (AQ) on malaria incidence and consequence as well as on the acquisition and maintenance of anti-malarial immunity in treated children. We conducted a cross-sectional study on children aged 6 to 59 months living in two villages in northern Benin, subjected or not to SMC. Sociodemographic and clinical data as well as repeated blood samples were collected from 440 children (before, during and after SMC treatment). Samples were analyzed for malaria infections by RDT, microscopy and PCR. Anti-malaria immunity was assessed to investigate the repertoire of antibody responses to critical antigens using a panel of 28 antigens targeting PfEMP1, GLURP and MSP1 by Luminex assay.Despite the implementation of the SMC, the prevalence of malaria remained similar in treated and untreated villages. During the follow up, malaria prevalence by PCR rather increased during SMC in both villages and decreased, after the SMC in the treated village. No significant impact of SMC was observed on the dynamics and level of antibodies against PfEMP1 and other malaria antigens suggesting that in an area of high seasonal malaria transmission, SMC implementation do not impact acquisition and maintenance of anti-malaria immunity.

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NEUREGULIN 1 DECREASES HEME-INDUCED INFLAMMATION IN INDUCED PLURIPOTENT STEM CELLS-DERIVED ENDOTHELIAL CELLS FROM CHILDREN WITH INTRAVASCULAR HEMOLYSIS

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Hemolysis associated with malaria and sickle cell disease SCD leads to activation of vascular endothelial cells and this modulates migration and adhesion of inflammatory cells. Both diseases result in systemic elevation of free heme leading to oxidative stress and subsequent inflammation and damage to vascular endothelial cells. Previous studies have used cobalt protoporphyrin IX, PPIX to induce heme scavengers to decrease proinflammatory cytokine production in hemolysis associated diseases. However, development of appropriate models to test interventions against heme induced damage to host cells have been limited. Recent studies have revealed that a neuroprotective factor Neuregulin1, NRG1 mediates human brain vascular endothelial cell protection. We differentiated patient derived induced pluripotent stem cells iPSCs into endothelial cells ECs and used them as a model to assess vascular endothelial integrity during exposure to free heme. We hypothesized that NRG1 can modulate heme induced vascular inflammation and endothelial cell dysfunction. Blood and urine samples were used to generate iPSCs from children with SCD and malaria presenting at Korle Bu Teaching Hospital in Accra Ghana. iPSCs derived endothelial cells (iPSC-ECs) expressed CD 31 and CD144 as expected. Biomarkers associated with vascular injury Ang1&Ang2, proinflammatory chemokine and cytokines CXCL10 TNF α IL 1 IL 6 IL 10 and brain derived neurotropic factor BDNF, were assessed in plasma and compared. iPSC-ECs controls were treated with heme, PPIX and NRG1. Patient derived iPSCs from HbSS and HbAS children differentiated to ECs displayed decreased growth and cellular dysfunction under heme treatment. Moreover proinflammatory factors CXCL10 Ang2/Ang1 and BDNF increased in plasma of SCD children infected with Plasmodium falciparum. In addition, PPIX and NRG1 increased survival and proliferation of iPSC-ECs and reduced endothelial dysfunction. In conclusion our patient derived EC could be used as a model for assessing individualized vascular injury and inflammation during SCD or malaria pathogenesis and determined that NRG1 can be used to increase EC survival

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IDENTIFICATION OF BIOMARKERS ASSOCIATED WITH MALARIA IN PREGNANCY AND CLINICAL CORRELATION WITH OUTCOMES

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In most tropical areas, pregnant women are at increased risk of malaria, as a consequence of the massive sequestration of parasitized red blood cells

in the placenta. Malaria in pregnancy (MiP) may alter placental functions leading to anemia, prematurity, and low birth weight. Although there are several tools to diagnose malaria infection during pregnancy, there is currently no test to assess placental dysfunction. Various biomarkers associated with placental dysfunction that are of high specificity should be studied in the context of MiP to evaluate their predictive value. Plasma and dried blood spots from a recent diagnostic clinical trial "LAMPREG" which enrolled 2500 women in Ethiopia will be used for samples and clinical data. To evaluate if there is a differential host response between symptomatic and asymptomatic women, we will measure the plasma level of the following inflammatory markers: CRP, vWF, hepcidin. Also, the gene expression of multiplex cytokines panels will be studied using droplet digital PCR in order to assess the host inflammatory response. Additionally, a metabolomic approach will be implemented to map the host response during MiP. Metabolomics will be performed using targeted and untargeted approaches, across several liquid chromatography mass spectrometry platforms. We will conduct analysis for both small molecules and lipids, to obtain a full metabolite coverage. We will use the manufacturer's built-in databases for putative identification of metabolites at the tandem mass spectrometry level.

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HISTOPATHOLOGICAL CHARACTERISTICS OF DISCRETE BRAIN REGIONS DURING PLASMODIUM FRAGILE EXPERIMENTAL CEREBRAL MALARIA IN A NONHUMAN PRIMATE MODEL

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Cerebral malaria (CM) is a diffuse encephalopathy associated with the detection of Plasmodium spp. in blood. The prognosis of CM is poor, with 15-20% of cases being fatal and resolved cases often resulting in persistent neurological deficits. P. fragile has been previously used to model P. falciparum infection due to its ability to replicate severe malaria in rhesus macaques (RMs). Prior work identified the presence of P. fragile in cerebral vasculature of RMs but did not explore immune involvement or parasite burden within discrete cerebral compartments. We therefore hypothesized that P. fragile infection of RMs would result in CM pathology and differential sequestration of infected red blood cells (iRBCs) in the vasculature of distinct brain regions. An adult male RM (n=1) was intravenously inoculated with $20x10^6$ P. fragile iRBCs. Peripheral parasitemia and anemia were quantified by Giemsa staining of thin blood smears and assessment of plasma hematocrit levels, respectively. Euthanasia and terminal tissue harvest was conducted at 2.5 weeks post infection. Select brain regions were formalin fixed and paraffin embedded and stained with hematoxylin and eosin. Parasite burden in each brain region was determined by a trained veterinary pathologist by selecting 100 blood vessels and quantifying those containing hemozoin (HZ) pigment. At necropsy, peripheral parasitemia was 8.6%, plasma hematocrit was 27.1% indicating anemia, and iRBCs were observed in all brain sites. Petechial hemorrhages were observed grossly in white matter and hemorrhage was observed microscopically in the temporal cortex and the pons. Parasite burden was greatest in the cerebellum (16%), followed by the parietal lobe (11%), frontal lobe (10%), medulla (10%), temporal lobe (9%), basal ganglia (9%), occipital lobe (8%), and pons (6%). HZ was observed in iRBCs within the capillaries and white blood cells (WBCs), indicative of an ongoing immune response. Taken together, these data indicate that P. fragile infection of RMs is a suitable model for examination of CM pathogenesis. Additional studies are underway to identify the role of WBC infiltration in CM pathogenesis.

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COMPARISON OF PLASMODIUM FALCIPARUM GROWTH IN VITRO AND IN VIVO IN HUMANISED MICE

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In vitro culture has been used to study Plasmodium falciparum erythrocytic cycle for years, allowing the characterisation of genes and testing of therapies. However, it is known that P. falciparum undergoes genetic changes under continuous culture and there are limitations in the host-parasite interactions that can be explored in vitro. Humanised mice (HuMice) are immunodeficient mice that can be engrafted with human cells and tissues. They are the only small animal model that can be used to study P. falciparum in situ and may provide a unique opportunity to model human malaria infection. We have successfully established P. falciparum infections in HuMice and have used two distinct approaches to determine parasite changes in vitro and in vivo. Here we compare parasite growth and gene expression in vitro, and in vivo in the presence (HIS-RBC-HuMouse model) or absence (RBC-HuMouse model) of a human immune system. DRAG and NSG humanised mice were engrafted with either 1) human RBCs (hRBCs) alone to maintain infection in vivo (RBC-HuMouse model); or 2) with human immune cells and hRBCs to determine the effect of the human immune system (HIS) on parasite growth in vivo (HIS-RBC-HuMouse model). We established two different HIS-RBC-HuMice models to characterise changes in parasite growth in vivo. First, we used stem cells to reconstitute the human immune system (SC-HIS HuMouse model), allowing the development of functional human immune system cells including B and T cells. Secondly, we established a new approach using PBMCs (PBMC-HIS HuMouse) allowing for the reconstitution of mature immune cells. Using these approaches, we aim to use RNA-Seq to determine the gene expression of P. falciparum in these models and identify genes implicated in parasite growth in vivo. We also aim to evaluate how predictive in vitro assays for the assessment of therapeutics are in these models using monoclonal antibodies. Finally, we discuss the opportunities and limitations of each approach and outline considerations for the selection of models appropriate to research questions.

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GENERATION OF A PLASMODIUM BERGHEI LINE EXPRESSING A HALOTAGGED PARASITOPHOROUS-VACUOLE MEMBRANE PROTEIN TO STUDY TARGETED PROTEIN DEGRADATION DURING LIVER STAGE MALARIA

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As malaria continues to be a global public health concern, the need for the development of novel therapeutics becomes more prominent in the face of antimicrobial resistance and difficult-to-treat infections. During the liver stage of malaria, parasites infect hepatocytes and reside within an intracellular parasitophorous vacuole (PV), which is delineated by a membrane (PVM)

and decorated by essential plasmodial proteins. These proteins sit at the host-parasite interface with their C-terminal domain exposed to the host cytosol. This project aims to provide a proof-of-concept that induced proximity can be utilized to engage host degradation processes against malaria, representing a novel avenue for the development of therapeutics. To start, we engineered a Plasmodium berghei (Pb) line that expresses a C-terminal fusion of the PVM protein UIS4 with the HaloTag (HT), a domain known to bind HaloTag ligands (HTL). The engineered transgenic parasite was genotyped using PCR, completed the malaria life cycle in a mouse infection model, and expressed the UIS4-HT fusion protein during infection of Huh7 human hepatoma cells. Using the UIS4-HT parasite along with a Halo-proteolysis-targeting chimera (HaloPROTAC) designed to bind the host E3 ligase VHL, we then asked if targeted protein degradation (TPD) can be harnessed to degrade malarial PVM proteins and disrupt the development of liver stages. Infection assays and high-content microscopy experiments demonstrated that UIS4-HT liver stages can bind to a HTL functionalized with a fluorophore and a HaloPROTAC. However, even though the HaloPROTAC was confirmed to trigger degradation of HT proteins in HEK cells, it had no detectable impact on the formation of UIS4-HT liver stages. In conclusion, this study generated and characterized a Pb transgenic parasite expressing a HaloTagged version of the PVM protein UIS4 and demonstrated its functionality at binding HTL compounds during infection. This transgenic parasite will enable mechanistic studies on TPD as well as on other induced proximity approaches during the liver stage of malaria.

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PATHWAYS OF MALADAPTIVE REPAIR FOLLOWING SEVERE MALARIA ASSOCIATED ACUTE KIDNEY INJURY

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Malaria is a leading cause of acute kidney injury (AKI) and a risk factor for persistent kidney disease. We leveraged a prospective cohort of children with severe malaria to identify biomarkers on admission and at one-month follow-up associated with persistent and chronic kidney disease (CKD). Between 2014 and 2017, we enrolled 600 children aged 6 months to 4 years admitted to two tertiary hospitals in Uganda. AKI was defined using the Kidney Disease: Improving Global Outcomes (KDIGO), persistent kidney disease was defined at one-month follow-up based on a 1.5-fold increase in creatinine over estimated baseline or an eGFR<90mL/min per 1.73m2 using the Bedside Schwartz equation. CKD was defined in a subset of children at 12 months follow-up. Biomarkers were tested on cryopreserved plasma samples to evaluate pathways of kidney function, tubulointerstitial stress, endothelial and immune activation. The mean age of children was 2.1 years and 43.7% were female. The prevalence of AKI on admission was 45.3% with 9.3% of survivors having persistent kidney disease at one-month follow-up. All biomarkers except for CRP, CXCL10 and IL-18 were associated with severe and persistent AKI (adjusted $p<0.05$). Of those initial biomarkers, 13 predicted persistent kidney disease following AKI (BUN, sVCAM-1, P-Selectin, Angpt-2, sFlt-1, Tenascin C, TIMP-1, Tenascin C, sIL-2R, sTREM-1, sTNR1, NGAL, OPN, TFF3). We measured biomarkers at one-month and six biomarkers were significantly associated with persistent kidney disease at one-month (P-Selectin, MMP-1, sIL-2R, sTREM-1, sTFNR1, NGAL). Biomarkers that predicted mortality over follow-up were MMP1, sTREM-1, sTNFR1 and NGAL. At one-month follow-up biomarkers of endothelial activation and tubulointerstitial inflammation were associated with maladaptive repair leading to CKD at one-year follow-up. In the present study we identified putative pathways of maladaptive repair associated with progression from AKI to CKD in children with severe malaria. Interventions targeting endothelial activation and tubulointerstitial injury represent potential targets to improve long-term kidney health.

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DRIVERS OF LONG-LASTING INSECTICIDE-TREATED NET UTILIZATION AND PARASITAEMIA AMONG UNDER-FIVE CHILDREN IN 13 STATES WITH HIGH MALARIA BURDEN IN NIGERIA

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Although Nigeria has made some progress in malaria control, there are variations in progress across administrative levels (States). This study investigated the factors associated with and utilisation of long-lasting insecticide-treated net (LLIN) and parasitaemia among under-five children in 13 States with high malaria burden. Data from the 2015 Nigeria Malaria Indicator Survey and 2018 Demographic and Health Survey were analysed. The 13 study states were stratified into two based on whether they had increased or reduced parasitaemia between 2015 and 2018. Random-effects logit models were fitted to identify independent predictors of LLIN utilisation and parasitaemia. α set at 0.05. LLIN was used by 53.4% of 2844 children, while parasitaemia prevalence was 26.4% in 2018. Grandchildren (AOR=5.35, CI: 1.09-26.19) were more likely to use LLIN while other relatives (AOR=0.33, CI: 0.11-0.94) were less likely compared to direct children of household-heads. Furthermore, LLIN use was more common in children whose mother opined that only weak children could die from malaria (AOR=1.83, CI: 1.10-3.10); more likely among children whose mothers obtained net from ANC or immunisation clinics (AOR=5.30, CI: 2.32-12.14) and campaigns (AOR=1.77, CI: 1.03-3.04). Children aged 24-59 months compared to 0-11 months (AOR=1.78, CI: 1.28-2.48), those in whom fever was reported (AOR=1.31, CI: 1.06-1.63) and children of women with no formal education (AOR=1.89, CI: 1.32 - 2.70) were more likely of parasitaemia. The likelihood of parasitaemia was higher among children from poor households compared to the rich (AOR=2.06, CI: 1.24-3.42). The odds of parasitaemia were 98% higher among rural children (AOR=1.98, CI: 1.37-2.87). In conclusion, the key drivers of LLIN utilisation and parasitaemia were mainly related to socioeconomic factors. These should be targeted as part of integrated malaria elimination efforts.

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UPTAKE OF FOUR OR MORE DOSES OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA DURING PREGNANCY WITH SULFADOXINE PYRIMETHAMINE (IPTP-SP) IN ZAMBIA: A SECONDARY ANALYSIS OF THE 2018 MALARIA IN PREGNANCY SURVEY DATA

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In Zambia approximately 25% of pregnant women show evidence of placental infection at delivery. The Zambian government is implementing the malaria in pregnancy (MiP) policy including intermittent preventive treatment of malaria during pregnancy with sulfadoxine pyrimethamine (IPTp-SP). However, the latest (2018) malaria indicator surveys (MIS) showed low uptake of four doses of IPTp-SP at 5%. This study determined the prevalence and predictors of the uptake of four or more doses of IPTp-SP in Zambia. We conducted a secondary analysis of the 2018 MIS dataset comprising 4, 044 women (15—49 years). The survey covered all ten provinces of Zambia. Only 1,381 (34%) women who delivered in 2018 or after the new IPTp-SP policy was introduced were included in our final sample. Descriptive statistical analysis was carried out to summarise participant characteristics and IPTp-SP uptake. Univariate

logistic regression was carried out to determine association between the explanatory and outcome variables. Explanatory variables with a p-value less than 0.20 on univariate analysis were included in the multivariable logistic regression model and crude and adjusted odds ratios along with their 95% CIs, p-value <0.05 were computed. Only 7.5% of the participants received IPTp-SP 4+. The province of residence and wealth quintile were significantly associated with uptake of IPTp-SP doses; participants from Luapula (aOR=8.72, 95%CI [1.72—44.26, p=0.009]) and Muchinga (aOR=6.67, 95%CI [1.19—37.47, p=0.031]) provinces were more likely to receive IPTp-SP 4+ compared to those from Lusaka province. Conversely, women in the highest wealth quintile were significantly less likely to receive IPTp-SP 4+ doses compared to those in the lowest quintile (aOR=0.32; 95%CI [0.13—0.79, p=0.014]). In conclusion, these findings confirm low uptake of four or more doses of IPTp-SP in the country. Preventive strategies should target women in urban provinces with low malaria transmission to ensure adherence to the IPTp-SP guidelines. Interventions should include health messages with emphasis on the new policy of four or more doses of IPTp-SP.

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PREVALENCE OF MALARIA CLINICAL PHENOTYPES DURING ROUTINE CONSULTATION IN HOSPITAL DISTRICT HEALTH OF COMMUNE 4, MALI

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Seasonal Malaria Chemoprevention (SMC) significantly has reduced malaria incidence in target population since its implementation in Mali in 2012. However, the recent studies have demonstrated a change in the epidemiology of malaria in the context of SMC, constituting an obstacle to its long-term implementation in Mali.This study aims to determine the prevalence of severe malaria during routine consultation at hospital district of commune 4 from July to December 2022. Sociodemographic and clinical phenotype data on malaria were collected on tablets. SPSS software version 22 was used for data analysis and Chi2 test for comparison of qualitative variables with a significance threshold at 5%. A total of 559 patients aged 0 to 15 years were enrolled. Age group 5 to15 was the most represented (51.7%) and severe malaria according to WHO definition frequency was 40%. Clinical malaria phenotype varied significantly according to age groups (48.9% in under 4 years vs. 39.4% in older children aged 5 to 15 years, p = 0.02). Severe malaria was dominated by convulsion (53.3%), followed by obnubilation 48.4%, severe anemia (41.3%), coma (34.6%), and respiratory distress (21.1%). Our data show a high prevalence of severe malaria and the need to explore association between severe malaria and Plasmodium falciparum genetic diversity in areas under SMC.

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ASSOCIATIONS BETWEEN ANOPHELES VECTOR DENSITY AND MALARIA INCIDENCE IN TWO ADJACENT UGANDAN DISTRICTS WITH AND WITH OUT INDOOR RESIDUAL SPRAYING

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Five years of Indoor Residual Spraying (IRS) with Bendiocarb and Actellic from 2014-2019 reduced malaria incidence among children in the Tororo district of Uganda from 2.96 to 0.040 episodes/person/year. A switch to clothianidin-based IRS formulations in 2020 was associated with a resurgence of malaria to pre-IRS levels. This study explores associations between Anopheles vector density and malaria incidence in two adjacent districts with and without IRS. Data was collected from September 2020 through January 2023 in 661 participants from 61 households in Tororo (IRS) and 23 households in Busia (without IRS). Individuals were followed at a study clinic and malaria was defined as fever and a positive thick blood smear. Mosquitoes were collected via CDC light traps set every two weeks in participant sleeping rooms. The exposure of interest was the mean vector density from the previous month. The outcome was whether an individual had at least one case of malaria per month. Mixed effects Poisson regression with a log-link was used to estimate the relative risk of malaria adjusted for age. In the IRS district, >1 An. funestus mosquito captured per collection was associated with a 41.8% increase in risk of malaria the subsequent month (95% CI: 24.6-61.2%; p<0.001), but was not associated with malaria in the non-IRS district. Interestingly, >1 An. gambiae s.l. mosquito was associated with a 21.9% decrease in malaria risk in the IRS district (95% CI: 10.7-31.8%; p<0.001), compared to 41.6% increased risk in the non-IRS district (95% CI: 11.3-80.1%; p=0.005). Future work will classify An. gambiae s.l. mosquitoes to the sub-species level. These findings suggest that ongoing IRS in Uganda may be leading to selection pressures with heterogeneous responses by vector species. These changes might be contributing to the malaria resurgence observed in IRS districts like Tororo which had previously achieved very low transmission.

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A GEOSTATISTICAL ANALYSIS OF USE OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY AMONG PREGNANT WOMEN IN NIGERIA

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Malaria infection during pregnancy is a major public health problem in Nigeria, with substantial risks for the mother, her foetus, and the neonate. Intermittent preventive treatment of malaria in pregnancy (IPTp) is a full therapeutic course of antimalarial medicine given to pregnant women at routine antenatal care (ANC) visits to prevent malaria and maternal and foetal anaemia. In line with the World Health Organization's recommendation, Nigeria, in 2014, adopted the use of at least three doses of Sulfadoxine-pyrimethamine (SP), the recommended medicine for IPTp in the country, during ANC visits. However, data from the 2018 Nigeria Demographic and Health Survey (NDHS) and the 2021 Malaria Indicator Survey (MIS) indicate that only 17% and 31% of pregnant women respectively took the recommended dose. Relying on data from the 2013, 2018 NDHS and 2021 MIS, we used a model-based geostatistical approach within a Bayesian framework to estimate trends in IPTp-SP usage across the subnational levels of Nigeria and to determine specific locations with recorded improvements in 2018 and 2021 when compared with 2013. We further compared the pattern of usage at the subnational levels, among pregnant women who sought ANC at public and private healthcare provider. Our findings highlights Nigeria States with lagging improvements in IPTp-SP usage and the need for locally tailored interventions that will improve usage of the preventive measure across the country.

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MALARIA PREVALENCE IN CHILDREN WITH A HISTORY OF EXPOSURE TO SEASONAL MALARIA CHEMOPREVENTION & EXIT FROM THE TARGET: RESULTS OF A CROSS-SECTIONAL STUDY IN SOUTHERN SENEGAL

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Seasonal malaria chemoprevention (SMC) was adopted in Senegal in 2013 and implementedin the south of the country in children aged 3-120 months. The evaluation of this strategy ismost often done in its target. This study seeks to determine the prevalence of malaria in childrenwith a history of SMC exposure and out of target.This cross-sectional study was conducted between September and December 2016 in theregions of Kédougou, Kolda, Tambacounda and Sédhiou in southern Senegal. The studypopulation was children who had exited the SMC target. The inclusion criteria were to be aged11-14 years, to have taken SMC at least once and to be apparently healthy with a negative RDTfor malaria. A questionnaire was administered and a blood sample taken for a mixed smear andblotter paper for each participant. A real-time PCR of the 18S gene were performed forPlasmodium falciparum identification.A total of 226 children, with a mean age of 11.8 (+/- 0.8) years and a sex ratio (M/F) of 1.5,were recruited in this study. The proportions of children with a history of taking SMC were33.6% for 2013, 87.6% for 2014, 38.5% for 2015 and 0.9% for 2016. The number of childrenhaving taken at least 3 monthly cycles of SMC was higher in 2013, 2014 and 2015 with 51.3%;83.3% and 82.7% respectively. The prevalence of malaria by PCR 19.46%. The proportions ofpositives were higher in children aged 11 (34.09%) and 12 (47.73%).Children who have been protected by SMC become potential reservoirs again when they leavethe target. Extension of this strategy to all the population is urgently needed.

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ASSOCIATION BETWEEN BEDNET USE AND MALARIA PREVALENCE BY AGE GROUP IN RARIEDA SUB-COUNTY, WESTERN KENYA, 2015-2020

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Malaria remains a leading cause of illness in western Kenya, particularly among school-aged children (5-14yrs). Identifying whether lack of insecticide-treated bednet (ITN) use by this age group is a factor driving high prevalence is important to guide targeted public health interventions. From April 2015-March 2020, year-round household surveys were conducted in Rarieda sub-county to assess malaria prevalence and ITN use. An average of 1,330 households (HH) were randomly selected to be surveyed each year. A questionnaire was administered to each HH member (or caregiver) to collect data on sleeping structure characteristics, ITN ownership and use, and self-reported fever in the past 2 weeks. Participants were tested with a pLDH/HRP2-based malaria rapid diagnostic test (RDT) irrespective of the presence of fever. Prevalence ratios were obtained by modified Poisson regression. Overall, 21,837 questionnaires and malaria tests were administered in 6,419 enrolled HH. ITN access (≥1 ITN/2 people per HH) was 41.2%. Reported ITN use the night before the survey was 81.0%: 87.5% (<5yrs), 74.7% (5-14yrs), 83.1% (15+yrs). Malaria prevalence was 29.7%: 32.0% in <5yrs, 46.1% in 5-14yrs, 18.8% in 15+yrs and 19.0% of cases reported fever in the past 2 weeks (25.1% in <5yrs; 19.8% in 5-14yrs; 15.8% in 15+yrs). Not sleeping under an ITN the night before the survey was associated with higher malaria risk (41.6% vs 27.1%, PR=1.5, 95% CI 1.4 - 1.6, p=0.001). This was significant (p=0.001) in all age groups (<5yrs: PR: 1.6 [95% CI: 1.3 - 1.7]; 5-14yrs: PR: 1.2 [95% CI: 1.1 - 1.3]; 15+yrs: PR: 1.2 [95% CI: 1.1 - 1.3]). Fever in the past 2 weeks was associated with higher RDT positivity versus those without a fever (42.9% vs 27.7%, P=1.6, 95% CI 1.5 - 1.6, p<0.001) in all age groups (<5yrs: PR: 1.7 [95% CI: 1.5 - 1.9]; 5-14yrs: PR: 1.5 [95% CI: 1.4 - 1.6]; 15+yrs: PR: 1.4 [95% CI: 1.3 - 1.6]). ITN access remains well below globally accepted targets in western Kenya. Non-use of ITNs was associated with malaria among all ages. Children 5-14yrs had the highest malaria prevalence and reported the lowest ITN use. Improving ITN access and use could help to reduce malaria prevalence in this age group.

5482

THE PRESS TOUR: AN OUT-OF-THE-BOX APPROACH TO IMPROVE MALARIA MESSAGING IN MADAGASCAR

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Malaria caused 2.4 million cases and >500 deaths in Madagascar in 2021. Behaviors like using bednets and promptly seeking healthcare can reduce morbidity and mortality and the media can be a powerful channel for sensitizing the public, but journalists do not typically receive malaria-related training. We aimed to train journalists to increase the quality and quantity of malaria messaging in Madagascar. In Nov 2021, PMI Madagascar, the US Embassy Public Affairs' Office, and the National Malaria Program held a 5-day workshop for 18 journalists (7 TV, 4 radio, 5 written, 2 online) followed by 5 days of field visits to communities to learn more about malaria-related activities and concerns. In Feb 2023, we evaluated the results of this training by emailing a questionnaire to each journalist to collect the number of and references for products (articles, broadcasts, and posts on malaria) and the estimated reach per product type and outlet 12 months before and 12 months after the training, and perceptions of changes in their malaria-related knowledge and reporting quality. All 18 journalists answered the quantitative questions, while 13 answered the qualitative questions. The median number of malaria-related products per journalist increased from 1 (IQR 0-2) to 3 (IQR 2-5.8), increasing the estimated reach per journalist from a median of 15,500 (IQR 0-306, 300) to 326,185 (IQR 65,000-1,425,000) people. Among 13 journalists who responded, all reported that their approach changed from copying press releases to investigative reporting and individual storytelling. Other self-reported improvements included writing skills (10/13; 77%), knowledge of public health (11/13; 85%), knowledge of malaria (12/13; 92%), understanding of the US government role in malaria control (12/13; 92%), and importance of a community health approach to malaria control (9/13; 69%). This training was a simple way to help sensitize the public through key malaria messaging, by improving the quantity and likely the quality of malaria reporting via mass media. The results spurred the Ministry of Health to plan a similar press training on immunization and family planning in 2023.

5483

AN EXAMINATION OF NATIONAL SURVEYS AND PROGRAM REVIEWS TO DOCUMENT ACHIEVEMENT OF ANTENATAL CARE AND IPTP TARGETS IN NIGERIA

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In 2012, the World Health Organization updated the Intermittent Preventive Treatment of malaria during pregnancy (IPTp) coverage indicator to a minimum of three doses. In 2014, Nigeria set the national target of 100% of women attending ANC to receive IPTp. This study reviewed national survey data for antenatal care (ANC) attendance and IPTp provision from the 2013 and 2018 Demographic Health Surveys (DHS) and the 2015 and 2021 Malaria Indicator Surveys (MIS). Extracted from the national malaria program reviews (MPR) of the National Malaria Strategic Plans (NMSP) of 2014 and 2019 were explanations of program implementation issues. ANC4 attendance and IPTp uptake (1st and 3rd doses) were compared using descriptive statistics. The 2015 MIS did not document ANC 4th visit, so attendance in the remaining surveys was 51%, 57%, and 52% (X2=160.0, df2, p <0.0001). The slow increase of ANC attendance and drop in 2021 meant that opportunity to acquire three IPTp doses was not possible for most women. Over the four surveys, IPT1 increased from 23% to 47% to 64%, then dropped to 58%. IPTp3 rose from 6% to 19% then dropped to 16.6% before increasing to 31% (X2= 1755, df3, p<0.0001). The MPR reports identified four factors inhibiting achievement of the ANC and IPTp targets including insecurity (terrorism, civil unrest), poor integration of malaria in pregnancy into reproductive and maternal health programs, inadequate procurement and stock-outs of SP, and logistical hurdles (lack of vehicles and fuel). By not meeting ANC4 and IPTp1 targets, limits were set for IPTp3 uptake. As other researchers have suggested, NMSPs embody global targets and may not reflect local realities. Local governments, who deliver the bulk of ANC and IPTp services, must be part of the process of setting and planning how to achieve targets.

5484

EFFECT OF BEDNETS USE ON UPTAKE OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY; FURTHER ANALYSIS OF THE 2019 GHANA MALARIA INDICATOR SURVEY DATA

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Malaria in pregnancy constitutes a persistent public health threat in malaria-endemic areas of Africa, with substantial adverse maternal and foetal outcomes, due to low uptake of malaria preventive measures. The combined use of multiple interventions against malaria such as bednets and intermittent preventive treatment of malaria in pregnancy with sulphadoxine-pyrimethamine (IPTp-SP) is greatly recommended by WHO, to achieve maximum impact. However, the use of one intervention may influence the uptake of other interventions. This study explored the effect of bednet use on the uptake of IPTp-SP in Ghana. The data source was the 2019 Ghana Malaria Indicator Survey. Stata version 16.0 was used for data analysis. Weighted frequencies and proportions highlighted participant variables. Bednet use and IPTp-SP uptake were considered the main independent and outcome variables. Survey-adjusted bivariate and multivariate logistic regression analyses were done at 95% confidence interval and 5% level of significance. A total of 2308 women who had children within the last 12 months were involved in the analysis. Participant characteristics were such that 34.4%, 32.5% and 33.1% of respondents were aged 15-24 years, 25-34 years and 35-49 years respectively with a mean age of 29.70 years (SD = 9.65). The national uptake of 1 dose and at least 3 doses of IPTp-SP were 91.7% and 65.0% respectively. While, bednet ownership stood at 80.0%, use of bednets among pregnant women was 52.5%. The combined use of bednet and IPTp-SP was 49.0%. The determinants of uptake of at least 3 doses of IPTp-SP were attending ≥4 ANC visits [aOR = 2.59, 95% CI: 1.67, 4.03; p = 0.006] and exposure to messages on malaria in last 6 months [aOR = 1.34, 95% CI: 1.07,1.67; p = 0.011]. The use of bednets was strongly associated with twice the odds of uptake of IPTp-SP among pregnant women [aOR = 2.02, 95%CI: (1.29, 3.15); p = 0.003]. The combined use of bednets and uptake of IPTp-SP among Ghanaian women is low. Maternal use of bednet positively enhances their uptake of IPTp-SP. Interventions to improve uptake of multiple doses of IPTp-SP should also emphasize the use of bednets to achieve maximum impact.

5485

POSITIVE EFFECTS OF INDOOR RESIDUAL SPRAYING (IRS) IN MALARIA PREVENTION IN NGOMA DISTRICT

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In last years Rwanda has faced different health problems due to some diseases that were leading to the death and suffering, among them, we found Malaria. After the government of Rwanda identified this rising in prevalence of Malaria developed policies to reduce number of death and people affected by Malaria. The method that was used is spray of medication (IRS indoor residual spraying) in all houses that was done in 2019 and 2020. Ngoma district is in the Eastern province of Rwanda between Kirehe and Kayonza districts as well as in other part of the country the spray was done, hence it gave outstanding results in that period. This abstract describes the way malaria spraying medication was effective in prevention of Malaria in Ngoma district. The prevalence of simple malaria, severe malaria and death from malaria before home spraying and after showed there was tremendous reduction. The number shows that in two years before home spraying (2017-2018) simple malaria cases were 4 406 225 cases, severe malaria were 24 946 cases and deaths from malaria were 812 cases while after IRS the number decreases tremendously at the extent simple malaria were 1 350 479 cases, severe malaria were 7 250 cases and number of death were about 255 cases. Percentage of simple malaria cases incidence drop down from 69.35% to 30.65% while the percentage of severe malaria cases reduced from 70.94% to 29.06% and the deaths percentage of malaria cases drop down from 68.60% to 31.40% All these show that IRS should be a continuous measure to be implemented as it gave effective results.

5486

MENTORSHIP-BASED TASK-SHIFTING APPROACH FOR COMMUNITY HEALTH OFFICERS IMPROVES ANTENATAL CARE ATTENDANCE AND INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY SERVICES IN LOWER-LEVEL FACILITIES IN GHANA

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Inadequate numbers of midwives at the sub-district level remain a barrier to providing antenatal care (ANC) services in Ghana. A 2019 Community-based Health Planning Services (CHPS) policy implementation assessment revealed that only 15% of CHPS zones have resident midwives to provide ANC services, leaving out most communities. Community Health Officers (CHOs) who operate CHPS zones are trained mainly to offer essential maternal and child health services. Although CHOs have some knowledge of ANC services, they lack adequate skills to provide ANC, including malaria in pregnancy (MIP) interventions such as intermittent preventive treatment of

malaria during pregnancy (IPTp) in the communities they serve. PMI Impact Malaria collaborated with the National Malaria Elimination Program to build on other CHO capacity-strengthening efforts by introducing a mentorship-based task-shifting training approach to address the challenge. CHOs in CHPS zones without midwives received a practical-based 3-day training to gain skills in history taking, documentation, physical examination, ITN distribution, IPTp services, and case management of MIP. This training was followed by a period of mentorship by midwives from nearby facilities who were paired with the CHOs, to serve as mentors to support the CHOs in developing competence in ANC. The district mentors made facility supervisory visits 4 and 12 months after the training. A total of 185 CHOs were trained on IPTp services and case management of MIP with an overall knowledge gain of 16.5% points (average pre-test score 72.5% and post-test 89%). CHOs mobilized pregnant women through intensified education during the home visit and outreach services. They provided basic ANC to pregnant women with the support of midwives' mentors, increasing ANC attendance from 52,117 to 58,044 in 18 months. IPTp1 coverage increased from 59.9% to 75.2%, and IPTp3 increased from 29.1% to 56.5% within the same period. This pilot demonstrates that through carefully designed mentorship-based task-shifting initiatives, CHOs can be supported to provide ANC and IPTp services at peripheral health facilities.

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PAYMENT SYSTEM FOR COMMUNITY ACTORS DURING THE 2021 AND 2022 INSECTICIDE-TREATED NET (ITN) MASS DISTRIBUTION CAMPAIGNS IN MADAGASCAR

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To prevent malaria in districts at risk, Madagascar conducted mass ITN distribution campaigns in 2021 (all 101 higher-burden districts) and 2022 (10 of 13 elimination districts). More than 91,000 community actors (authenticating agents, community health volunteer mobilizers, storekeepers, and distribution agents) and local supervisors were mobilized to implement the distribution activities. During the previous mass campaigns (2010, 2013 and 2015), community actors' allowances were sent by bank to district level and payment was made through the health facility responsible party. In 2018, the campaign's national coordination committee (NCC) attempted to process payment by mobile money, but it took two years, from November 2018 to December 2020, for community actors to get paid because of long delay in setting up the mobile payment system and far distance between payment place (cash point) and beneficiaries. During the 2021 and 2022 campaigns, to ensure timely payment of community actors, the NCC set up a hybrid payment system: i) proximity payment through civil society organizations, targeting 91,546 community actors in 2021 and 6,020 in 2022; and ii) payment by mobile money directly to 6,232 local supervisors in 2021, and 20 in 2022.As a result of this hybrid payment, 91,510 (99%) of 91,546 community actors (2021) and 5,978 (99%) of 6,020 agents (2022) who were paid via proximity payment and 6,220 (99.8%) of the 6,232 local supervisors (2021) and all 20 supervisors in 2022 who were paid via mobile money received their allowances within one month of completing their work. This payment system substantially shortened the lag between work and payment and allowed direct payment of beneficiaries without intermediaries. Through this successful experience, the National Malaria Program and its partners plan to scale up and standardize this approach for other ITN distribution activities that involve community actors.

5488

IMPACT OF KNOWLEDGE, ATTITUDES, AND PRACTICES REGARDING LONG-LASTING IMPREGNATED NETS ON THE PREVALENCE OF MALARIA INFECTION AMONG CHILDREN UNDER FIVE YEARS OF AGE IN THE DODJI-BATA DISTRICT OF SOUTHERN BENIN

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For good effectiveness of LLINs, several factors must be taken into account, including effective use, integrity, durability, and, in general, knowledge, attitudes, and practices towards LLINs. The purpose of this study was to assess household knowledge, attitudes, and practices regarding LLINs and to determine the impact of these elements on parasite prevalence among children under 5 years of age. Data were collected using an administered questionnaire based on the MIILDA User. Overall "knowledge, attitude, practice" scores are calculated and ranked using Bloom's threshold. Relationships between the independent variables and the prevalence of malaria infection are compared using a chi-2 statistical test.Of 402 children seen in the households, 199 subjects were female and 203 subjects were male .The age range of children from 12 to 59 months was the most represented. In the households surveyed, 97.96% recognized mosquito nets as a means of controlling malaria. Of the children selected, 89.80% owned a net and 89.94% of these children had spent the night before the survey under the net. Nearly 7 out of 10 households used nets throughout the year; however, the number of people occupying a net was more than 2 in 90% of the cases, which makes the nets less effective and negatively influences the malaria infection rate in this community. The malaria infection rate was 11% . Physical inspection of the fabric integrity of the LLINs seen in the households revealed a proportion of 25% with holes, while 40% of the nets seen were from the 2020 campaign and were of the Olyset Plus type. The overall knowledge, attitude, and practice towards LLINs were satisfactory in the study area. However, reinforcement of communication in the community must be done for a change of behavior such as the provision of mosquito nets for children under 5 years of age in the households. Continuation of net distribution strategies must be effective to ensure adequate coverage of households with nets to avoid an exaggerated number of people occupying a net. Ongoing monitoring and evaluation of the use and durability of LLINs should be conducted to limit misuse to reduce malaria infection rates.

5489

DETERMINANTS OF MISSED OPPORTUNITIES FOR PERENNIAL MALARIA CHEMOPREVENTION TAKING CUES FROM INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY, VITAMIN A SUPPLEMENTATION AND VACCINATION DELIVERY AMONG CHILDREN 0-24 MONTHS UNDER PROGRAMMATIC CONDITIONS: A SYSTEMATIC REVIEW

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Despite a World Health Organization recommendation for the use of perennial malaria chemoprevention (PMC) in endemic areas, currently only Sierra Leone implements PMC at scale. A major bottleneck to policy uptake was the limited efficacy of the original 3-dose schedule, exacerbated in real-world settings by poor implementation and coverage. Missed opportunities for PMC uptake during immunization clinics are an important contributor to poor coverage. This review, planned for June 2023, will systematically identify and synthesize evidence on possible determinants of missed opportunities for PMC drawing valuable lessons from literature on the implementation of intermittent preventive treatment in pregnancy (IPTp), vitamin A supplementation (VAS), and childhood vaccination. Searches will include electronic bibliographic databases, grey literature and bibliographies

of retrieved articles. Inclusion criteria will include: quantitative and qualitative or mixed methods research studies; studies assessing determinants of missed opportunities for IPTp, IPTi, VAS or vaccination; conducted in sub-Saharan Africa; reports and peer-reviewed or grey literature. Search concepts will include 'Intermittent preventive treatment', 'Factor', 'Barrier', 'Determinant', Infant', 'Routine immunization clinic', 'Malaria', 'Coverage', 'Vitamin A supplementation', 'Missed opportunity', 'Policy uptake' etc. Lists of titles and abstracts of articles retrieved will be exported to Endnote library and duplicates removed, and eligible full articles will be retrieved. Quality assessment of the studies will be done using relevant checklists to deal with the risk of bias. A descriptive analysis of the selected studies will be done with a narrative synthesis to bring the findings together. Data extraction will be aided by a tool and verified by a second reviewer. Pre-existing themes used by the authors will be identified and stratified based on user or provider perspectives. This review will contribute to the development of a conceptual framework for addressing missed opportunities for PMC to facilitate uptake and scale up.

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LOST TO FOLLOW-UP AND LOW INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCYAT ANTENATAL CARE SETTINGS IN LIBERIA

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In 2018, Liberia implemented WHO-recommended intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine. The 2020 Liberia Demographic and Health Survey found that 87% of women with a pregnancy in the last four years attended at least four antenatal care (ANC) visits during their most recent pregnancy; 40% of them reported taking at least three IPTp doses (IPTp3). To assess the gap between high ANC attendance and low IPTp3 uptake, we conducted a retrospective review of ANC records of women 15-49 years old who initiated ANC between November 2020 and January 2021 at 33 randomly selected ANC sites in Bong, Nimba, and River Gee Counties. All selected ANC sites were public health facilities (clinic, health center, hospital). A woman who had ANC1 at a given site and never returned to that site was defined as lost to follow up (LTFU). We conducted multivariable logistic regression to investigate factors associated with LTFU. Among 1724 women registered for ANC1, 50% returned to the same site for ANC2, 32% for ANC3, and 19% for ANC4. Overall, IPTp3 uptake was 30% and 9% (141/1644) of women tested at ANC1 were diagnosed with malaria. Among the 878 women who returned for ANC2 services at the same site, 38% completed ANC4; of those 59% received IPTp3. LTFU ranged from 25% in River Gee to 47% in Nimba and 70% in Bong. Women with malaria were more likely to be LTFU (aOR= 1.9; 95% CI:1.3-2.9). Maternal age (aOR=1.0; 95% CI:0.98-1.3), parity (aOR=1.0; 95%, CI:0.9-1.1), ANC site (clinic aOR=1.0 [95% CI:0.8-1.4], and health center vs hospital (aOR=0.9 [95% CI:0.6-1.2]) were not associated with LTFU after ANC1. Compared to those attending ANC at hospitals, women attending ANC at clinics were more likely to receive IPTp3 (aOR= 3.4; 95% CI: 1.8-6.6). Retention in ANC was low, which impedes optimal delivery of IPTp. To improve ANC retention, it is important to better understand and address the factors that prevent women who initiate ANC from attending all recommended visits. It is also critical to understand factors contributing to missed opportunities at ANC to provide IPTp, particularly in hospital settings.

5491

THE ROLE OF COMMUNITY LEADERS IN SEASONAL MALARIA CHEMOPREVENTION: BUILDING STRATEGIES TO COMMUNITY ENGAGEMENT IN NORTHERN MOZAMBIQUE

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Seasonal malaria chemoprevention (SMC) is a highly efficacious and effective intervention to prevent malaria infections in areas where the malaria burden is high, and transmission is seasonal. SMC is implemented in northern Mozambique since 2020, administering monthly courses of sulfadoxine plus pyrimethamine and amodiaquine (SPAQ) to children aged 3–59 months. Sensitization and mobilization are carried out before the distribution by community leaders, members recognized as authorities by the community, using a door-to-door approach. A qualitive study was conducted in 2021 in Nampula to assess acceptability of SMC. The presented work describes the contribution of community leaders to the implementation of the SMC campaign. Twenty key informant interviews were conducted with key stakeholders at community, provincial, national and district level and twenty focus group discussions (FGD) were carried out with caregivers of children who received SPAQ, community distributors (CD) and CDs supervisors. Thematic analysis was performed using Maxqda10 software, and themes were identified and categorized following prevalent topics. Community distributors reported that, 'community leaders went to the community to inform' caregivers about SMC medicines, thus 'they [caregivers] accepted to receive the medicine'. District officials perceived that 'the population joined in because of the community leadership' guiding and informing the community. Caregivers talked about the role of community leaders who 'recommended us to participate once the campaign started' and explained the benefits of SMC for children. Participants at community and district level reported that, community mobilization led by community leaders and their direct involvement in the SMC campaign helped deliver accurate information to communities and contributed to their acceptance of the intervention. Community leaders should be recognized authorities that can help further promote dissemination of information on, and acceptance of SMC.

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COVERAGE AND FACTORS ASSOCIATED WITH UTILIZATION OF PYRETHROID-PIPERONYL BUTOXIDE TREATED NETS IN MALARIA ENDEMIC REGION, WESTERN KENYA

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Increased resistance to pyrethroid based Long-Lasting Insecticidal Nets (LLINs) informed WHO recommendation to deploy Piperonyl Butoxide (PBO) based LLINs. Kenya adopted use of PBO nets in endemic areas, though coverage is not known. We determined coverage and factors associated with utilization of PBO nets in a malaria endemic county, Western Kenya. We conducted cross-sectional study with multi-stage sampling in Matayos Sub-County, Busia County. Data were collected using questionnaire from June-July 2022. Data was analyzed by Stata version 16. Universal coverage was defined as ownership of one PBO net for two household members. Proper utilization was defined as sleeping under a mosquito net the previous night, net usage on all days of the week, hanging the net adequately. Data was collected on net ownership, access, utilization. Proper utilization of nets was the dependent variable. We calculated measures of central tendency and dispersion for continuous variables and proportions for categorical variables. Chi-square was used to test for association between dependent and independent variables.

Variables with a p-value< 0.05 were considered statistically significant. A total of 402 participants were interviewed; mean age was 41.2 years (±16.7 years), 268 (66.7%) resided in rural areas, 313 (77.9%) were female, 287 (71.4%) were married, 181 (45%) had formal education and 348 (86.6%) had informal occupations. Among all respondents, 347 (86.3%) had nets, 92.8% (322/347) were PBO and 261 (64.9%) households attained universal coverage. The odds of a household utilizing a PBO net if the household head had informal occupation was 71% less than households whose head had formal occupations (aOR=0.29, 95% CI=0.11-0.78). The odds of households that had not attained universal coverage utilizing a PBO net was 99.9% less than households that had attained universal coverage (aOR=0.01, 95% CI=0.01-0.03). Universal coverage of PBO nets was below the national target. Informal occupation and universal coverage were found to be associated with the utilization. We recommend continuous distribution of nets through additional innovative channels.

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PSYCHOSOCIAL FACTORS INFLUENCING INSECTICIDE-TREATED NET USE AND CARE IN LIBERIA

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In Liberia, which has year-round malaria transmission, ownership and use of insecticide-treated nets (ITN) is a key strategy for malaria control. To assess the association of psychosocial determinants with consistent ITN use (i.e., daily) and net care (i.e., tying up nets when not in use), Breakthrough ACTION and the National Malaria Control Program conducted a Malaria Behavior Survey in 2021. Standard questionnaires were administered to 5822 individuals (4677 women and 1145 of their male partners) from 3719 households. Psychosocial factors, including attitudes towards nets, confidence in one's ability to use a net every night, and perceptions of others' use of nets (norms), were assessed based on agreement with a series of statements. Responses were scored (1 for agreement, 0 for uncertainty, and -1 for disagreement) and summed into factor-specific scales. Scale scores greater than 0 defined presence of relevant psychosocial factors. In 2454 households with at least one net (66%), 4192 (72%) and 4308 (74%) respondents reported consistent use and tying up nets when not in use, respectively. In multivariate regression, factors associated with consistent net use included favorable attitudes towards ITN use (OR: 2.1, 95% CI: 1.6-2.7), confidence in one's ability to use a net every night (OR: 7.4, 95% CI: 5.8-9.5), and perceived community use (OR: 1.4, 95% CI: 1.1-1.6). Factors associated with net care included knowledge that nets can prevent malaria (OR: 1.3, 95% CI: 1.1-1.6) and favorable attitudes towards both net use (OR: 2.1, 95% CI: 1.7-2.8) and net care (OR: 2.3, 95% CI: 1.2-4.3). Net sufficiency (1 net per 2 household members) was not correlated with consistent net use; however, each additional net reported in a household was associated with increased net care (OR: 1.1, 95% CI: 1.0-2.3). These results suggest that interventions to promote favorable attitudes towards nets, strengthen confidence in one's ability to use nets consistently, and strengthen community norms may increase consistent net use. Net care may sustain household supplies of nets; interventions should seek to increase positive attitudes towards nets to boost net care.

5494

PREVENTION OF MALARIA IN PREGNANT WOMEN AND ITS EFFECTS ON MATERNAL AND CHILD HEALTH, THE CASE OF CENTRE HOSPITALIER DE KINGASANI II IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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During pregnancy, malaria causes life-threatening outcomes to the mother and the newborn. The strategies to control malaria during the pregnancy rely on management malaria cases and anemia, and preventive measures such as intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP) and the use of insecticide-impregnated mosquito nets (ITN). Therefore, this study aimed to provide updated data of the benefit of ITN and IPTp-SP on the birth weight of the newborn and the hemoglobin level of the mother. This cross-sectional analytical study was conducted among 467 women in labor in the Maternity of Centre Hospitalier de Kingasani II, in Democratic Republic of the Congo. Data collection was conducted using a structured questionnaire that was pre-tested in a face-to-face interview. The chi-square test was used to compare the proportions. Multivariate analysis (logistic regression) was also used to identify variables significantly associated to IPTp-SP compliance, ITN use, low birth weight and to maternal anemia, with the 95% of the confidence interval. The ITN ownership rate was 81% (95%CI: 77-84) and the ITN use rate was 66% (95% CI: 62-70). Sixty-five percent (95% CI: 60-69) reported having received at least three doses of IPTp-SP. Mothers who used ITN had a higher hemoglobin level compared to those who did not (9.4mg/dl IIQ: 8.7-9.9 versus 11mg/dl IIQ: 9.8-12.2, p=0,026). The non-use of the ITN was associated with low birth weight (aOR=3: 2.1-6.2; p< 0.001) and anemia in pregnant women (cOR =2.41: 1.16-5.01; p=0.01). The use of the ITN and taking at least 3 doses of IPTp are associated with good birth weight. The number of doses of IPTp received during antenatal care is associated with the maternal hemoglobin level in the third trimester of pregnancy. Additional strategies to improve IPTp-SP coverage and compliance may reduce maternal anemia associated with malaria during pregnancy.

5495

INCREASED MALARIA INCIDENCE FOLLOWING IRRIGATION PRACTICES IN THE ENDORHEIC RIFT VALLEY BASIN OF SOUTH ETHIOPIA

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Water resource development practice such as irrigation is key to ensuring economic growth and food security in developing countries. However, vector-borne diseases like malaria spread linked to such development have been a concern. The study was done to determine the impact of irrigation on malaria incidence and vector mosquito abundance in southern Ethiopia. Eight years of malaria morbidity data were extracted from the medical registers of health facilities, and mosquitoes were surveyed in both irrigated and non-irrigated settings. Malaria incidence, case distribution across age and sex, seasonality, parasite proportion, and mosquito density were analyzed and compared between irrigated and non-irrigated settings. The result showed that annual mean malaria incidence was 6.3 higher in the irrigated (95% CI: 0.7 – 33.6) than in the non-irrigated settings (95% CI: 1.2 – 20.6). Although a remarkable decline in malaria incidence was observed for three successive years (2013 - 2017), a significant resurgence between 2018 and 2020 was noted following the introduction of irrigation schemes. The densities of adult Anopheles mosquitoes were 15-fold higher in the irrigated settings compared to non-irrigated. Higher malaria incidence coupled with enhanced adult Anopheles density in the irrigated villages has important implications for designing tailored control interventions in such development settings

5496

UNBOUND PIPERAQUINE EXPOSURE IN CHILDREN AND PREGNANT WOMEN RECEIVING DIHYDROARTEMISININ-PIPERAQUINE AS MALARIA CHEMOPREVENTION

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Dihydroartemisinin-piperaquine (DHA-PQ) is highly effective for malaria chemoprevention, but standard dosing is based on pharmacokinetic (PK) data from non-pregnant adults, which may not be optimal for children and pregnant women. We previously reported that PK exposure of PQ is reduced significantly in the context of childhood development, pregnancy, and efavirenz (EFV)-based antiretroviral therapy. However, as PQ is >99% protein-bound, it is important to assess potential alterations in protein binding during childhood development and pregnancy which may lead to changes in the pharmacologically active unbound drug fraction (fu) relative to total PQ. We therefore investigated the fu of PQ in children, pregnant women, and those receiving EFV to inform PK interpretation of changes in total drug exposure. Plasma samples from 0 to 24 hr after the third chemoprevention dose of DHA-PQ were collected in children at 32 and 104 wks of age, pregnant women at 28 wks gestation receiving or not receiving EFV-based antiretroviral therapy, and women 34-54 wks post-partum not receiving EFV (control adults). Unbound PQ was quantified via ultrafiltration and liquid chromatography-tandem mass spectrometry, with fu calculated as PQunbound/PQtotal. The geometric mean fu was 27% ($p<0.0001$), 38% ($p<0.0001$), and 23% ($p<0.0001$) greater in children at 32 and 104 weeks of age, and pregnant women receiving EFV, respectively, compared to that in control adults. The fu did not differ between pregnant and control adults ($p=0.66$). Altered PQ fu is potentially due to developmental changes in children impacting protein concentrations and binding capacity and PQ displacement from plasma proteins by EFV. These results indicate that an increase in PQ fu modestly compensates for the significant decrease in total PQ exposure we previously reported. This appreciation should be considered if optimizing dosing guidelines based on total PQ PK results. Further study during the terminal elimination phase (e.g. on day 28 post-dose) would help better characterize unbound PQ exposure and thus the overall efficacy of PQ for malaria chemoprevention in these special populations.

5497

RECEIPT OF SEASONAL MALARIA CHEMOPREVENTION BY AGE-INELIGIBLE CHILDREN AND ASSOCIATED FACTORS IN NINE IMPLEMENTATION STATES IN NIGERIA

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Seasonal malaria chemoprevention (SMC) has rapidly been scaled up in Nigeria, reaching nearly 27 million children in 2022. As part of implementation quality standards, SMC community distributors are expected to ensure that only age-eligible children (aged 3 - 59 months) receive SMC medicines during the monthly distribution cycles. However, difficulties in determining children's age and caregivers' desire for older children to receive protection from malaria, among other factors, may lead to older children receiving SMC medicines. We extracted data from a 2022 end-of-round SMC household representative surveys and analyzed data of 3,299 caregiver-child pairs sampled from nine SMC-implementing states in Nigeria. Mixed-effects multivariable logistic regression models were fitted to explore the association between receipt of SMC by age-ineligible children and covariates. The mean age (±SD) of the children was 6.4 (1.4) years, 30.3% (95% CI: 27.8 - 32.9) of whom received at least one dose of SMC medicines in 2022. The majority (60.6%) of the over-age children who received SMC medicines were aged 5-6 years, while 19.5% were 7-year-olds and the rest (19.9%) were aged 8-10 years. We observed higher odds of an age-ineligible child receiving SMC among caregivers who had poor knowledge of SMC age of eligibility (OR: 1.8, 95% CI: 1.2 - 2.6, $p=0.002$), compared with those who had good knowledge of the age of eligibility. Notably, higher odds of receipt of SMC were also found among age-ineligible children whose caregivers had high confidence in SMC (OR: 2.3, 95% CI: 1.3 - 4.2, $p=0.007$), compared with those whose caregivers had low confidence in SMC. It was also found that age-ineligible children whose caregivers were older had lower odds of receiving SMC than those whose caregivers were younger. The study shows that a substantial proportion of age-ineligible children received SMC, with important implications for SMC implementation fidelity, effective coverage, impact and cost-effectiveness. The findings underscore the need for prioritizing programmatic quality improvement strategies to minimize the administration of SMC to ineligible children.

5498

ASSESSMENT OF HEALTH SYSTEM'S FUNCTIONALITY AND READINESS FOR PERENNIAL MALARIA CHEMOPREVENTION IMPLEMENTATION IN OSUN STATE, NIGERIA

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Malaria is a major cause of childhood mortality in many parts of the world. Prevention, diagnosis, and treatment are essential to reduce its impact. Most Nigerians are susceptible to malaria, which continues to be a public health issue despite advancements over the past two decades. PMC with sulfadoxine pyrimethamine (SP) is recommended by World Health Organization for the prevention of malaria in children <24 months to reduce the disease burden and death due to malaria. The implementation of PMC is critical for reducing malaria burden, improving health and promoting sustainable development. We assessed the health system's functionality and readiness for the deployment of PMC in Osun state, Nigeria looking at malaria cases data, uptake of childhood immunization, availability and training of health care workers on service delivery, data capturing and reporting. A cross-sectional random sample of 105 health facilities (public and private) was selected to extract data from the National Health Management Information System (NHMIS) registers on parameters of functionality and readiness between 2021-2022. We established a trend for malaria cases in the first year of life, which increased as the age of the children increased and peaked at 12 months. Approximately 96.8% of PHCs diagnosed malaria using rapid test kits, while about 16.0% confirmed malaria diagnosis using microscopy and 9.6% use clinical diagnosis. A decreasing pattern in the number of children who were vaccinated from birth up to 15 months was observed. The majority of health facilities reported having at least one health worker who has been trained on: immunization (96.1%), vaccine management/handling and cold chain (94.8%), data reporting (93.5%), disease surveillance and reporting (84.4%) and monitoring of service delivery (83.1%) in the past 2 years. The findings showed the distribution of uncomplicated malaria cases, which could help to determine where to place touchpoints for SP administration during PMC implementation. A sustainable strategy is required to prevent drop-outs in children who initiate childhood vaccination.

5499

INSECTICIDE TREATED NETS (ITNS) USE AND MALARIA PREVALENCE AMONG CHILDREN UNDER FIVE IN NIGERIA

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Malaria poses a greater risk to children under the age of five years due to its high morbidity and mortality. Nigeria contributes 27 percent to the malaria burden and 32 percent to the malaria deaths. Insecticide - Treated Nets (ITNs) use has been proven to be an effective preventive intervention for the control of malaria. We examined the relationship between the utilization of ITNs and the prevalence of malaria in children under five in Nigeria. Data were drawn from the most recent (2021) Demographic and Health Surveys (DHS). Logistic regression was used to analyze and establish the relationship between ITN use and malaria positivity (from blood smear result), controlling for wealth index, urban/rural residence, child's age in months, sex of the child, ITN use, geographic region, sex of head of household, age and education level of the mother. The study included 10,717 children under five with a blood smear test result- 27% urban and 73% rural. Only 38% of children under five used an ITN while 40% tested positive for malaria. Of note, the child under five sleeping under a net was not associated with malaria positivity (AOR: 1.06; 95% CI: 0.91-1.22). Factors associated with malaria positivity included increasing wealth quintile (AOR ranging from 0.18 to 0.59), geographic regions (AOR ranging from 1.47 to 1.63, 95% CI), child age in months (AOR: 1.02; 95% CI: 1.02-1.03), child's sex (AOR: 0.87; 95% CI: 0.78-0.96). Study findings suggest that malaria positivity may be influenced by multifaceted factors from the individual to the community/regional level. Community-level ITN use may be a better correlate of malaria prevalence than individual net use in Nigeria. Observed socioeconomic differences including wealth quintile, region, and maternal education level suggest that there may be underlying inequities among children under five that need to be addressed with targeted interventions in order to ensure malaria prevention in a heterogeneous setting like Nigeria.

5500

ENTOMOLOGICAL INDICES PREDICT PARASITOLOGICAL MALARIA TRANSMISSION INDICES ACROSS VILLAGES IN WESTERN KENYA

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Understanding the underlying relationship between malaria entomological and epidemiological indices could be useful in utilizing one as a predictor of the other to inform the transmission spectrum. This is important for evaluation of new interventions and policy. In this study we evaluated how well entomological indices of Anopheles densities, human biting rate (HBR), entomological inoculation rate (EIR) could be associated with malaria test positivity rates in Western Kenya. The collection of mosquito vector species was done using CDC light traps in five rural villages of Teso South sub-County in Busia County. The health facility under-five and over-five outpatient department (OPD) register datasets for the period March and June 2021 was extracted from the health facilities and used to calculate malaria test positivity rates for each of five villages in this study. Vector species densities, human biting rate (HBR) and entomological inoculation rates (EIR) were calculated using standard methods for each of the villages. Multilevel models were then run in R statistical software to determine the association between entomological and epidemiological indices. Significant association was observed between epidemiological indicator (malaria test positivity) and anopheline mean density (OR 1.12, 95% CI 1.08 - 1.16), HBR (OR 1.37, 95%CI 1.19 - 1.57). No significant association was observed between epidemiological indicator (malaria test positivity) and EIR (OR 1.04, 95% CI 0.96 - 1.13). The study results suggest that there is an association between malaria test positivity rate and entomological indices of mean densities, HBR but not EIR and therefore these measures can be used as proxies for test positivity rates.

5501

QUANTIFYING SPATIAL HETEROGENEITY OF MALARIA IN THE ENDEMIC PAPUA REGION OF INDONESIA: ANALYSIS OF EPIDEMIOLOGICAL SURVEILLANCE DATA

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As control efforts progress towards elimination, malaria is likely to become more spatially concentrated in few local areas. The purpose of this study was to quantify and characterise spatial heterogeneity in malaria transmission-intensity across highly endemic Indonesian Papua. We analysed individual-level malaria surveillance data for nearly half a million cases (2019-2020) reported in the Papua and West Papua provinces and adapted the Gini index approach to quantify spatial heterogeneity at the district and health-unit levels. In this context, high Gini index implies disproportionately distributed malaria cases across the region. We showed malaria incidence trends and the spatial and temporal distribution of sociodemographic characteristics and aetiological parasites among cases. While Papua province accounted for the majority of malaria cases reported in the region and had seen a rise in transmission since 2015, West Papua province had maintained a comparatively low incidence. We observed that Gini index estimates were high, particularly when the lower spatial scale of health units was evaluated. The Gini index appears to be inversely associated to annual parasite-incidence, as well as the proportions of vivax malaria, male sex, and adults. This study suggests that areas with varying levels of transmission-intensities exhibited distinct characteristics. Malaria was distributed in a markedly disproportionate manner throughout the region, emphasising the need for spatially targeted interventions. Periodic quantification and characterisation of risk heterogeneity at various spatial levels using routine malaria surveillance data may aid in tracking progress towards elimination and guiding evidence-informed prioritisation of resource allocation.

5502

IMPROVING EVIDENCE FOR ACTION: LESSONS FROM PANAMA'S SUCCESSFUL EFFORTS TO STRENGTHEN CASE-FINDING AND CASE-REPORTING

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In 2022, Panama reported just over 7000 malaria cases, continuing the year-over-year increase that began in 2018 when just 735 cases were reported. Alongside this ~10-fold rise in reported cases are significant improvements in case-finding and case-reporting. Two major milestones

include: (1) the introduction of rapid diagnostic test available to Community Health Workers (CHWs) in 2017 and Vector Control Technicians in 2019 (referred as community testing (CT)), in hard-to-reach and highly endemic, Indigenous communities and (2) the national roll-out of a nominal, locality-level electronic surveillance system (SISVIG) and visualization dashboard (DHIS2) in 2020. We performed a review of key indicators obtained from SISVIG/DHIS2, describing improvements in case management, timeliness of case notification, and completeness of case records. Our results showed that in 2022, more than 44,000 diagnostic tests were reported nationwide, representing a modest 8% increase in overall testing compared to 2018. However, the number of tests conducted by CHWs increased 6-fold over the same time, accounting for 17.2% of tests in 2022. CT impact was especially apparent in the Panama Este region where regional health staff efforts to maintain high testing and adequate stock levels contributed to a 60% decline in reported cases in the final 6 months of 2022 compared to the same period the year before; the 3 remaining endemic regions increased by 63% during this time. The surveillance review showed that time between case detection and case notification decreased nearly 3x; from 74 days in 2020 to 27 in 2022. As a result, national decision-makers are better positioned to enact strategies based on readily available, real-time data. Ongoing (2023) efforts to maintain a high number CT through the low season, provide effective and complete treatment, routinely perform control slides, and proportionately target locality level interventions based on recent burden can be directly linked to enhanced surveillance. Lessons from Panama's experience improving evidence to inform case-reducing actions can guide countries with equally ambitious elimination goals.

5503

ASSESSING THE QUALITY OF MALARIA DATA REPORTED IN THE DISTRICT HEALTH INFORMATION SYSTEM VERSION 2 AND FACILITY REGISTERS IN GHANA

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Accurate, timely and consistent data are essential for decision-making in health care. Ghana's malaria data is first recorded in paper registers and collated into paper reporting forms at the facility level, and subsequently entered in District Health Information System Version 2 (DHIMS2). In 2022, Ghana's malaria data reporting accuracy in DHIMS2 ranged from 90%-100%. However, the reported data from this hybrid electronic and manual system has not been verified. In support of the Ghana NEMP, the USAID-funded CHISU program conducted a Data Quality Audit using the WHO Data Quality Review (DQR) methodology in 25 healthcare facilities in eight districts from three regions. In each region, the districts with the highest and lowest reporting accuracy scores were sampled (facilities selected randomly). Data from five outpatient department malaria care variables from the previous three months were audited for accuracy and sources of data errors. The verification factors computed were categorized as either within-accuracy-range of 95% - 105% or out of the accuracy range, incorporating a margin of ±5% error of perfect congruence of 100% on the verification factor. The proportion of verification factors within-accuracy-range was then expressed as a percentage of both within-range and out-of-range. The cumulative accuracy score of Facility Register (paper) against DHIMS2 Verification was 45.9%. The accuracy score of Register (primary source) and Reporting forms (paper) was 47%; the score for Reporting forms (paper) and DHIMS2 data was 83%. Data inaccuracy occurred most during tallying and aggregation of data from the registers onto the reporting forms at the facility level. Sources of errors included use of improvised and outdated registers, lack of standardized tally sheets, data transcription errors, and inability of district hospitals' EMR to generate accurate reports. Based on these findings, CHISU recommends for GHS to make standardized registers/ tally sheets available in the short term and train staff appropriately, and to invest in facility-level register digitization in the long term.

5504

EARLY EFFECT ASSESSMENT OF MALARIA COMMUNITY CASE MANAGEMENT (MCCM) INTERVENTIONS ON THE BURDEN OF MALARIA IN FACILITIES IN TANZANIA

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Malaria remains a significant public health challenge in Tanzania, with high rates of morbidity and mortality among pregnant women and children under age five years. Tanzania initiated malaria Community Case Management (mCCM) in June 2022 in hard-to-reach communities with the highest burden, enabling community-based testing and treatment of uncomplicated malaria and timely referral of severe malaria to neighboring health facilities. Our aim was to assess the early effect of mCCM interventions on the burden of malaria in health facilities. We compared the number of attendees and confirmed malaria cases in outpatient departments (OPD) and the test positivity rate (TPR) between 46 facilities located in villages with mCCM and 464 facilities located in villages without mCCM across 8 councils during two time periods between July and December in 2021 (pre-mCCM) and 2022 (during mCCM). Routine facility malaria data were extracted from the District Health Information System-2 and analyzed. Between July and December 2022, a total of 11,655 patients were tested by malaria rapid diagnostic test through mCCM in the 8 councils. Among these, 3,142 tested positive (community TPR=27.0%). In facilities located in mCCM villages, OPD attendance per 1000 population decreased by 19 visits, from 195 in 2021 to 176 in 2022 (p-value < 0.001). The TPR increased from 26.4% in 2021 to 28.5% in 2022 (p-value <0.001). In contrast, OPD attendance per 1000 population decreased by 12 visits, from 219 in 2021 to 207 in health facilities in the same councils but located in villages without mCCM (p-value <0.001). The TPR also decreased from 33% in 2021 to 31% in 2022 (p-value <0.001). The difference in difference model showed 2.2% additional increase in TPR in mCCM compared to non-mCCM between the two periods (p-value= 0.035). While the changes in the selected indicators before and after mCCM implementation in the two populations were statistically significant, the differences were too small to remark on the effectiveness of mCCM on healthcare use. Further research is needed to evaluate the long-term impact of mCCM on malaria burden and healthcare use in Tanzania.

5505

USING DATA FROM PREGNANT WOMEN IN MALARIA SURVEILLANCE: WHO IS MISSING?

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To address the challenge of monitoring malaria infection at the community level, pregnant women attending antenatal care (ANC) are proposed as a pragmatic surveillance sentinel group. Malaria screening during ANC provides a measure of the malaria burden among pregnant women but also a proxy for infection levels for children under age 5. According to the 2021 World Malaria Report, 74% of women used ANC services at least once during their pregnancy. While this is high, ANC utilization differs by area,

wealth, and other factors. ANC users are not representative of all pregnant women. If countries were to adopt an ANC malaria surveillance strategy, it is essential to know if malaria prevention behaviors of women who attended ANC are different than those who did not attend ANC. This analysis used data from Demographic and Health Surveys (DHS) and Malaria Indicator Surveys (MIS) in 27 countries in sub-Saharan Africa between 2013-2021 capturing 185,697 women. The outcome of interest is use of an insecticide treated net (ITN) by women the night before the survey. The analysis includes a weighted descriptive pooled statistic and individual country weighted logistic regression models adjusting for age, residence (urban/rural), wealth quintile, education, parity, prior death of a child, and malaria endemicity. Among women age 15-49 who had a live birth in the five years preceding the survey, 10.5% (95% CI: 10.0%-10.9%) did not attend ANC for their most recent live birth. Only 9% of women who did not attend ANC slept under an ITN the night before the survey, compared to 52% of those who had any ANC. Results of the adjusted individual country regression analysis showed that those who slept under an ITN were significantly more likely to have attended ANC as compared to those who slept under an ITN in 18 of the 27 countries (p-value <0.05). This analysis provides additional insights into the malaria prevention behaviors of women who did not attend ANC as compared to those who attended ANC. Malaria surveillance systems need to take this difference into account as the malaria prevalence among those that attended ANC is likely to be lower than those who did not attend ANC.

5506

PRIVATE SECTOR INVOLVEMENT IN THE FIGHT AGAINST MALARIA IN MADAGASCAR

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In Madagascar, 405,605 people with fever sought care in private health facilities in 2022 compared to 290,000 in 2018. The NMF3 (Nouveau Modele de Financement phase 3) private sector program aims to increase private sector provider adherence to national malaria control guidelines in Madagascar, with a focus on stocking and using RDTs, prescribing ACTs and injectable artesunate according to guidelines, and selling LLINs. This program covers all 23 regions of the country. The Ministry of Health (MOH), the National Malaria Control Program (NMCP), the Regional Council of the Physicians Order (CROMs) and PSI Madagascar collaborated to integrate private health centers (PHCs), pharmaceutical wholesalers, pharmacies and drug depots into the national health system. Six health promoters and an mRDT quality supervisor work with the MOH and NMCP teams to conduct regular formative supervision using a provider behavior change communication approach and Medical Detailing, an approach to positively influence the providers fever and malaria management behaviors. Experts also provide continuing medical education to private providers. The program initially gave a 90% subsidy for ACTs, but the subsidy reduced to 60% in phase two. Malaria Rapid Diagnostic Test (RDT) orders by the pharmaceutical wholesalers has been stable since 2018. However, ACT orders reduced from 7,698 425,00 in 2018 to 1,492,550. In 2022, in the 551 PHCs supported by the NMF3 program, 97% of suspected malaria cases were tested compared to 70% in 2018, and 94.36% of confirmed cases were treated appropriately compared to 86% in 2018. 80% of the PHCs use the national external consultation register, and 200 of these centers (36%) are registered in the national reporting system and report into DHIS2.The project has had a positive impact on the continued availability of antimalarial commodities and improved case management, and the integration of private sector data and reports into the national reporting system. The next steps in 2023 are to continue to improve provider performance, register 100% of the 551 PHCs in DHIS2 and to increase the number of targeted PHCs to 650.

5507

MALARIA SERVICES SUPERVISIONS ACCELERATE DECLINE IN MALARIA-RELATED DEATHS IN CHILDREN UNDER FIVE YEARS IN TANZANIA: A QUASI-EXPERIMENTAL STUDY

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Tanzania instituted the Malaria Services and Data Quality Improvement (MSDQI) supervision package for evaluation and improvement of malaria case management at the facility level. MSDQI was initially piloted between 2017–2019 and widely expanded from 2020. This quasi-experimental study evaluates the association between MSDQI and malaria-related deaths among children under five years. We used the time Jan 2017– Dec 2019 and Jan 2020–Dec 2022 to create period variables representing the time before and after the MSDQI intervention, respectively. The intervention group constituted facilities that received at least one MSDQI supervision from 2020. Facilities that never received MSDQI supervisions constituted the control group. Using a linear mixed effects model, we modeled the monthly proportion of malaria-related deaths out of all deaths in children <5 years. The primary exposure variable (MSDQI supervision) was an interaction term between period and intervention (difference in difference estimator). The model was adjusted by season at the time of death, malaria transmission strata classified from a combination of survey and routine malaria data (high, moderate, low, and very low), and residence (urban, rural, and mixed). A total of 1,804 facilities (1,088 MSDQI and 716 non-MSDQI) that reported deaths in children <5 years during the study period were included in the analysis. There was a total of 77,718 deaths, among which, 7,254 (9.3%) were attributed to malaria by a provider. Our model predicted an overall decline in the proportion of <5 malaria-related mortality from 15.1% to 9.1% in MSDQI-facilities, and from 15.4% to 11.5% in non-MSDQI facilities, representing a 2.2% reduction in mortality in MSDQI compared to non-MSDQI facilities (p-value=0.013). Facilities with three or more MSDQI supervisions demonstrated a 3.8% reduction in mortality (p-value=0.001). Malaria-related mortality in children <5 years significantly declined in all facilities, regardless of MSDQI supervision; however, reductions were greater in facilities that received MSDQI supervision, particularly for facilities that received three or more supervisions.

5508

DIVERSITY, DISTRIBUTION, AND METHODOLOGICAL CONSIDERATIONS OF HAEMOSPORIDIAN INFECTIONS AMONG GALLIFORMES IN ALASKA

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Avian haemosporidia are globally ubiquitous blood-borne parasites, infecting a significant percentage of avian populations. Warming climates increase the viable habitat of vectors leading to range expansion, and compiling baseline data for future comparative analysis is important for predicting the long-term range of haemosporidia as range expansion of

vector populations risks exposure of naive species to infection. Using samples spanning 10-degrees of latitude in Alaska, we provide the first comparative assessment of avian haemosporidia distribution of Arctic Alaska with subarctic host populations for four species of grouse and three species of ptarmigan (Galliformes). We found a high overall prevalence for at least one haemospordian genus (88%; N=351/400), with spruce grouse (Canachites canadensis) showing the highest prevalence (100%; N=54/54). Haemoproteus and Plasmodium lineages were only observed within grouse, while Leucocytozoon species were found within both grouse and ptarmigan. Further, different Leucocytozoon lineages were obtained from blood and tissue samples from the same individual, potentially due to the differential timing and duration of blood and tissue stages. Using both Leucocytozoon and Haemoproteus/Plasmodium primer sets during PCR, we were able to identify different Leucocytozoon lineages within 55% (N=44/80) of sequenced individuals, thereby detecting coinfections that may have otherwise gone undetected. The commonly used Haemoproteus/Plasmodium primers amplified Leucocytozoon for 90% (N=103/115) of the products sequenced, highlighting the potential value of alternate primers to identify intra-genus co-infections and the importance of obtaining sequence information rather than relying solely on PCR amplification to assess parasite diversity. Overall, this dataset provides baseline information on parasite lineage distributions to assess the range expansion associated with climate change into Arctic regions and underscores methodological considerations for future studies.

5509

GEOSPATIAL MODEL OF MOSQUITO BREEDING HABITATS AND SOME PHYSICOCHEMICAL CHARACTERISTICS IN DELTA STATE, NIGERIA

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Female mosquitoes are responsible for the serious disease burdens ravaging many regions of the world. Due to the limited information on geospatial model of mosquito breeding habitats and physicochemical characteristics (hereafter PCC) in Delta State, this study was designed. Six Local Government Area in Delta State, Nigeria was mapped out. Multiplex pen and GPS device were used to determine PCC and geographically map breeding habitats. Immature stages of mosquitoes were collected using 350 ml deep ladle and scooping spoons for density calculation. Breeding site characteristics was recorded using WHO template. Four hundred and sixty-six (466) breeding sites were assessed between April, 2020 and July, 2022. Mosquito density was higher in Isoko North and Okpe than in other LGAs. Geospatially, highest mosquito density was recorded in the western communities of all LGAs except Ukwani and Aniocha South. pH was slightly acidic in all LGAs except in Isoko North. Water in Ukwani and Ika North were turbid (62 and 70%), puddles (37 and 40%) and contained more of Anopheline mosquitoes whereas in other LGAs, water was clear, of diverse habitats and contained more of Anopheline mosquitoes. Waters of breeding sites were majorly of rain sources, and when both Anopheline and Culicine larvae coexist, waters were clear and of man-made source. Water temperature (To), pH, total dissolve solids and conductivity were at optimum levels. To and pH was highest in breeding sites where Anopheline and Culicine coexisted. The differences between total dissolves solids, density of mosquitoes and conductivity in the breeding sites were significant ($p< 0.05$) whereas water temperature and hydrogen concentration were not significant in breeding sites ($p> 0.05$). The implication of this results is that it can be adopted for potential vector control programs. Therefore, strengthened need is required for further studies on expanded focus and on manipulating these breeding site factors to minimize mosquito abundance.

5510

ANALYSIS OF SENTINEL SURVEILLANCE DATABASES FOR MALARIA AND ITS CLIMATIC FACTORS IN SENEGAL, FROM 2012 TO 2019

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Endemic in Senegal, Malaria is a climate-sensitive vector-borne disease for which sentinel surveillance notes a weakness in correlating morbidity with climatic factors data. Hence the interest in analysing malaria surveillance data and its climatic factors on a national scale through an analytical cross-sectional study (01/01/2012-31/12/2019) including predictive modelling of malaria incidence and climate data (2020-2023). It required a database integrating National Malaria Control Programme and the National Civil Aviation and Meteorological Agency data with a multi-variate analysis according to the vector autoregression. Findings showed that malaria incidence rate evolves identically from year to year following 3 phases: (i) first almost zero from January to May, (ii) then gradually increases with an accentuation in August-September, and (iii) finally decreases progressively from November to December with however a heterogeneity of the importance of the incidence (Kédougou: 12.55‰, Bakel: 7.34‰ contrary to Louga: 0.16‰). Apart from wind strength and average temperature, which evolve in opposite directions, all other climatic factors follow the same dynamics as malaria incidence, which precedes them by an average duration of 2.5 ±1 month and 1 ±0.5 month for rainfall and hygrometry respectively. The causal links found between malaria incidence and rainfall are decreasing in Dakar ($p=4.18.10-6$), Ziguinchor ($p=0.0007957$), Diourbel ($p=0.001917$), Kedougou ($p=0.004038$) and Bakel ($p=0.0332$). Other links were also observed in Bakel between incidence and the minimum ($p=0.005873$) and maximum ($p=0.01216$) temperatures. The predictive modelling shows a downward trend in malaria incidence between 2020 and 2023. This is with the exception of the sites of Dakar, Diourbel, Podor and Ziguinchor where an increase is a forecast. However, climatic factors do not follow the same trend overall. Thus the importance of synchronous (multisectoral) and integrated surveillance of malaria and its climatic factors according to the One Health approach in order to better meet the requirements of pre-elimination in Senegal.

5511

MALARIA END GAME IN WEST TIMOR: STRATEGY TO FIND AND ELIMINATE MALARIA IN LAST DISEASE POCKETS

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The National Malaria Control Program of the Republic of Indonesia is dedicated to malaria elimination by 2030. In Nusa Tenggara Timur (NTT), an area of more than 500 islands with a 5.5m population, the accelerated goal is elimination by 2028. Our presentation focus is on West Timor, with a population of 2.0m (2020) and the least favorable socio-economic status of all 33 Indonesian provinces. Several malaria strategies were adopted. The most unique was the use of community-based volunteers trained to educate and promote malaria protection, to recognize malaria signs and symptoms, and identify and refer patients experiencing fever to the community health centre. An innovative friendly competition between districts was established to accelerate sub-national malaria-free certification.

Five of 22 geographic locations are now certified malaria-free. Another novel method was adopted from the national malaria control program using the algorithm, called "1-2-5", concentrating limited resources to rapidly report the index case on Day 1, do further in-depth case surveillance and treatment on Day 2, and follow-up surveillance and management on Day 5. Currently, in West Timor, the first cohort of 23 volunteer cadres are active with ongoing training to scale up numbers. The poster presents datasets, analytics, disease burden mapping, and E-SISMAL data extracted from the NTT Province Malaria Elimination Scoping Study and Gap Analysis for Acceleration of Malaria Elimination (2022). With an API ranging from 0.08 to 1.51 cases per 1000 population, our goal of zero indigenous malaria in West Timor is not complete. Using village volunteers and the 1-2-5 algorithm must continue for malaria elimination to achieve the 2028 goal. Achieving zero malaria is critical to preventing cross-border transmission to Timor-Leste which is adjacent and malaria-free.

5512

COMPARISON OF ESTIMATES OF MALARIA TRANSMISSION INTENSITY DERIVED FROM THE FACILITY-BASED TEST POSITIVITY RATE VERSUS HOUSEHOLD, MALARIA-INDICATOR STYLE SURVEYS

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Measuring malaria transmission intensity using the entomological inoculation rate (EIR), while considered the reference standard, is notorious difficult. Instead, surrogate measures that are less resource intensive are frequently employed by researchers and control programs. The P. falciparum parasitemia rate (PfPR) – usually in children – is used in Malaria Indicator Surveys (MIS) and remains the most common surrogate measure of transmission intensity. Yet, household-based surveys are costly and time-consuming to perform. In addition, an MIS can only provide an estimate of malaria transmission intensity at a single point in time. By comparison, routine data derived from healthcare facilities, including test positivity or disease incidence, is relatively inexpensive and accessible. In addition, these measures can be monitored at regular intervals to providing information on how transmission may vary over time. Despite these advantages, the test positivity rate (TPR) is sensitive to issues unrelated to malaria transmission including the incidence of other febrile illness in the community. To determine if healthcare facility surveillance accurately reflects village-level malaria transmission, we compared concurrent test positivity rates (TPR) for malaria rapid diagnostic tests (RDT) to PfPR2-10 estimates from a MIS for 35 villages within the Bugoye sub-county in western Uganda. Overall PfPR2-10 in Bugoye was 5.8% overall, but varied significantly between villages, ranging from 0.0% to 31.7%. 1,869 RDTs were performed in 2-10-year-olds during the study period, with a 45.1% TPR overall, varying from 25.0% and 63.6% between villages. The relationship between PfPR2-10 and TPR was found to vary significantly between parishes and to be influenced by the distance from villages to the nearest health center. These results suggest that predicting village-level variation in malaria transmission intensity based on hospital records may be difficult without an understanding of local drivers of healthcare utilization.

5513

USING EPIDEMIOLOGICAL AND ENTOMOLOGICAL DATA TO ASSESS REMAINING EXPOSURE TO MALARIA VECTORS IN RURAL COMMUNITIES IN THE PERUVIAN AMAZON

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Malaria is one of the diseases with the heaviest toll on rural human populations. In 2022, more than 27 000 cases were detected in Peru, with 85% reported in the Amazonian Region of Loreto. Within Loreto, rural communities are the most affected by the disease. Hard-to-reach populations have lower accessibility to health services and are often at greater risk of malaria exposure. One of the key ways to reduce and eliminate malaria transmission is to understand the limitations of current protection levels and identify gaps that need to be addressed by national malaria control plans (NMCP). In this project, we assess the remaining exposure to malaria vectors for users of long-lasting insecticidal nets (LLIN) in three rural communities from Mazan, Loreto. We integrated entomological and epidemiological data using mathematical methods to adjust mosquito exposure by human behavior. Our analysis demonstrates marked intraseasonal variation in Ny. darlingi hourly abundance during the wet season, especially from March to May. Furthermore, communities within the Mazan watershed showed higher levels than in the Napo watershed in all months except May, when hourly abundance was similar between Libertad (Mazan w.) and Urco Mirano (Napo w.). Behavior-corrected exposure indices allowed us to determine that most of the remaining exposure occurred indoors, with a smaller proportion outdoors. However, the analysis per community revealed village-specific exposure patterns. First, Gamitanacocha (Mazan w.) had most of the remaining exposure indoors, with only 9.75% outdoors. Conversely, Libertad and Urco Mirano showed similar patterns, with around 20% outdoors and 80% indoors. Overall, we found that most of the remaining exposure to malaria vectors occurs indoors, both while awake - out of the LLIN - and while sleeping - inside LLIN. Based on our analysis, Peruvian NMCP should strengthen measures focused indoors, such as indoor residual spraying. Still, a significant amount of exposure happens outside in some communities, highlighting the need to consider the micro-heterogeneity of malaria exposure at the local level in the context of regional transmission.

5514

PUBLIC-PRIVATE PARTNERSHIP IN MALARIA CASE REPORTING IN PAPUA PROVINCE, INDONESIA: A FORMATIVE RESEARCH

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The Papua Province in Indonesia contributes approximately 90% of total malaria cases in Indonesia. However, stagnation in the progress of the malaria program has been observed since 2018, partly due to poor reporting rates from private health facilities. While some districts in Papua Province have established public-private partnership activities, the effectiveness of the partnerships may not be optimal. The current formative study aimed to identify barriers and opportunities in performing partnership practices in health facilities for tailored malaria control strategies. A qualitative study was conducted in four districts in Papua Province from October to December 2022. In-depth interviews (IDIs) and focused group discussions (FGDs) were conducted with nine target groups across the health system and community, including private practices, clinics, hospitals, private laboratories, and pharmacies. Data analysis followed the framework approach. A total of 244 participants were involved in the IDIs and 45 participants joined the FGD. In the four districts, only 101 (41.4%) health facilities have established partnerships in the malaria program. The IDIs revealed that 20% (49/244) of participants did not understand the objectives of the partnerships, and 40.5% (99/244) did not know about the process of initiating partnerships. The FGD highlighted perceived barriers to establishing partnerships, such as disparities in benefits between partners and a lack of legal documentation of the partnerships. Perceived opportunities include the willingness to initiate partnerships, particularly

in malaria case finding and management and in malaria surveillance. The current study emphasizes the engagement of private health facilities in tailoring malaria control strategies in high-endemic areas.

5515

USING LOT QUALITY ASSURANCE SAMPLING METHODS TO ASSESS COVERAGE AND QUALITY OF SEASONAL MALARIA CHEMOPREVENTION DELIVERY IN NEW GEOGRAPHIES: FINDINGS AND LESSONS FROM NORTHERN MOZAMBIQUE

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In November 2020, Malaria Consortium introduced Seasonal Malaria Chemoprevention (SMC) in, Mozambique, to evaluate its effectiveness, feasibility, and acceptability in new geographies. SMC involves administering four monthly doses of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) during peak malaria transmission to children aged 3-59 months. Community distributors visit households monthly to reach eligible children. In January 2021, an end-of-cycle household survey was conducted evaluate SMC coverage & quality & pinpoint areas for improvement before the next cycle. In Nampula province, Mecuburi & Malema districts were surveyed using the Lot Quality Assurance Sampling method to estimate SMC coverage. 920 respondents were surveyed across 23 Health Facility Catchment Areas (HFCAs), with 13 in Mecuburi & 10 in Malema. A sample size of 40 households per HFCA (8 per settlement) was randomly selected using probability proportional to size sampling. Sixteen indicators were defined and HFCAs were classified based on whether targets were reached or not. A standardized questionnaire was administered to participants, covering SMC coverage & quality, caregivers' awareness and knowledge of SMC, & COVID-19 procedures followed by community distributors (CDs). A total of 920 people were surveyed, with 520 in Mecuburi & 400 in Malema. Results showed that 80.87% of households with eligible children were visited by community distributors (CDs) in both districts, & 85.2% of eligible children received day 1 SP+AQ. Of those, 93.7% completed the three-day course & 94.0% had their treatment directly observed by CDs. The awareness & knowledge about SMC varied between the two districts, with Mecuburi having higher rates for awareness (95.8%), knowledge of purpose (85.1%), & knowledge about managing adverse drug reactions (88.4%) compared to Malema (69.7%, 64.9%, and 69.5%, respectively). The knowledge surrounding SMC was enhanced in later cycles as we employed improved communication strategies such as radio broadcasts & health facility lectures in addition to community-based outreach.

5516

NEED TO REDUCE CLIENT WAIT TIMES DURING ANTENATAL CARE VISITS: LESSONS LEARNED FROM THE MALARIA SERVICES AND DATA QUALITY IMPROVEMENT (MSDQI) IN TANZANIA

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Client satisfaction with antenatal care (ANC) services has been linked to the quality of services provided and the extent to which needs are met. In Tanzania, the quality of malaria care is captured through Malaria Services and Data Quality Improvement (MSDQI) supportive supervision and includes assessment of client satisfaction. To identify parameters that might lower ANC client satisfaction, PMI Impact Malaria in collaboration with health management teams analyzed exit interview data of 939 pregnant women across 373 health facilities collected through MSDQI in Katavi, Lindi and Mtwara from 2021 to 2022. Interview questions assessed malaria testing, laboratory services, provision of and usage instructions for prescribed medicine, how to use insecticide-treated nets (ITNs), counseling for follow-up, client wait time, and health care worker (HCW) interaction with the client. The overall level of client satisfaction among the pregnant women interviewed was 89%; 98% were satisfied with malaria testing, 90% with receiving other laboratory tests, 90% for communication during HCW interactions, 87% with instructions on using medication and ITN's at home, 82% with counselling on follow-up visit, and 73% on receiving all prescribed medicine. Overall, 40% of clients waited for less than one hour, while 53% waited for 1-3 hours; 7% waited for more than 3 hours and were less satisfied with the wait time to receive services. Despite satisfaction in most of the assessed elements, further analysis is needed to understand potential reasons for longer waiting time and whether this can be reduced, as well as the nature of dissatisfaction with receiving prescribed medicine. Better understanding of drivers of client satisfaction might help to improve the quality of care delivered through ANC.

5517

IDENTIFYING REPORTING AND FOLLOW-UP CHALLENGES IN MALARIA CASE INVESTIGATION USING THE 1,3,7 STRATEGY IN A SUB-SAHARAN AFRICA PRE-ELIMINATION SETTING

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The Zambia National Malaria Elimination Program recently implemented the 1,3,7 strategy in select pre-elimination districts. The strategy aims to report malaria cases within one day of diagnosis, investigate and classify them within 3 days, and respond with reactive case detection within 7 days. We conducted an implementation evaluation of an SMS-based 1,3,7 program in two health facility catchments (HFCs) in Southern Province, Zambia. Here, we report a preliminary analysis of program performance. From April 2022 to April 2023, cases were passively identified through individual case-based notification SMS messages. Cases were considered "missed-in-reporting" if they appeared on a subsequent bi-annual review of health facility registers but were not previously reported by SMS. Cases were considered "missing follow-up" if they were successfully captured by the 1,3,7 system but reactive case detection was not done. Reasons for missed reporting or follow-up were assessed qualitatively. In total, 47 cases were registered through passive case detection. Of these, 6 (13%) were missed-in-reporting, with a third missed around public holidays. Mistrust of malaria rapid diagnostic tests (e.g. suspected false positive results) was also identified as a contributing factor to missed-in-reporting in two instances. Of the 39 eligible cases, 14 (36%) were not followed up. The most common reasons for missed follow-up were index cases being outside the HFC (43%) and failure to locate the index household (14%). Four index cases residing in a densely populated boarding school setting presented a challenge for reactive case detection. Twenty-four (51%) cases were reported within 1 day while only four cases (10%) were followed within the stipulated 7 days. Testing alternate reporting mechanisms and tools for malaria case notification can help identify key implementation challenges

in adaptation of the 1,3,7 strategy to the sub-Saharan Africa context. Enhanced supervision around non-workdays and training is essential to avoid missing cases, while improved inter-HFC coordination can help ensure follow-up of cases that span HFC boundaries.

5518

RAPID ASSESSMENT OF MALARIA SURVEILLANCE SYSTEM AT DISTRICT LEVEL IN MOZAMBIQUE

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An assessment of the Mozambique malaria surveillance system (MSS) in 2018 identified multiple challenges preventing the system to achieve its purpose of facilitating evidence-based decision-making for malaria control and elimination. In response, Mozambique's National Malaria Control Program initiated intensive efforts to strengthen the system. The aim of the rapid assessment was to assess the status of the MSS in 2022 in relation to following parameters: performance; context and infrastructure; process; and behaviour. The assessment comprised a survey, secondary data analysis and mixed methods data collection. District Malaria Focal Points (DMFPs) from 28 districts were surveyed. Performance of the MSS in terms of completeness, timeliness and accuracy of data reporting showed In 2022, 93% (90% in 2018) of districts reported to the central database DHIS2 each month. Timeliness of data reporting increased to 89% (30% in 2018) of expected reports received on time in 2022. Precision of reporting decreased to 53% (70% in 2018). 100% of districts reported having action plans including decisions based on electronic data. Guidelines and SOPs were available in 89% of districts. 100% of DMFPs reported having access to DHIS2. 100% of districts reported having a designated technician responsible for ensuring data management of reports. 76% of DMFPs consider reporting forms easy-to-follow and 100% reported that DHIS2 was easy-to-use, however, in 25.1% of districts, a key challenge was computer availability. Overall, most respondents reported being motivated to execute data-related activities and felt districts were promoting a culture of information (70.3%). DMFP's perception to perform basic data analyses and interpretation was higher (mean 92.9%) than their self-reported capacity during testing (mean 89.6%). This assessment shows that after intensive efforts, the MSS at district level in Mozambique is useful for decision-making. However, accuracy of data remains suboptimal and infrastructure such as computers and continued training must be guaranteed for an optimal use of the system.

5519

A PROTOCOL USING SOCIAL NETWORK SAMPLING AND ANALYSIS TO QUANTIFY HUMAN MOBILITY PATTERNS AND THEIR EFFECTS ON MALARIA TRANSMISSION IN BORDER AREAS OF THE BRAZILIAN, ECUADORIAN, AND PERUVIAN AMAZON

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Understanding human mobility's effects on malaria transmission is a challenge to elimination. While cell phone data are an important tool to measure mobility, coverage is sparse or non-existent in the remotest parts of the Amazon, where malaria transmission is often highest. Furthermore, cell phone data has other limitations, including the inability to identify reasons of mobility, which limits the ability of malaria control programs to tailor interventions to populations traveling for specific reasons. As a result, other approaches to measure mobility are needed in the Amazon and other remote regions. Here, we describe a social network survey protocol designed to estimate mobility patterns (magnitude, timing, duration) and their drivers across the northern Amazon spanning Brazil, Ecuador, and Peru, including across country borders. Our study uses a Respondent Drive Sampling approach with three waves of data collection. The first wave consists of 40 total initial nodes (20 spanning the Ecuador-Peru border along the Pastaza river; 20 spanning the Brazil-Peru border along the Amazon and Yavari rivers). Between four and six key informant interviews are administered in each initial node, half of whom are women. Key informants are asked about where people in their community travel to and from, the reasons for travel, the timing (e.g. season), and duration of stay. Responses are then ranked such that Wave 2 communities can be selected. Wave 2 data collection consists of interviewing key informants in 2 communities per initial node, while Wave 3 consists of conducting interviews in 2 communities per Wave 2 node. Across all waves, this design allows for 210 communities to be surveyed across the region. Results from the first wave of data collection along the Pastaza river spanning the Ecuador-Peru border indicate that each key informant survey takes only 20 minutes, and 107 unique communities were identified from the 20 initial nodes. These data will be linked to malaria surveillance and environmental data using Bayesian network autocorrelation models to estimate the effects of mobility on transmission.

5520

PLASMODIUM FALCIPARUM - P.VIVAX BIVALENT VACCINE DEVELOPMENT USING LC16M8Δ / AAV VIRAL VECTORS PLATFORM ACHIEVES STERILE PROTECTION AND TRANSMISSION BLOCKING

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In 2021, Malaria affected approximately 247 million cases worldwide and killed 629 thousand people. Five Plasmodium species affect humans: Plasmodium falciparum and P. vivax are responsible for approximately 99% of cases. Although P. falciparum is the deadliest, P. vivax is the most geographically spread. The problem is that P. vivax-infected areas have been expanding in recent years. Moreover, P. falciparum and P. vivax concurrent infections have been observed in several areas. There is a need for an effective vaccine against both P. falciparum and P. vivax, but no research has been done. Recently, we have developed a multistage P. falciparum vaccine based on LC16m8Δ (m8Δ)/adeno-associated virus (AAV) effective both for pre-erythrocytic (100% protection) and sexual stages (>99% transmission blocking; TB). The present study aims to apply this P. falciparum vaccine to develop a Pf/Pv bivalent vaccine with high protection levels and TB efficacy. We developed a Pf/Pv bivalent vaccine [m8Δ-Pf/Pv(s25-CSP)] harboring the fusion gene encoding the pre-erythrocytic stage antigen PvCSP and the sexual stage antigen Pvs25 into the m8Δ-Pf(s25-CSP) vaccine. Protective and TB efficacies of the heterologous m8Δ-Pf/Pv(s25-CSP) prime/AAV-Pf(s25-CSP)+Pv(s25-CSP) mix vaccine-boost immunization regimen were assessed by PfCSP- or PvCSP- transgenic (TG) sporozoite challenge and direct membrane feeding assay in a murine model. The Pf/Pv bivalent vaccine induced robust PfCSP-, PvCSP-, Pfs25- and Pvs25- specific functional IgG antibodies with a titer of more than 105 and achieved potent sterile protection up to 70% during challenge. Subsequently, when examining the TB efficacy, the vaccine regimen induced a high level of TB activity, more than 85% against P. falciparum and 98% against P.vivax. In this study, we have successfully developed a Pf-Pv bivalent vaccine based on the m8Δ/AAV viral platform

with high protective and TB efficacies. Accordingly, we are planning to evaluate the safety, immunogenicity, and vaccine efficacy in the rhesus monkey model.

5521

DELIVERY STRATEGIES FOR MALARIA VACCINATION IN AREAS WITH SEASONAL MALARIA TRANSMISSION

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The WHO has recommended the use of the RTS,S/AS01 malaria vaccine, including seasonal vaccination, in areas with seasonal malaria transmission. No other routine childhood vaccines are currently delivered following a seasonal schedule or beyond two years of age in these countries. Therefore new approaches are required for the delivery of RTS,S/AS01 in areas with seasonal malaria transmission. This study identified the potential strategies to deliver RTS,S/AS01 in areas with seasonal malaria through a series of high level discussions with international and national immunisation and malaria experts. These strategies were then explored through in-depth interviews with malaria and immunisation programme managers, health workers, caregivers and community stakeholders in Mali, a country with highly seasonal malaria. A national level workshop was held to confirm the qualitative findings and work towards consensus on an appropriate delivery strategy for Mali. Four delivery strategies were identified: age-based vaccination delivered via the Expanded Programme on Immunization (EPI); seasonal vaccination via mass vaccination campaigns (MVCs); a combination of age-based priming vaccination delivered via EPI clinics and seasonal booster doses delivered via MVCs; and a combination of age-based priming vaccination doses and seasonal booster doses, all delivered via EPI clinics. The latter was the preferred strategy for delivery in Mali identified during the national workshop. Participants recommended that supportive interventions, including communications and mobilisation, would be needed for this strategy to achieve required coverage. These findings can be used alongside other research and practical, economic and contextual considerations, to make decisions on the delivery of RTS,S/AS01 in areas with seasonal malaria transmission. Further implementation research and evaluation is needed on these new delivery strategies, and their supportive interventions within clearly defined contexts to achieve the impressive impact achieved with seasonal vaccination in trial conditions.

5522

INFLUENCE OF NATURALLY ACQUIRED PLASMODIUM FALCIPARUM AND SCHISTOSOMA HAEMATOBIUM INFECTIONS ON ANTIBODY RESPONSE TO FIVE MALARIA CANDIDATE VACCINES IN PREGNANT GHANAIAN WOMEN

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Women become susceptible to malaria and anaemia during pregnancy. As part of malaria elimination efforts, VAR2CSA, a Plasmodium falciparum (Pf) candidate vaccine (CV) is in clinical trial in Africa to evaluate its efficacy, while intermittent preventive treatment for malaria in pregnancy (IPTp) is administered during Antenatal Care Visits (ANC). WHO recommends Praziquantel for schistosomiasis treatment in the second trimester, but pregnant Ghanaian women are exempted from mass drug administration. In sero-epidemiological studies, antibody response to Pf CV have been associated with clinical malaria protection. However, Schistosoma haematobium (Sh) infection could modulate antibody response to CV. Our main objective was to identify factors that could influence antibody responses to five Pf CV. In all, 1153 pregnant women (ANC:707 and delivery:446) participated in a cross -sectional study in two hospitals in the Volta Region of Ghana. Pf infection was detected by microscopy and qPCR and Sh infection by microscopy. Antibody responses directed against VAR2CSA, Pfs48/45, CSP, AMA-1, GLURP-R0 were quantified by ELISA. Multivariable regression models determined underlying factors associated with antibody responses to Pf CV. Prevalence of Pf infection was 24% at ANC and 12% at delivery, 3.7% and 1.6% of women were infected with Sh respectively at ANC and delivery. Low antibody response to VAR2CSA CV [coefficient: -1.011, p=0.013] was associated with placental malaria (PM) infection when adjusted for age, insecticide treated net (ITN) and IPTp. Previous ITN use at ANC [coefficient: 0.68, p=0.02] was associated with antibody response to GLURP-R0. At delivery, IPTp was associated with decreased antibody response to GLURP-R0 VC [coefficient: -0.56, p=0.037]. Sh infection, gravidity and age was not associated with antibody response to malaria CV. We report a high PM prevalence at delivery despite the use of IPTp and ITN during pregnancy. IPTp was significantly associated with lower antibody response to GLURP-R0 VC, suggesting a lower stimulation of immune response due to parasite clearance.

5523

COMPUTATIONAL DESIGN OF A NON-GLYCOSYLATED STABILIZED PFS48/45 IMMUNOGEN ENABLES A POTENT MALARIA TRANSMISSION-BLOCKING NANOPARTICLE VACCINE

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A vaccine that disrupts the transmission of Plasmodium from humans to mosquitos would interrupt the parasite lifecycle and reduce morbidity and mortality within the human population. The Pfs48/45 protein is a leading antigen candidate for a transmission-blocking vaccine against P. falciparum. Domain 3 (D3) of the protein contains the most potent transmission-blocking epitopes, but production challenges have limited vaccine development. For example, a non-native N-linked glycan is required for recombinant production of D3 in eukaryotic expression systems. Here we used a computational design strategy (SPEEDesign) to create stabilized non-glycosylated Pfs48/45 immunogens that retain the potent transmission-blocking epitope. One immunogen contains seven amino acid changes from the native sequence, which result in >10 °C higher thermostability and >20-fold higher purification yields. This immunogen can be genetically fused to a nanoparticle carrier to produce a single-component vaccine that elicits potent transmission reducing antibodies in rodents at low doses. The non-glycosylated nature of this immunogen and its high production yields make it uniquely suited to diverse vaccination platforms like mRNA, recombinant protein, and viral vectors. Finally, the SPEEDesign strategy used to create this immunogen is a generalizable method that can be used to create improved vaccines targeting diverse pathogens, especially parasites with unique glycosylation patterns that are not recapitulated by recombinant expression platforms.

5524

A POTENT AND DURABLE MALARIA TRANSMISSION BLOCKING VACCINE DESIGNED FROM A SINGLE-COMPONENT 60-COPY PFS230D1 NANOPARTICLE

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There were an estimated 247 million cases and 619,000 deaths worldwide due to Malaria. The majority of these deaths were children under the age of 5. With the rise in parasite resistance to antimalaria drugs, a malaria vaccine is desperately needed. Malaria vaccines can be broken down into three major classes: Pre-erythrocytic vaccines, Blood Stage vaccines, and Transmission Blocking vaccines (TBVs). TBVs function by reducing disease transmission by breaking the continuous cycle of infection between the human host and the mosquito vector, specifically by reducing the infection of the mosquito. The gametocyte surface protein Pfs230 is a leading TBV candidate. Pfs230 is a large multi-domain protein and antibodies with transmission reducing activity (TRA) map to Domain 1 (D1). Here we show that a 60-copy nanoparticle composed of the fusion of Pfs230D1 to the catalytic domain of dihydrolipoyl acetyltransferase protein (E2p) results in a single-component nanoparticle (Pfs230D1-E2p) composed of 60 copies of the fusion protein with high stability, homogeneity, and production yields. Pfs230D1-E2p also correctly presents a potent human transmission blocking conformational epitope within Pfs230D1 as shown by the ability of human mAb LMIV-01 to bind to the nanoparticle. Pfs230D1-E2p elicited a potent and durable antibody response with high TRA after two vaccinations of New Zealand White rabbits when formulated in two distinct adjuvants suitable for translation to human use (Alhydrogel and AddaS03). This single-component nanoparticle vaccine may play a key role in malaria control and has the potential to improve production pipelines and cost of manufacturing of a potent and durable TBV.

5525

EFFECTIVENESS OF A MULTI-STAGE VACCINE FORMULATION IN MALARIA VIVAX TRANSMISSION-BLOCKING

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Outside the African continent, the predominant species causing the malaria disease is Plasmodium vivax. Given their complex live cycle, the parasite provides many potential targets for the development of vaccines, such as a transmission-blocking vaccine (TBV) which prevents the parasite development in the mosquito. This study aimed to evaluate the effect of two TBV formulation produced in an adenovirus associated virus (AAV) vector targets antigens Pvs25 and PvCSP (LC16m8Δ/AAV-Pv(s25-CSP)). This effect was evaluated through DMFA with P. vivax blood samples collected from patients diagnosed with malaria vivax and mosquitoes of Anopheles spp. from a colony of Manaus, Amazonas, Brazil. Four groups of 120-150 females were fed with P. vivax blood: control and the vaccine formulation in the 1:5, 1:10 and 1:50 dilution, in independent experiments for each type of vaccine formulation (monovalent - P. vivax - VF1; bivalent VF2 - P. vivax and P. falciparum). The mosquitoes were dissected after 7 days to calculate the transmission-blocking activity (TBA) which is calculated observing the presence of oocysts in the midgut of the treated group divided by the control group and the transmission-reducing activity (TRA) which verify the number of oocysts in the treated group also divided by the number of oocysts in the control group. After 4 isolates of P. vivax tested against the VF1, the TBA was 75.6%, 59.8% and 34.5% in the 1:5, 1:10 and 1:50 dilution, respectively. The VF2 was analyzed in five P. vivax isolates. The TBA rates 85% in the 1:5 dilution; 52.9% and 20.9% at 1:10 and 1:50 dilutions, respectively. All dilutions were also able to reduce the number of oocysts compare to the control in both vaccine formulation ($p<0.0001$), demonstrating a TRA of 95.9%, 85.0% and 78.7% in the 1:5, 1:10 and 1:50 VF1 dilutions, respectively; 98.9%, 94.1% and 66.8% in the 1:5, 1:10 and 1:50 VF2 dilutions, respectively. The 1:5 and 1:10 dilutions demonstrated high TBA and TRA in both VF. Based in these results it is possible to initiate preclinical studies using rhesus monkeys to confirm the efficacy and safety of these vaccine formulations.

5526

BIOINFORMATIC APPROACH TO DESIGN A PLASMODIUM FALCIPARUM PFRIPR MULTI-EPITOPE VACCINE CONSTRUCT

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Malaria infections remain an enormous contributor to global fatalities with an estimated death toll of 619,000 in 2021 and 77% of deaths being children aged under 5 years. Transmitted via mosquito, Plasmodium falciparum is the most lethal parasite of its genus but has evaded many treatment and vaccine efforts due to its complex life cycle and redundant invasion mechanisms. Epitope-based vaccines hold significant promise for malaria vaccine development due to their ease of development and ability to target dominant regions in antigenically variable pathogens. The recently characterized protein P. falciparum merozoite Rh5 interacting protein (PfRipr) is nonredundant, highly conserved, and essential for erythrocyte invasion, making it an ideal target for a bloodstage malaria vaccine. Using P. falciparum sequences collected from Burkina Faso and Uganda, we assessed the immunogenic potential of PfRipr epitopes with regard to T-cell receptor binding and B-cell recognition. T-cell receptor binding was predicted using NetMHCpan searching against MHC I and II alleles with high regional frequencies. Using an in-silico 3D model of PfRipr predicted via AlphaFold, tertiary structures of all PfRipr sample sequences were predicted via SWISS-MODEL then analyzed by ElliPro to identify linear and discontinuous B-cell epitopes. Putative epitopes were filtered using allele coverage, conservation, antigenicity, and allergenicity. Between the two datasets, there were 19 matching epitopes with 7 MHC I, 9 MHC II, 1 linear, and 2 discontinuous. These epitopes were used to design a multi-epitope-based bloodstage vaccine construct against P. falciparum. To validate their predicted immunogenicity, epitopes can be further investigated using in silico protein stabilization and docking simulations, in vitro methods such as HLA stabilization or T-cell activation assays, and in vivo methods using transgenic mouse models. The pipeline of immunoinformatic analyses formulated in this project can be further applied to P. falciparum sequence datasets collected from other malaria endemic regions to develop vaccines effective against circulating strains.

5527

HUMORAL IMMUNE RESPONSES TO THE CENTRAL REPEAT REGION OF PFCSP INDUCED BY A VIAL-VECTORED PLASMODIUM FALCIPARUM VACCINE PLAY CRITICAL ROLES IN PROTECTION IN A MURINE MODEL

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We have previously constructed a viral-vectored vaccine platform consisting of the attenuated replication-competent vaccinia virus strain LC16m8Δ

(m8Δ) and adeno-associated virus (AAV). A heterologous m8Δ-prime and AAV-boost immunization regimen (m8Δ/AAV) provided 100% protection in a murine model. The aim of this study is to elucidate the vaccine protection mechanism using mutated parasites. It is widely recognized that a successful pre-erythrocytic malaria vaccine should induce not only humoral immune responses but also CD8+ T-cell-mediated immune responses to inhibit the infection of the liver by sporozoites and to eliminate any resulting liver-stage parasites that develop in hepatocytes. Our previous study showed that recombinant human adenovirus type 5 (AdHu5)/AAV harboring the pfcsp gene induced robust CD8+ T-cell-mediated immune responses, but partially protected mice against sporozoite challenge (60%). A fundamental question is why the m8Δ/AAV is more effective than the AdHu5/AAV with the same pfcsp antigen gene. To investigate the vaccine mechanism, we generated two lines of transgenic parasites based on PfCSP/Pb parasite; deletion of H-2Kd-restricted T-cell epitope of PfCSP (PfCSPΔCD8/Pb), replacement of NANP-repeat region of PfCSP with the corresponding region of PvCSP (PfCSP-Pv repeat/Pb). The m8Δ/AAV vaccine provided 80% and 20% protection against PfCSPΔCD8/Pb and PfCSP-Pv repeat/Pb, respectively. These results suggest that the central repeat region of PfCSP plays critical roles in protection, which is consistent with the data that the immune sera have high levels of anti-sporozoite neutralizing activity, as evaluated in vitro sporozoite neutralizing assay. In the mouse model, protection of our vaccine is mainly due to humoral rather than cellular immunity. In the previous study, the CSP-specific antibodies and CD4+ T-cell responses induced by vaccination with RTS,S/AS01 have been correlated with protection in clinical trials. We are generating a new parasite that is deficient in CD4 epitope to further evaluate the vaccine mechanism.

5528

DETERMINANTS OF VACCINE COVERAGE AND ACCEPTABILITY OF MALARIA VACCINE IN CHILDREN AGES 6-23 MONTHS IN MALAWI: A HEALTHCARE PROVIDER'S PERSPECTIVE

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Developing appropriate interventions for immunisation in young children requires a detailed understanding of immunisation levels and factors affecting coverage among children. Although there has been an increase in the overall coverage of DPT3 from 84% to 94% between 2016 and 2020, only 78% of the 28 districts in Malawi achieved the targeted coverage of greater than 80% in 2020. This indicates that there is still a gap in childhood vaccine coverage within the country. Additionally, understanding the acceptability of a vaccine before rollout helps in generating appropriate interventions to improve vaccine coverage. The main objective of this research project was to evaluate the determinants of vaccination coverage and acceptability of the RTSS malaria vaccine in children aged 6-23 months in Malawi. A systematic review of 12 full-text articles was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses framework to identify research articles that address the acceptability and coverage of vaccines in young children in Malawi. Secondly, a qualitative study design using purposive sampling of 20 healthcare workers at the Zomba District Health Office was conducted. Data were collected using in-depth telephonic interviews. Qualitative data were analysed using thematic content analysis to establish themes related to factors that affect the coverage and acceptability of the malaria vaccine. Vaccine coverage and acceptability were affected by: limited transportation, limited immunisation training for healthcare providers, socioeconomic status of the caretaker, education of the mother, community knowledge of the vaccine, trust in the health system, male gender's influence on health decisions, the load and coherence of healthcare workers and caregivers, and the perceived malaria burden and effectiveness of the vaccine. Health promotion efforts on increased immunization service resources, and healthcare worker training for immunization services can contribute to addressing low vaccine coverage and acceptance.

5529

VACCINE-INDUCED PFRH5 HUMAN MONOCLONAL ANTIBODIES SHOW BROADLY NEUTRALIZING ACTIVITY AGAINST PLASMODIUM FALCIPARUM CLINICAL ISOLATES

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Blood-stage malaria vaccines target the pathogenic phase of the malaria parasite life-cycle, therefore preventing the disease progression upon infection of the erythrocytes by merozoites following the primary liver-stage infection. The Plasmodium falciparum reticulocyte binding-like protein homologue 5 (PfRH5) is increasingly moving towards being the lead blood-stage malaria vaccine candidate, with recent promising clinical trial outcomes. As malaria vaccine development has for long been hampered by the extensive genetic diversity of naturally circulating parasites, we performed ex-vivo growth inhibition assays (GIA) to assess the inhibitory potential of vaccine-derived monoclonal antibodies (mAbs) to PfRH5 in P. falciparum clinical isolates. Our data reiterate previous reports on invasion inhibition by both vaccine-induced antibodies to PfRH5 and to the receptor basigin. We observed a dose-dependent inhibition of the parasite invasion across all vaccine-induced mAbs, with three main GIA groups, high, medium and low. Overall, while no significant difference was observed in the antibody susceptibility levels between the clinical isolates and the control lines, there was a lower susceptibility in clinical isolates across all dilutions for the most potent mAb (R5.016). Surprisingly, we observed a moderate inhibition levels with R5.011 (median = 50.14%) and R5.001 (median = 41.64%), previously reported to be lowly-inhibitory in isolation. Furthermore, we also observed the earlier reported synergistic effect of R5.011 when the later was combined with the least inhibitory mAbs used in this study, namely R5.001, R5.007 or R5.008. Ongoing analyses consisting of targeted amplicon deep sequencing of PfRh5 will permit genotype-phenotype association studies for antibodies with variation in inhibitory levels (R5.016). Data from the ongoing analyses will be presented at the conference.

5530

SUPERIOR FUNCTIONAL ANTIBODY ACTIVITY OF A DELAYED-BOOST VACCINATION REGIMEN WITH THE PLASMODIUM FALCIPARUM BLOOD-STAGE VACCINE RH5.1/MATRIX-MTM IN 5-17 MONTH OLD TANZANIAN INFANTS

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Plasmodium falciparum (Pf) reticulocyte binding protein homologue 5 (RH5) is the leading blood stage malaria vaccine candidate antigen. Non human primate vaccine studies have established the in vitro growth inhibition activity (GIA) as a correlate of protection against blood stage Pf challenge; defined as a threshold of GIA>60% at 2.5mg/mL purified total IgG. However RH5 vaccines have not previously consistently reached this threshold in humans. Vaccine induced GIA was higher using RH5 protein in adjuvant vaccines than viral vectored vaccines and in Tanzanian infants compared to UK adults. A delayed fractional (DFx) regimen of RH5 protein in adjuvant was also more immunogenic than a monthly regimen in UK

adults. We further assessed dose and regimen in 12 adults and 48 infants (age 5-17 months) vaccinated with soluble protein RH5.1 in Matrix-M (MM) adjuvant in a Phase Ib age de-escalation trial in Tanzania. Adults were vaccinated in 2 regimens: monthly (0-1-2 months, 10-10-10µg RH5.1) and DFx (0-1-6 months, 50-50-10µg RH5.1). Infants were vaccinated in 3 regimens: monthly, DFx and delayed (0-1-6 months, 10-10-10µg). A fourth infant group with high prior malaria exposure was vaccinated in a DFx regimen. Vaccines were given in 50µg MM. Vaccinations were well tolerated with no safety concerns. The most commonly reported adverse events (AEs) were injection site swelling and subjective fever. Solicited AEs were generally mild-moderate and all spontaneously resolved within a few days. As expected humoral immunogenicity was higher in infants than in adults. The average peak GIA in all infant groups exceeded the target 60% threshold with no impact of prior malaria exposure. Importantly, the delayed infant group showed the highest overall GIA, with each infant exceeding the target GIA. The delayed regimen also showed significantly higher serum anti-RH5 IgG at 10 months post final vaccination. These data suggest the importance of delayed rather than DFx dosing for RH5.1/MM in 5-17 month old infants. This delayed RH5.1/MM dosing regimen will now progress to a Phase IIb trial in 5-17 month old infants in Burkina Faso to assess efficacy against clinical malaria.

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STRUCTURES OF VAR2CSA WITH HOST RECEPTOR REVEALS TARGETABLE INTERFACES FOR NEXT GENERATION PLACENTAL MALARIA VACCINE DESIGN

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Placental malaria is caused by the accumulation of Plasmodium falciparum parasites in the placenta, resulting in poor pregnancy outcomes including mortality for mothers and their offspring. Parasite sequestration is mediated by binding of the parasite protein VAR2CSA to its receptor chondroitin sulfate A (CSA) on the surface of the syncytiotrophoblast. VAR2CSA is a 350 kDa polymorphic multi-domain protein of the PfEMP1 variant surface antigen family, and the leading vaccine candidate to prevent placental malaria. We determined atomic-resolution structures of the full-length P. falciparum ectodomain of VAR2CSA from strain NF54 in complex with CSA, and VAR2CSA from strain FCR3 by cryo-electron microscopy. This study provides the structural definition for a full-length PfEMP-1 family member. Six Duffy-binding-like (DBL) domains and two Interdomain (ID) regions interact in an interwoven manner to stabilize VAR2CSA. The structures resemble the number 7 with a stable core flanked by a flexible arm. CSA traverses the core domain by binding within channels in the core. The CSA-binding elements are conserved across VAR2CSA variants and are flanked by polymorphic segments, suggesting immune selection outside CSA-binding sites. Receptor-free and receptor-bound VAR2CSA are structurally similar, indicating no major domain rearrangement is required to bind CSA. Structure-guided design leveraging the full-length structures of VAR2CSA produced a stable immunogen that retains the critical conserved functional elements of VAR2CSA. The novel VAR2CSA vaccine construct is expressed at much higher levels than the full-length protein and elicited antibodies that prevent adherence of infected erythrocytes to CSA. This design forms a strong foundation for the development of potent strain-transcending placental malaria vaccines.

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THE INNOVATIONS IN MALARIA VACCINE DEVELOPMENT PROGRAM (IMV)

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The Innovations in Malaria Vaccine Development contract (IMV) is funded by the US Agency for International Development (USAID) and implemented by PATH. The IMV is designed to solve key underlying challenges in the preclinical development and clinical evaluation of next-generation malaria vaccines. It consists of three Workstreams: the circumsporozoite protein (CS) workstream, the blood stage (BS) workstream focused on RH5 and other antigens in the RH5 complex, and the combination (CS+BS) workstream. A common core strategy of all the IMV projects is to build on existing data to identify and advance next-generation vaccine candidates, inducing a more potent and durable immune response that interferes with critical steps in the parasite life cycle—namely, the initial infection of hepatocytes and the progression of asexual BS infection leading to clinical disease. By focusing on the potency of immune responses, the IMV is aiming to increase the durability of protection of future vaccines—an important limitation of the first-generation vaccine, RTS,S/AS01 (RTS,S). In partnership with an international consortium inclusive of the University of Oxford, Statens Serum Institut, Scripps Research, Walter Reed Army Institute of Research, Johns Hopkins University, the University of Texas at Austin, and others, the IMV continues to make significant progress in all three workstreams. Recent advances include establishing RTS,S as a benchmark in an advanced preclinical model of malaria infection, which is available for comparison testing of novel CS-based vaccine candidates. Other advances include development of an improved quantitation method of CS antibody responses across all regions of the molecule. Most recently, the IMV has advanced a next-generation particalized RH5-based BS vaccine candidate to Phase 1 clinical trial. Here, we will present an overview of the above and other key accomplishments, platform areas of interest (such as mRNA-LNP), lessons learned, and future directions.

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TRENDS IN THE PREVALENCE AND COMMUNITY KNOWLEDGE AND PRACTICES WITH REGARDS TO PROBABLE TYPHOID FEVER IN SANTA HEALTH DISTRICT - CAMEROON

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This study aimed at determining the trend in the prevalence, risk factors and community knowledge and practices regarding probable typhoid fever in Santa Health District. Two study designs were used: A retrospective study design which laboratory hospital records (2014 to 2018) were reviewed to determine the trend in probable typhoid fever and a cross-sectional community-based study design to assess the knowledge and practices regarding probable typhoid fever (TF) in 250 households. Data was collected using laboratory data review sheets and structured questionnaire respectively for the two study designs. Data was entered in excel and Epi-Info version 7.2 statistical software which were later exported to SPSS Version 25 for analysis. Chi-square test of independence was used to determine relationship between risk factors of typhoid fever and logistic regression was used to adjust for confounders. Level of significance was set at P-value < 0.005. The results showed that the prevalence of typhoid fever varied significantly ($\chi 2 = 202.73$; $P = 0.0001$) over the study period with the year 2016 recording the highest prevalence of 2016 (24.4%) and the least prevalence 511 (6.2%) was recorded in the year 2015. Of the 250 participants enrolled in the KAP study, 60% of the respondents reported that at least one member of their household had suffered from TF

episode once, while 62% of the respondents were aware of TF disease, 57.2% of respondent knew its control methods but poor practices (hand washing with soap). We therefore conclude that there was a linear trend in the prevalence of typhoid fever across the year 2014 to 2018 with a general increase in prevalence. The level of knowledge of TF was high (62%) with poor practices toward typhoid fever prevention. Also, socio-demographic factors had no influence on the high typhoid fever prevalence (60%) reported by the participants. Based on these results, we recommend intensive health education and prevention programs targeting this community to increase preventive practices and decrease incidence, prevalence, morbidity, and mortality due to poor preventive measures on typhoid fever and other enteric diseases.

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CHOLERA OUTBREAK IN SPECIAL INSTITUTIONS MACHAKOS COUNTY, KENYA, 2022

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Kenya experienced widespread cholera outbreaks in 1997-1999 and 2007-2010. The re-emergence of cholera in Kenya in 2022 indicates that cholera remains a public health threat. Understanding the risk factors is important for preventing future outbreaks. This study aimed to identify risk factors for the cholera outbreak in Machakos school for the deaf and Machakos main prison during the time period Oct 2022-Nov 2022. This was a cross-sectional study carried out in Machakos county. Outpatient (OPD) and laboratory registers were reviewed from Oct 2022 through Nov 2022 as well as active case search was conducted. Data were abstracted and a line list was developed. Descriptive and analytical statistics were conducted. Multivariate analysis was conducted to identify independent factors associated with cholera. A total of 214 clinically suspected cases of cholera and 3 deaths were reported (overall case-fatality rate [CFR], (1.4%), over 75.5% (161/214) of the cases recorded were from the age group below 20yr majority being male 54.2% (116/214). Most positive cases were reported from the prison department 54.2% (19/35) and from the age group between 21-30 17% (6/35). Vibrio cholerae O1, serotype Ogawa, was the predominant isolated strain. The Attack rate in prison was 4.4% (40/900) and in school for the deaf 46.5% (174/374). One had 7 times the odds of being a case with the disease for not washing hands before eating OR 7.5 95% CI(1.27-44.08) P-0.02.There was a confirmed cholera outbreak affecting both institutions access to clean water is necessary for the prevention of cholera infection. institution to treat water refilled by tankers before consumption and Machakos county to intensify efforts to expand access to improved sanitation facilities and clean drinking water.

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SEROPREVALENCE OF VIBRIO CHOLERAE IN HAITI, 2017

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In Haiti and areas combating cholera epidemics where disease surveillance capacity is limited, case counts often fail to accurately estimate the true burden of cholera. In 2017, we conducted a seroepidemiologic survey of cholera in Cerca-la-Source and Mirebalais, Haiti to estimate disease prevalence and identify risk factors for seropositivity during the waning phase of the first Haitian cholera epidemic. We collected dried blood spot samples on filter paper from adults and measured serum vibriocidal antibody titers against Vibrio cholerae O1. A serum Ogawa or Inaba vibriocidal antibody titer of ≥ 320 was considered seropositive. We used a raking procedure to apply survey weights based on the population distribution of age, gender, and communal sections from a census, and a random intercept to account for clustering by household. We used logistic regression to test for associations between potential risk factors and seropositivity. We enrolled 99 households with 156 individuals in Cerca-la-Source and 118 households with 121 individuals in Mirebalais. The prevalence of serum vibriocidal antibody titers was 12.4% (95%CI 6.76 - 20.0) in Cerca La Source and 9.54% (95%CI 4.91 - 16.0) in Mirebalais. Prevalence of the Ogawa serotype was 9.73% (95%CI 5.38 - 16.0) in Cerca-la-Source and 8.75% (4.28 - 15.0) in Mirebalais, which was higher than the prevalence of the Inaba serotype in Cerca-la-Source (2.69%, 95%CI 0.49 - 8.00) and Mirebalais (2.73%, 95%CI 0.57 - 7.00). There was a moderate association between poverty and seropositivity (OR 2.33, 95% CI 0.93 - 5.84, P = 0.07). There was no association between self-reported cholera or diarrhea and seropositivity. These seroprevalence estimates from 2017 suggest a high recent burden of infection during the waning phase of the first Haitian cholera epidemic. Improved epidemic disease surveillance programs to monitor cholera and guide public health interventions in Haiti are necessary.

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EFFICACY OF TYPHOID CONJUGATE VACCINE AGAINST CULTURE-CONFIRMED SALMONELLA TYPHI - A SYSTEMATIC REVIEW AND META-ANALYSIS

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After the emergence of extensively drug-resistant strains, Typhoid has become a serious public health threat in many low- and middle-income countries. World Health Organization has recommended a new typhoid conjugate vaccine as the control strategy in typhoid-endemic countries. We performed a systematic review and meta-analysis to estimate the vaccine efficacy (VE) of the typhoid conjugate vaccine against culture-confirmed Salmonella Typhi. A systematic literature search was conducted in electronic databases including Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase up to 5 January 2023. Randomized control trials comparing the efficacy of typhoid conjugate vaccine with control were eligible for inclusion. Two reviewers independently screened, extracted data and assessed the risk of bias of included studies. Certainty of evidence for key outcome was evaluated using the GRADE methodology. The outcome of interest was typhoid fever confirmed by the isolation of Salmonella enterica serovar Typhi in blood. We calculated pooled risk ratios (RRs) and VE (1 – RR as a percentage) with associated 95% confidence intervals. Four RCTs contributed to the quantitative analysis in this review, including 111509 (mean 27877) participants. All of the trials were conducted in typhoid-endemic countries, trial participants ages ranged from 6 months to 16 years. Overall VE of a single shot of typhoid conjugate vaccines against culture-confirmed S. Typhi at 2 years post-immunization was 83% (95% Confidence Interval (CI): 77%, 87%). We also conducted subgroup analysis by age group. Compared with control, TCV has demonstrated greater efficacy among children aged > 5 years to 16 years, VE: 87% (95% CI: 80%, 91%) in this age group as compared to the younger children aged 6 months to 5 years, VE: 73 % (95% CI: 53%, 85%). The existing data from included trials provides promising results on the efficacy of TCV in typhoid-endemic countries. Future research on the long-term efficacy of conjugate vaccines and their impact on enteric infection and shedding is warranted.

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FECAL PH AS A MARKER OF CHRONIC MALNUTRITION OR STUNTING AMONG CHILDREN HOSPITALIZED FOR DIARRHEA AND OTHER NON-DIARRHEAL PATHOLOGIES

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Fecal pH is a simple, non-invasive and inexpensive diagnostic tool used for initial screening of certain gastrointestinal diseases. Elevated fecal pH indicates reduction of beneficial microbiota in gut, especially Bifidobacteria

and commensal Clostridia, which has emerged as a key factor contributing to chronic malnutrition or stunting. Bifidobacteria and Clostridia clusters XIVa and IV are considered as important gut symbionts in infants and abundance of these in the gut is indicative of optimum linear growth. These microbiota contribute to formation of acidic feces by producing short chain fatty acids (SCFAs) as a byproduct of their fermentation process, which is acidic in nature and have a significant effect on fecal pH. Thus an elevated fecal pH passively denotes to decrease of these microflora in the gut. The purpose of this cross-sectional study was to investigate the association of fecal pH with stunting in hospitalized children and was conducted on 200 children aged 06-24 months getting admitted in icddr,b Dhaka Hospital with diarrhea and Dhaka Shishu Hospital for other non-diarrheal pathologies. Length-for-age Z scores (LAZ) was measured and data on factors affecting linear growth was recorded. Fecal pH was measured on freshly collected stool samples. Multivariate linear regression analysis was performed to explore relationship between fecal pH and LAZ scores. The mean fecal pH of diarrheal and non-diarrheal children was 5.54±0.98 and 5.95±0.76, respectively. Pearson correlation between fecal pH and LAZ scores of non-diarrheal children showed a statistically significant inverse correlation (-0.21, p<0.01) and a similar trend was also observed in scatter plot. After inclusion of factors affecting linear growth into the regression model, a statistically significant inverse association between fecal pH and LAZ scores was observed in non-diarrheal children (p<0.01). Elevated fecal pH in non-diarrheal children was found to have significant association with stunted growth, making fecal pH a possible indirect determinant of childhood stunting. However, such associations did not apply for diarrheal children.

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IMMUNOGENICITY AND TOLERABILITY OF DIFFERENT DOSE SCHEDULES OF TYPHOID CONJUGATE VACCINE IN NEPAL

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Previously, the Vi-typhoid conjugate vaccination (Vi-TT) was found to be efficacious in Nepalese children under 16 years of age. In the current study we assessed the immunogenicity of Vi-TT (Typbar TCV, Bharat Biotech International, India) at 9 and 12 months of age and after a booster dose at 15 months, at Patan Hospital, Kathmandu. Fifty participants each were recruited in the 9- and 12-month groups. Seroconversion (4-fold rise in IgG antibody titre) was 100% in both groups. Post-booster, the 9-month group showed significantly higher IgG seroconversion than the 12-month group. Several study visits occurred outside protocol windows due to COVID19 pandemic. All participants who attended visits per protocol (n=27 in the 9-month and n=32 in the 12-month groups) showed IgG seroconversion following the first dose. However, after the second dose, seroconversion rates were 80% in the 9-month group and 0% in the 12-month group (p<0.001). Vi-TT is immunogenic at both 9 and 12 months of age. The longer interval between doses in the 9-month group was associated with a stronger response to a booster.

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DIARRHEA EPIDEMICS IN DHAKA, BANGLADESH BEFORE AND DURING THE COVID-19 PANDEMIC: AN EPIDEMIOLOGICAL INVESTIGATION

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Moderate to large diarrhea epidemics are commonplace in Bangladesh. However, it remains to be investigated whether the characteristics of diarrhea epidemics changed in the context of the COVID-19 pandemic. This study examined the attributes of patients presented to a specialized diarrheal disease hospital (icddr,b Hospital) in Dhaka, Bangladesh during two recent diarrhea epidemics in Dhaka and its neighboring areas: one occurring in 2022, amidst the pandemic, and another in 2018, immediately preceding the pandemic. We identified the duration of epidemics objectively as the period when daily patient visits exceeded the 90th percentile of daily visits in the last two epidemic-free years before the pandemic (2017 and 2019). Dhaka Hospital treated 29212 and 59971 diarrheal patients during the 2018 (April 2 - May 12) and 2022 (March 6 - May 1) epidemics, respectively. Compared to 2018, individuals presenting during the 2022 epidemic were more frequently children under five years (37.0% vs 26.3%, p < 0.001), and less frequently drank tap water (52.8% vs 77.8%, p < 0.001) and belonged to a family with a monthly income less than USD100 (5.9% vs 13.0%, p < 0.001). Vibrio cholerae was the most common enteric pathogen, with a comparable isolation rate between the two periods (28.4% in 2022, 27.2% in 2018, p = 0.632). The detection rate was also comparable for enterotoxigenic Escherichia coli (12.3% vs 14.2%, p = 0.283), Campylobacter (10.5% vs 13.2%, p = 0.111), and rotavirus (8.6% vs 7.8%, p = 0.603). Of the V. cholerae isolates, 98.7% belonged to the O1 serogroup and El Tor biotype. The Inaba (71.8%) and Ogawa (67.3%) serotypes predominated in 2022 and 2018, respectively. Of the patients, 98.8% presented with watery stools and 85.9% with vomiting. While the patients presented less frequently with some dehydration during the pandemic (17.8% vs 28.8%, p < 0.001), the proportion of severe dehydration was comparable (51.7% vs 53.6%, p = 0.474). The in-hospital case fatality rates were low in both periods (0.05% vs 0.04%, p = 0.580). V. cholerae served as the primary agent in both diarrhea epidemics, with a serotype shift from Ogawa to Inaba during the pandemic.

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RISK FACTORS FOR SYMPTOMATIC AND ASYMPTOMATIC INFECTION WITH DIARRHEAGENIC E. COLI IN INFANTS OF PERI-URBAN LIMA, PERU

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Diarrheagenic E. coli (DEC) are responsible for around 30 to 40% of diarrheal episodes in children less than five years of age. Only few and pathotype specific studies describe factors associated to symptomatic and asymptomatic infection with DEC. We aimed to determine the factors associated with symptomatic and asymptomatic infection with DEC and persistent diarrhea in children under one year of age, in peri urban areas of Lima, Perú. The database of a passive diarrhea comunity-based surveillance study of 1034 Peruvian infants followed from 2 to 12 months of age was retrospectively analyzed. We used random effects model regression to assess associated factors. Overcrowding (OR: 1.5, p=0.007, 95% CI: 1.12-2.11) and storing water in medium-sized containers (up to 10L) (OR: 1.6, p=0.024, 95% CI: 1.06-2.45) increased the risk of DEC infection and having started complementary feeding doubled the risk of DEC infection (OR: 2.0, p=0.003, 95% CI: 1.27-3.30). Children who had started feeding, had more diarrhea due to DEC (OR: 2.7, p<0.000, 95% CI: 1.55-4.58) and higher risk of EPEC (OR: 3.5, p=0.001, 95% CI: 1.64-7.5) and EAEC (OR:1.9, p=0.019, 95% CI: 1.11-3.31) symptomatic and asymptomatic infection. Males had more diarrhea due to DEC (OR: 1.5, p=0.015, 95% CI: 1.09-2.12) and for each additional month of age, the risk decreased (OR:0.9, p=0.009, 95% CI: 0.88-0.97). EAEC as a single pathogen doubled the risk of persistent diarrhea (OR: 2.5, p=0.023, 95% CI: 1.14-5.6). We concluded that there is a greater risk of infection with DEC in overcrowded homes and in those who stored water inmedium-sized containers and in male children who have started complementary feeding. The risk decreased with age. These pathogens should be routinely looked for in young children, especially EAEC which was associated with persistent diarrhea.

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FACTORS ASSOCIATED WITH PERSISTENCE OF STUNTING AT THE END OF THE FOLLOW-UP PERIOD AMONG BANGLADESHI CHILDREN WITH DIARRHEA

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Stunting, a form of malnutrition, characterized by impaired linear growth in the first two years of life, affects one child out of four globally. The prevalence of stunting in Bangladesh is also high. However, we don`t have adequate information about the burden and ramification of persistence of stunting. Thus, the primary aim of this study was to determine the factors associated for persistence of stunting. We performed a secondary analysis of data collected in the 'Antibiotics for Childhood with Severe Diarrhea (ABCD)' trial. For the purposes of this study, children aged 2-23 months who had complete records for height, weight, age, and sex were selected. We have compared between two groups of children: one group had stunting during enrolment and recovered on day-90 follow up and other group was enrolled with stunting and that persisted up to day-90 follow up period (cases). We expressed weight and height as z-scores. Children with height-for-age-z-score <-2 categorized as stunted according to WHO guidelines. Out of 1431 children, 589 were enrolled with stunting (z score < - 2) and 542 remained stunted on day-90 post-discharge follow-up. Thus, the number of cases was 542 and control was 877. The cases more often presented with lack of vaccination following EPI schedule, had illiterate mothers, and were less often partially or exclusively breastfeed on day-90 post-discharge follow up compared to those who didn`t have persistent stunting (for all, $p < 0.05$). Therefore, the study results underscore the importance of continuation of vaccination following EPI schedule, breast feeding up to 2 years of age, and parental education that may help to reduce the burden of persistent stunting and their consequence.

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COMPARATIVE CHARACTERISTICS OF CHILDREN HOSPITALIZED FOR ACUTE, CHRONIC AND WITHOUT MALNUTRITION

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The application of clinical and laboratory methods revealed diverse findings among children hospitalized for acute, chronic and without malnutrition. However, their comparative data are limited to under 5 children. Data were extracted from the electronic data system of the Dhaka Hospital of icddr,b from 2019–2021. Among 1881 children under the age of 5, 177 children, 239 children and 652 children were eligible for the acute malnutrition, chronic malnutrition and well-nourished groups, respectively. We compared these children separately. Among 1068 children, 889 (83%) had diarrhea. The prevalence of acute and chronic malnutrition in diarrheal children was, respectively, 14% and 17%. After adjusting for age and sex in the multiple regression model, hyponatremia (Na <135 mmol/L) was found to be significantly higher [aOR = 2.33 (95% CI: 1.50, 3.61); p<0.001] and raised creatinine was significantly lower [aOR = 0.52 (95% CI: 0.30, 0.90); p=0.020] in acute malnourished children. Both anemia (Hb <11.5 gm/dl) and thrombocytosis (Platelet >400 x 109/L) were significantly prevailing in chronic malnutrition cases [aOR = 2.21 (95% CI: 1.60, 3.07); p<0.001 and aOR = 2.44 (95% CI: 1.78, 3.33); p<0.001]. Children with acute and chronic forms of malnutrition were more often observed non-breastfed [aOR = 2.32 (95% CI: 1.60, 3.38); p<0.001 vs. aOR = 2.10 (95% CI: 1.46, 3.02); p<0.001] than well-nourished children. The incidence of hypernatremia was substantially lower in children who were acutely and chronically malnourished (both p<0.050) compared to well-nourished children. Thus, the children hospitalized for acute, chronic and without malnutrition need to be identified separately for their appropriate management framework.

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FACTORS ASSOCIATED WITH MORTALITY IN SEVERELY MALNOURISHED HOSPITALIZED CHILDREN WITH DIARRHOEA WHO DEVELOPED SEPTIC SHOCK

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Septic shock can often lead to death, even in resourceful settings, if not handled carefully. Therefore, we sought to evaluate the factors associated with deaths in the context of severe malnutrition and also the effects of early, i.e., within 3 hours of diagnosing septic shock vs. late blood transfusion. In this retrospective chart analysis, we first prepared a case-record forms (CRFs) and collected relevant patient data from a digital patient management system at icddr,b hospital. Out of 276,523 under-five children admitted to this diarrhoeal hospital with the complaint of diarrhoea from the year 2013 to 2017. Patients are shifted to intensive care unit (ICU) immediately when they developed critical complications - such as respiratory distress, severe pneumonia with hypoxemia or respiratory failure, repeated hypoglycemia, severe sepsis, septic shock, altered level of consciousness. We found 93 severely malnourished children developed septic shock and received the blood transfusion at the ICU. Participants who aged between 2 to 59 months of age and of either sex were enrolled. Children who died constituted cases (n = 54), and the survived (n = 39) represented controls. We excluded children who received the blood transfusion for other causes and who left against medical advice. In both descriptive and multivariate analysis, we found that death was significantly associated with the requirement of fourth-line antibiotics (Meropenem plus Vancomycin), corticosteroids, and the addition of vasopressors on top of dopamine (all $p < 0.05$). However, the decrease of total serum calcium level (<2.12 mmol/L) was found significantly associated with death only after adjusting ($p < 0.05$). Even though the cases more often received early blood transfusion than the controls, the difference was insignificant ($p = 0.134$). When a severely malnourished under-five child develops septic shock, requiring vasopressors, fourth-line antibiotics, and corticosteroid, with reduced serum calcium, the probability of death increases significantly. Our findings underscore the gravity of close monitoring at these points and the niches for early interventions.

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ISOLATION AND WHOLE GENOME SEQUENCING OF A CRONOBACTER SAKAZAKII SEQUENCE TYPE 136 STRAIN, FROM READY-TO-EAT FOOD

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Cronobacter sakazakii is an emerging, infectious, Gram-negative, bacterium that can survive in extreme arid environments. This opportunistic pathogen is known to cause acute meningitis and necrotizing enterocolitis in neonates, elderly, and immunocompromised individuals. It has been linked primarily to contaminate powdered infant formula (PIF) and for causing PIF-related sporadic cases and foodborne outbreaks worldwide. Nevertheless, it has also been recovered from a wide range of foods. Molecular characterization studies have revealed a high level of species-level genetic polymorphism, encompassing unique clonal complexes and sequence types, frequently associated with foodborne illness and outbreaks. Currently, application of whole genome sequencing (WGS) has advanced bacterial typing and is widely utilized for precise strain identification to understand disease transmission. In this study, a C. sakazakii-like Gram-negative bacterial isolate SRL-72, from ready-to-eat

food prepared in the Southeast Asian region, was recovered and analyzed. Initial microbial identification was accomplished on VITEK 2, RT-PCR, and MALDI-TOF MS based analysis, following FDA's Bacteriological Analytical Manual and manufacturer's recommended protocols. WGS was completed on an Illumina MiSeq system, using a Nextera XT DNA library preparation kit and a 250-bp paired-end read MiSeq Reagent *v2* kit (500-cycle), following manufacturer's instructions. MALDI-TOF MS identified the C. sakazakii SRL-72 isolate as C. sakazakii with a high confidence value (99.9%). WGS analysis revealed the genome sequence of C. sakazakii isolate SRL-72 was 4,501,682 bp in length and distributed in 66 contigs Analysis further confirmed the genome of C. sakazakii isolate SRL-72 to be Sequence Type 136 for . C. sakazakii ST136 has been considered to be a highly stable clone with a high propensity to cause neonatal meningitis. Therefore, MALDI-TOF MS and WGS methods can be applied for rapid and precise identification of human-pathogenic C. sakazakii isolates of public health importance.

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TITANIUM DIOXIDE NANOPARTICLES CAN ACTIVATE HUMAN DENDRITIC CELLS AGAINST MYCOBACTERIUM LEPRAE INFECTION: A PROMISE FOR DENDRITIC CELL IMMUNOTHERAPY AGAINST LEPROMATOUS LEPROSY

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Leprosy is a chronic infectious disease caused by Mycobacterium leprae, which is still endemic in many parts of the world including Southern Texas. The two polar clinical forms of leprosy, termed tuberculoid and lepromatous, have polarized cellular immune responses, with complex immunological distinctions. Dendritic cells (DCs) are the primary antigen presenting cells in the immune system. TiO2 nanoparticles have shown to induce maturation of these cells leading to an inflammatory response. We aimed to evaluate the effect of potassium incorporated TiO2 nanostructures, KTiOx, in the response of human monocyte-derived-DCs to M. leprae. THP-1 human monocytes were differentiated and maturated into DCs using commercially available media, and then treated with KTiOx for 24 hours. Following, cells were infected with M. leprae at an MOI of 10:1 for 24 hours. Activation of transcription factor NF-kB and IRF was assessed through reporter plasmid systems. Secreted human cytokines were measured in the culture supernatants by a multiplex ELISA system. We observed that KTiOx nanoparticles increased DC phagocytic activity without activation of inflammatory transcription factor NF-kB. An increase in the levels of secreted IFN-α and TNF-β upon M. leprae infection in cells treated with KTiOx was also detected. IFN-β and its downstream gene IL-10 are preferentially expressed in disseminated and progressive lepromatous lesions, while the TNF-β gene is identified as a major risk factor for early-onset leprosy. It is possible that this wider KTiOx area can activate more DCs due to an increase in the contact area. This study demonstrates the effect of nanostructures of KTiOx in the in vitro activation and modulation of human DCs against an infectious disease with a puzzling immune spectrum. Our findings may prompt future therapeutic strategies such as DC immunotherapy for disseminated and progressive lepromatous lesions.

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CHARACTERIZATION OF MULTIDRUG-RESISTANT ESKAPE PATHOGENS ISOLATED FROM A PUBLIC HOSPITAL IN HONDURAS IN 2021

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The ESKAPE group of bacterial pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.) pose a global public health threat, commonly causing multidrug-resistant (MDR) nosocomial infections. A cross-sectional surveillance study was performed to identify antimicrobial resistance patterns for ESKAPE isolates collected from Hospital Escuela Universitario in Honduras in 2021. A total of 169 ESKAPE isolates were included for identification and antimicrobial susceptibility testing following the Clinical and Laboratory Standards Institute M100 guidelines. Vancomycin-resistant Enterococcus (VRE), methicillin-resistant S. aureus (MRSA), extended-spectrum β-lactamase (ESBL)-producing bacteria, and carbapenem-resistant (CR) pathogens were detected by the disk-diffusion test, E-test method, and minimum inhibitory concentration method by BD Phoenix M50. The majority of bacterial strains were isolated from skin and soft tissue secretions (44.4%), blood (29.6%) or body fluids (10.7%). The frequency among the ESKAPE isolates examined was K. pneumoniae 43.8%, A. baumannii 40.2%, P. aeruginosa 8.9%, E. faecium 3.0%, S. aureus 2.4%, and Enterobacter spp. 1.8%. Overall, 90.5% of the pathogens were MDR, including 100% of K. pneumoniae and A. baumannii isolates. ESBL-producing K. pneumoniae and Enterobacter spp. were detected in 12.2% and 33.3% of cases, respectively. A high prevalence of CR A. baumannii (100%) and P. aeruginosa (26.7%) was observed. No MRSA or VRE was observed among isolates. ESKAPE pathogens isolated from Hospital Escuela Universitario in Honduras demonstrated substantially high rates of MDR. ESBL and CR pathogens were frequently isolated from nosocomial infections. Antimicrobial surveillance targeting nosocomial MDR pathogens should be a high priority for the hospital infection control policy. Optimizing transmission control measures and antibiotic stewardship is advised for the adequate prescription of antibiotics to reduce selective pressure conducive to MDR.

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EPIDEMIOLOGY OF STAPHYLOCOCCUS AUREUS PATHOGENS CAUSING INVASIVE DISEASE IN PATIENTS SEEN AT MRC CLINIC, FAJARA THE GAMBIA

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Staphylococcus aureus is a major cause of both community and hospital-acquired infections around the world and one of the leading causes of infection in The Gambia particularly in children. Little is known about the genetic diversity of strains circulating in the country especially those causing invasive disease. We describe the epidemiology of S. aureus causing invasive disease in The Gambia. 134 invasive isolates obtained from clinical samples of patients seen at the MRC clinic in Fajara, The Gambia between 2014 and 2020 were analyzed in this study. Multilocus Sequence Typing (MLST) was used to characterize S. aureus strains. Antimicrobial susceptibility was determined using the Kirby-Bauer disc diffusion technique. Invasive S. aureus infection was more common in males (52%) while the highest number of isolates was obtained from children &lt 2 years. Blood specimens accounted for 81% of the isolates. Antibiotic susceptibility patterns strains were 6%, 87%, 51%, 97%, 98%, 93%, 97%, and 96% for penicillin, trimethoprim-sulphamethoxazole, tetracycline, chloramphenicol, gentamicin, erythromycin, cloxacillin and methicillin respectively. Difference in susceptibility to trimethoprim-sulphamethoxazole between the different age groups was statistically significant (P=0.030). A statistically significant difference between Methicillin-Susceptible Staphylococcus aureus (MSSA) and Methicillin-Resistant Staphylococcus aureus (MRSA) in susceptibility to penicillin, gentamicin and cloxacillin was also statistically significant. MLST identified 19 Sequence Types. Our study provides essential information on invasive S. aureus strains in The Gambia. Invasive S. aureus infections can be successfully treated with widely available antibiotics in the country. Discovery of MRSA strains calls for more care and continuous surveillance for early detection of changes in susceptibility patterns. There is need for closer monitoring of the genetic diversity and clonal dissemination of strains present in the country particularly those causing diseases for future consideration in vaccine adoption.

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SURVEILLANCE OF COLISTIN RESISTANCE PREVALENCE OF NOSOCOMIAL ORIGIN IN PERU

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Studying colistin resistance in nosocomial settings is crucial due to the growing threat of multidrug-resistant (MDR) Gram-negative bacterial infections. Low- to middle-income countries (LMIC) are particularly vulnerable to colistin resistance and understanding its epidemiology and risk factors can inform effective public health policies and interventions to combat antimicrobial resistance. A surveillance study conducted in Lima, Peru, collected 3703 bacterial isolates between January 2018 and October 2022. Clinical isolates were refrigerated and transported to the U.S. Naval Medical Research Unit No. 6 for identification and antimicrobial susceptibility testing. Bacterial isolates were identified using the MALDI-TOF Bruker and BD Phoenix automated system and tested for susceptibility using the Kirby-Bauer method and/or Phoenix. Colistin susceptibility testing (CST) was also conducted, and PCR was used to identify the mcr-1 gene associated with colistin resistance. Clinical and Laboratory Standards Institute 2022 guidelines were used for antimicrobial susceptibility testing (AST) interpretation. The most prevalent microorganisms subjected to CST were: Klebsiella pneumoniae (n=502), Pseudomonas aeruginosa (n=484), and Acinetobacter baumannii (n=203). AST revealed that over 85% (n=427) of K. pneumoniae, 83% (n=402) of P. aeruginosa and 96% (n=195) of A. baumannii were resistant to at least 2 different antibiotic families. CST analysis showed that 10% of K. pneumoniae were resistant to colistin, and 10% of those carried the mcr-1 gene. In addition, 5% (n=10) of A. baumannii and 3% (n=16) of P. aeruginosa isolates were resistant to colistin, and, interestingly, none carried the mcr-1 gene. Our findings demonstrate high levels of MDR among isolates, with observed resistance to colistin varying from 3 to 10%. Continuous surveillance of antimicrobial resistance to multiple classes of antibiotics is paramount in the nosocomial setting, with heightened importance in regions where antimicrobial treatment options are limited and colistin is an antibiotic of last resort.

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THE LEPTOSPIRAL PROTEIN LIC12254 INTERACTS TO INTEGRINS VIA THE RGD MOTIF

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Leptospirosis is a zoonosis globally disseminated caused by pathogenic spirochetes of the genus Leptospira. Understanding leptospiral pathogenic mechanisms is critical for the efficient development of vaccines and diagnostic tests. Outer membrane proteins are considered potential antigens could mediate interactions with host components, such as integrins, that are involved in cell regulation, proliferation, adhesion and immune response. The leptospiral RGD protein encoded by gene lic12254 was selected for study. In silico analysis was investigated by LipoP, Interprot and CELLO web servers. Protein conservation analysis in different strains of Leptospira was performed by BLASTp and a 3D model was assessed by I-TASSER and analyzed by PyMOL. The recombinant proteins LIC12254 and LIC12254ΔRAA (RGD mutated) were cloned in pAE vector and expressed in E. coli strains. The evaluation of interaction of LIC12254 protein via RGD motif to human integrins was evaluated by ELISA. In silico analysis showed that protein LIC12254 is probably located on the outer membrane and has two conserved domains, Omp85 and DUF5982. 3D models showed a beta barrel structure and protein conservation analysis identified a high sequence similarity among pathogenic strains. In addition, the RGD is present only in pathogenic species. The motif RGD in LIC12254 protein sequence was replaced by PCR techniques and genes lic12254 and lic12254ΔRAA were cloned successfully into the protein expression pAE vector and recombinant proteins were obtained from insoluble form. Recombinant proteins were observed in the expected size of 54 kDa by SDS-PAGE and confirmed by western blot. The evaluation of interaction of LIC12254 protein to human integrins showed that rLIC12254 was capable to interact with αVβ8 and α8 integrins in a dose-dependent manner. As expected, the interaction with rLIC12254ΔRAA was inhibited. Our results described rLIC12254 outer membrane protein capable of interact to human integrins via RGD motif. Thus, rLIC12254 could be involved in bacterial pathogenesis by adhesion process.

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CHARACTERIZATION OF ANTIGENIC SITES OF NEISSERIA GONORRHOAE USING HIGH-DENSITY PEPTIDE MICROARRAYS AND PSORALEN-INACTIVATED, WHOLE-CELL VACCINE IN MICE

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Neisseria gonorrhoeae infections are an urgent public health threat with over 100 million cases reported globally each year. The threat of N. gonorrhoaea, a sexually transmitted infection, has been further exasperated by the increase in drug resistant strains including against last line antibiotics necessitating the need for an effective vaccine. Vaccine development has been challenging due to a lack of clearly identified antigenic targets, a high degree of strain variability, and immune evasive mechanisms of the bacteria itself. Recent retrospective studies have indicated that vaccination against N. meningitidis, a closely related bacteria also of the Neisseria genus, using the protein-based meningococcal group B vaccine (4CMenB) may provide modest effectiveness of 23-53% against infection with N. gonorrhoaea—though the effect appeared short-lived. Further studies have sought to characterize cross-reactivity of different antigenic sites which may explain this protection. To assess different vaccine approaches to both known and unknown cross-reactive antigens we vaccinated mice with two different vaccines both with and without the mucosal adjuvant, dmLT. In the first case we utilized whole-cell, formalin inactivated N. gonorrhoaea (FA1090). In the second case Psoralen plus ultraviolet A light (PUVA) was used to create killed but metabolically active (KMBA) whole-cell vaccine. Antibody profiles were screened from four mouse serum pools using high-density peptide microarrays using proteins covering pre-selected membrane and intracellular proteins, where higher intensities indicated higher reactivity. We observed reactivity in all vaccines against 15 previously published antigenic sites in the 4CMenB vaccine. Further, we see reactivity equal to or greater than the suspected cross-reactive proteins against additional sites including other intracellular proteins and outer-surface membranes. These findings suggest that a multi-epitope vaccine can be developed using a PUVA-generated KBMA whole cell approach. Additional study is needed in mapping of possible epitopes for N. gonorrhoaea vaccine development.

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ORAL CHOLERA VACCINATION CAMPAIGN COVERAGE SURVEY IN GARISSA, WAJIR, TANA RIVER, AND NAIROBI COUNTIES, KENYA

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Kenya confirmed cholera outbreaks on October 19, 2022. The outbreak progressed to 17 counties Garissa and Tana River Counties had the highest attack rates of Cholera at 239.1& 231.1/100,000 population. Kenya conducted its first-ever Oral cholera vaccination campaign in February 2023, in Garissa, Wajir, Tana River and Nairobi. The survey assessed Cholera vaccination coverage, Risk communication strategies, knowledge attitude and practices on cholera and water sanitation and

hygiene practices related to cholera. A household-based survey was conducted, targeting persons aged one year and above. WHO formula for calculating immunization coverage was used to calculate the households to be interviewed.Multi-stage proportionate-to-size cluster sampling strategy was used to determine the number of clusters and randomly selected 7 households per cluster. Data was collected using a standard questionnaire. Data was analyzed for continuous and categorical variables. A total of 122 clusters, and 858 households were visited with 5456 eligible participants. Of the 861 households targeted 99.7% (858/861) were interviewed. Coverage at individual level was 93.2% (2640/2834). Majority of the females 58.8%(1553/2640) were vaccinated. Those aged 6-14 years were the most vaccinated 26.9%(709/2640). Of those vaccinated, 7.7%(202/2640) experienced adverse events.A good number of the respondents were aware of the Oral Cholera vaccination campaign 90.2% (774/858) and 98.6% (846/858) said that those sick should seek treatment in Health facilities. Those who did not treat their drinking water were 62.6% (537/858) and 10.7% (92/858) lacked latrines. Water scarcity was also an issue with 51% (438/858) reporting not having water in the last month. The vaccine coverage was within the acceptable range to provide prevention and stop infection transmission. However, there is need to strengthen Water, Sanitation and Hygiene interventions across all the counties in addition to oral cholera vaccine in order to control cholera and reduce deaths.

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LABORATORY EVALUATION OF THE IS2404 LAMP TEST FOR LABORATORY DIAGNOSIS OF BURULI ULCER DISEASE

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Buruli ulcer, caused by Mycobacterium ulcerans has emerged as an important public health problem in several rural communities in sub-Saharan Africa. Early diagnosis and prompt treatment are important in preventing disfiguring complications associated with the late stages of the disease progression. Presently there is no simple and rapid test that is appropriate for early diagnosis and use in low-resource settings where M. ulcerans is most prevalent. The study aimed to evaluate the use of crude DNA extract and the IS2404 LAMP test for rapid diagnosis of Buruli ulcer. We evaluated the LAMP method for detecting M. ulcerans in clinical specimens by investigating its performance with IS2404 PCR, a reference assay for detecting M. ulcerans. The effect of using crude and purified DNA extracts on the performance of the IS2404 LAMP test was also investigated. Seventy-five clinical samples from suspected BU cases were examined by LAMP and IS2404 PCR. A total of 49 positive samples were concordantly detected by both the LAMP and PCR tests. Additional two positive samples were detected by IS2404 PCR for which the IS2404 LAMP tests were negative. Also, both methods concordantly scored 24 samples as negative for Buruli ulcer while the LAMP assay discordantly scored two additional negative results. Taking the PCR results as a reference, the sensitivity and specificity of the LAMP test were 96.1% and 100% respectively. The lower detection limit of both the IS2404 LAMP and IS2404 PCR tests was 30 copies of IS2404. Nine of 30 samples were positive by both the IS2404 LAMP and IS2404 PCR when crude extracts of clinical specimens were used. Thus, the diagnostic sensitivity of the IS2404 LAMP test decreased with the use of crude DNA extract. In conclusion, the IS2404 LAMP test performed on purified DNA extracts d can be used as a simple and rapid test for the diagnosis of Buruli ulcer.

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PHENOTYPIC CARBAPENEMASE DETECTION ADAPTED FOR RESOURCE CONSTRAINED SETTINGS

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WHO has estimated that by 2050 as many as 10 million people will die annually due to antimicrobial resistance. Carbapenems are broad-spectrum antibiotics often used as a last line of defense for resistant gram-negative bacterial infections. Resistance to carbapenems from transmissible carbapenemase enzymes is on the rise, though the scale of this issue in many locations remains unclear due to high costs and complexity of current testing methods. We modified the Carba NP phenotypic assay to quickly and economically differentiate the three classes of carbapenemases. Varied antibiotic concentrations, indicator solutions, and reaction volumes were evaluated in an iterative manner to adapt existing 'Carba NP test II' chemistry to a low-volume, plate-based format to objectively measure absorbance on various plate readers. Reaction speed and capacity to differentiate KPC, NDM, and OXA-48 enzymes (class A, B and D enzymes, respectively) were evaluated to optimize detection at ambient temperature, without dedicated incubation at 37°C. Changes in absorption at 560nm in the phenol-red-imipenem indicator solution were consistently observed before visible color change. Compared to the Carba NP version II, reliable results were obtained at ambient temperature with 3mg/mL of imipenem (vs. 6 mg/mL), 2 µL of bacteria (vs. 20µL), reaction volumes of 40µL (vs. 130 µL), and in 15 minutes (vs 2 hours). Three patients at Emory University Hospital with carbapenem-resistant gram-negative bacterial infections had positive cultures tested using the modified assay. All patients were found to have Class A (e.g., KPC) carbapenemase-producing bacteria within 15 minutes. In one patient, the emergence of a carbapenemase-producing bacteria while on systemic antibiotic therapy was observed. The modified Carba NP developed in this study is a rapid and economical method to screen for carbapenemases and is adaptable for use in resource constrained areas to inform clinical care and mitigate transmission in healthcare settings. Furthermore, the platform could be adapted to detect resistance to other key antibiotics, such as ceftriaxone resistant Salmonella typhi.

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MOLECULAR CHARACTERIZATION OF EXTENDED SPECTRUM BETA-LACTAMASES (ESBLS) -PRODUCING KLEBSIELLA PNEUMONIAE AND ESCHERICHIA COLI ISOLATES FROM THE WESTERN REGIONAL HOSPITAL IN GHANA

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Extended spectrum beta-lactamases (ESBLs) are plasmid-mediated enzymes that hydrolyze beta-lactams except carbapenems and cephamycins but are inhibited by beta-lactamase inhibitors. Majority of ESBL plasmids also contain genes that confer resistance to a variety of non-beta-lactam antimicrobials. As a result, ESBL-producing isolates limit therapeutic options, contribute to treatment failure, increase morbidity and mortality, prolong hospitalization, and raise healthcare costs. This study determined antimicrobial resistance profiles and the presence of antibiotic resistance genes in K. pneumoniae and E. coli isolates from the Western Regional Hospital in Ghana. A total of 120 archived isolates recovered from blood, urine, wound, pleural aspirate, high vaginal, ear, and urethral swabs were used in the study. The Kirby Bauer agar disc diffusion method was used to determine the antimicrobial susceptibility profiles of the isolates. Multidrug-resistant strains were phenotypically screened for ESBL production by the double disc synergy test. All isolates with ESBL phenotypes were screened for blaTEM, blaSHV, and blaCTX-M genes by PCR. Very high resistance was observed for ampicillin (78.4%), cefazolin (59.3%), SXT (56.5%) and tetracycline (56.3%). Fairly high resistance was observed for nalidixic acid (46.4%), chloramphenicol (45.4%), cefpodixime (43.2%) and Cefuroxime (42.4%). Very low resistance was observed for imipenem (2.4%), doripenem (4.1%) and cefepime (4.2%) based on the CLSI inhibition zone size interpretation criteria (CLSI, 2012). Forty-two (34.7%) of the 120 isolates phenotypically expressed ESBLs. Of these, 33 (27.9%) were pure ESBLs and 8 (6.8%) were putative ESBL producers. Overall, 62.7% (n=69/110) of the ESBL genotypes expressed CTX-M types 1, 2 and 9 genes and followed by 60% (n=24/40) harbored in TEM (n=7), SHV (n=5), and OXA-1 (n=12) genes. The study showed a relatively high

level of ESBL-producing isolates at the Regional Hospital, largely the CTX-M type and underscores the need to routinely detect ESBL phenotypes and implement appropriate antimicrobial stewardship policies in health facilities.

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IN SITU GROWTH OF ZIF-67 ON HALLOYSITE NANOTUBES EMBEDDED IN CHITOSAN HYDROGEL FOR THERAPEUTICS IN PARASITIC INFECTIONS

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Reconstruction for major bone defects caused by trauma, tumors and other diseases is a persistent clinical challenge. A successful bone treatment must take into account a number of factors, including the stability of the materials, stable microenvironments, an ample blood supply, and sufficient osteogenic activity. Finding biomaterials is thus required to assist the surgery to be completed. As a potential tactic, hydrogels could offer an internal environment with adequate moisture, comparable to natural extracellular matrices (ECMs). In this study, we synthesize a novel kind of nanocomposite hydrogel film by growing ZIF-67 nanoparticles in-situ on halloysite nanotubes (HNTs), which were then combined with chitosan matrix for biomedical application. Then, FT-IR, UV-DRS, XRD, and HRSEM were used to characterize the synthesized materials. Halloysite nanotubes added to hydrogel significantly improved its thermal and mechanical properties. Gram-positive and gram-negative bacteria were used to test the antimicrobial effectiveness of hydrogel, and the results showed that hydrogel film had maintained its strong antibacterial activity. The haemolysis assay demonstrated the haemocompatibility of the fabricated hydrogel film. Based on the research, it was concluded that fabricated hydrogel film could be applied for biomedical application.

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ADHERENCE AND ACCEPTANCE OF ORAL AMOXICILLIN DISPERSIBLE TABLET FOR THE TREATMENT OF SICK CHILDREN IN KARACHI, PAKISTAN

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World Health Organization's Integrated Management of Childhood Illnesses (IMCI) guidelines suggest the use of amoxicillin for treatment of young infants with signs of Possible Serious Bacterial Infection (PSBI) where referral is not possible and for treatment of pneumonia in young infants and children. The suspension form of amoxicillin has been widely used for years; however, dispersible tablets (DT), a more user-friendly form of amoxicillin has been introduced in recent years. Experience from countries like Pakistan show mixed acceptance of DT formulation however adherence have been found to be better than oral suspension. In a cohort study of 535 caregivers presenting to primary healthcare centers in peri-urban Karachi, Pakistan children aged up to 5 years old were prescribed DT of Amoxicillin. Data was collected on day 8 of treatment with Amoxicillin DT. Frequencies and percentages are reported for responses. Mean age was 25 months (SD 18 months), indications included lower respiratory tract, ear and skin infections etc. At the time of prescription, 509 (98%) of mothers had never used dispersible tablets but 344 (69%) mothers thought that babies younger than 6month can easily be given DT. Post treatment, 383 (78%) mothers preferred Amoxicillin DT over Amoxicillin suspension for the following reasons: dissolves easily 423 (80%), can be stored without refrigerator 217 (41%), no special care needed for storage 310(59%), easy to understand dosage 229 (50%), freshly prepared medication every time 180 (34%), easy to store remaining tablets in blister packs 195 (37%), tastes better than suspension 264 (50%), and easy to carry during travel 151(28%). Very few complained about using DT form. Parents showed good adherence and acceptance of dispersible tablets. DT formulations can be introduced for general use in community settings.

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GROUP B STREPTOCOCCUS ACUTE SUPPURATIVE PAROTITIS IN A YOUNG INFANT

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Acute suppurative parotitis is a rare condition in young infants aged 0-59 days. It is characterized by swelling of parotid glands, fever, and pain, caused by drainage of pus into the oral cavity from the Stensen duct. Staphylococcus aureus is the most common organism while other gram-positive and gram-negative organisms are also documented. Prevalence is higher in male gender. In this report, we describe the case of a 55-day-old preterm young infant, previously healthy, admitted in the emergency department of The National Institute of Child Health, Karachi, Pakistan with complain of fever, reluctance to feed, and irritability with unremarkable general and oral physical examination. On second day of hospitalization, pre-auricular edema was observed bilaterally close to the angle of the jaw along with signs of inflammation, greater on the right side. Ultrasound findings showed bilateral parotid gland enlargement. Lab investigations showed neutrophilia with left shift and thrombocytosis, raised C reactive protein and positive blood culture for Streptococcus Pyogenes. Empiric antibiotic therapy was initiated with injection Ampicillin and Gentamicin and adjusted with Injection Meropenem when culture reports were available. The infant showed steady improvement of symptom and swelling after 48 hours of treatment and got discharged after 7 days. The repeat ultrasound done on 10th day after diagnosis which was normal, with resolved parotid swelling. This case illustrates the need for consideration of disease among young infants and its likelihood in both genders. It also emphasizes on the early institution of appropriate therapy of acute suppurative parotitis for faster recovery and prevention of complications. Furthermore, there is a need to investigate the causes and treatment of this disease in infants and should be considered as a differential diagnosis within this age group.

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EPIDEMIOLOGICAL BEHAVIOR OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) AT THE END OF THE COVID 19 PANDEMIC IN A HEALTH CARE CENTER IN MONTERÍA-COLOMBIA

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The epidemiological behavior of methicillin-resistant Staphylococcus aureus (MRSA) has been a major concern in healthcare centers worldwide. With the end of the COVID-19 pandemic, there has been an increased focus on other antibiotic-resistant pathogens, including MRSA.In Montería, Colombia, MRSA has been a constant problem in healthcare centers. With the COVID-19 pandemic, there has been an increase in demand for medical attention, which has increased the risk of MRSA transmission. Additionally, infection control measures, such as physical distancing and quarantine, may have been relaxed in some healthcare centers due to the need to prioritize care for COVID-19 patients. MRSA is a bacterial pathogen that is resistant to multiple antibiotics, making it difficult to treat. Moreover, it is highly contagious and can spread rapidly in healthcare settings if adequate infection control measures are not implemented. Therefore, the epidemiological behavior of MRSA at the end of the Covid 19 pandemic was evaluated in a health care center in Monteria, Colombia, during the period 2020-2022.A retrospective study was carried out, in which the records of bacterial isolates obtained in the different services of the health care center during the years 2020 and 2022 were consolidated. The biochemical identification tests and the definition of the antimicrobial susceptibility profiles for the isolated bacteria were performed with the automated MicroScan® system. An increasing prevalence of MRSA was found in the health care facility by year as follows: 2020 (9%), 2021 (51%) and 2022 (67%). In addition, the majority of MRSA cases were found to be acquired in the health care facility, suggesting that outbreaks were occurring in the health care facility.In conclusion, MRSA continues to be a major problem in health care facilities in Monteria, Colombia, and an increase in

the number of cases has been observed during the COVID-19 pandemic. It is important to implement adequate infection control measures to prevent and control the spread of MRSA in health care facilities.

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ISOLATION AND MOLECULAR IDENTIFICATION OF A STRAIN OF PSEUDOMONAS AERUGINOSA XDR (EXTENSIVELY DRUG RESISTANT) IN POLYTRAUMA PATIENTS IN MONTERIA, COLOMBIA

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Pseudomonas aeruginosa is a Gram-negative bacterium commonly found in the environment and in hospitals. Although some strains are harmless to humans, others can cause serious infections, especially in patients with compromised immune systems. P. aeruginosa strains that are extremely resistant to multiple antibiotics are called XDR (Extensively Drug Resistant). The aim of this study was to report the isolation and identification of a P. aeruginosa XDR strain in patients with polytrauma attended at a health center in the city of Monteria.Samples were taken from patients with polytrauma attended at a health center in the city of Monteria. The samples were processed in the microbiology laboratory by culture techniques and the P. aeruginosa XDR strain was identified by biochemical and antimicrobial sensitivity tests. Molecular identification of the strain was performed by PCR.A P. aeruginosa XDR strain was identified in four polytrauma patients. The strain showed resistance to multiple antimicrobials, including carbapenemics, making it a high public health risk strain. Molecular identification confirmed the presence of the strain.The report of the isolation and identification of a strain of P. aeruginosa XDR in patients with polytrauma is important from a public health point of view because this bacterium is known for its ability to resist multiple antibiotics, which makes it a threat to the health of the general population, especially for those who are hospitalized or who have weakened immune systems.In this sense, it is essential to take preventive measures to avoid the spread of the bacterium, such as infection control in health centers, training of health personnel in the proper management of infected patients and the implementation of epidemiological surveillance protocols for the early detection of infections. In addition, strategies for the appropriate use of antibiotics should be promoted to avoid the development of bacterial resistance.

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MYCOBACTERIUM LEPRAE ANTIGEN-SPECIFIC ANTIBODY PROFILING AND CYTOKINE ANALYSES REVEAL UNIQUE SIGNATURES OF LEPROSY AS WELL AS IMMUNE CHANGES WITH SCHISTOSOMA MANSONI CO-INFECTIONS

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The lack of commercially available laboratory tests for conclusive early diagnosis of leprosy has motivated the search for novel methods for accurate diagnosis and characterization of disease states. In addition, helminth infections appear to be associated with leprosy but immune mechanisms underlying these associations are not clear. We have developed a multiplexed 'Ab-omics' platform for deep biophysical characterization (both Fab & Fc ends) of a broad set of antigen-specific Abs including not only their isotype and subclass but also glycosylation and Fc receptor binding. Here, we apply the Ab-omics pipeline to sera from patients (n=35, from Minas Gerais, Brazil), clinically diagnosed with leprosy, using multiple Mycobacterium leprae antigens (Ag85B, GroES, Bacterioferritin, CFP-10, ML2567, PGL-1). Antigen-coated barcoded beads were incubated with serum and probed with various fluorescently labeled isotype and subclass probes, tetramerized Fc receptors and lectins. A feature selection model LASSO was used to identify biomarkers for leprosy. For T-cell mediated immune response, M. leprae stimulated PBMC were analyzed for cytokines and chemokines by flow cytometry. LASSO was able to identify signatures that distinguish leprosy+ and leprosy- samples with an AUC of 0.75. We also found statistically significant stronger FcR3A and FcR2B binding for the ML2567; stronger IgG, IgG2, FcR2A binding for GRoES; and stronger binding for FcR2A, FcR3B, IgG3 for the ML LAM in leprosy (without coinfection) compared to individuals without leprosy. T-cell response analyses revels higher TNF-α and CXCL8 associated with co-infection; IL17 and IFN-γ lower in co-infection. These immune profiles not only distinguish leprosy from non-leprosy but also suggest an impact of Schistosoma mansoni co-infection on both cell-mediated and humoral immunity. In addition, this Ab-omics approach can lead to discovery of biomarkers that complement clinical diagnosis as well as increase our understanding of the role of helminth co-infections in the susceptibility of clinical leprosy.

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MAPPING CHOLERA HOTSPOTS IN THE ELIMINATION PROCESS IN CAMEROON, 2016-2022

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According to the "Ending Cholera: A Global Roadmap to 2030" initiative of the Global Task Force for Cholera Control (GTFCC) in which Cameroon was enrolled, one of the requirements for identified countries is to have an updated map of their hotspots for prioritization of elimination actions, hence the objective of this study to identify cholera hotspots in Cameroon. We conducted a retrospective study of cholera data from the 10 regions of Cameroon with risk analysis carried out over a period of 06 years from January 2016 to December 2021. A 5-step approach was used. A preliminary mapping based on calculation of the relative burden of disease according to WHO threshold calibration was done. A second mapping used the vulnerability criteria, namely: geographical accessibility, hygiene and sanitation, movement of people, access to drinking water and geographical location. The third prioritization was made by integrating the first two. A final prioritization and mapping were obtained after reviewing the vulnerability criteria with joint national experts. A classification of districts included "low priority (LP)", "medium priority (MP)" or "high priority (HP)". Data were extracted from DHIS2 and MAPE forms; GTFCC guideline and additional EXCEL-developed data tools were used to analyze vulnerability criteria and enable risk classification. QGIS software was used to present Health district (HD) hotspot prioritization. The years 2019 and 2020 recorded the highest number of cases with 1931(35.2%) and 1895(34.5%) respectively. There was a drop in the number of cases in 2017 (from 78 to 22) after which, an exponential increase in cases with a peak in 2019 (1931 cases). Mapping identified 101 (53%) priority HDs, of which 29 (15%) were of high priority, bringing the percentages of at-risk population to 63.3%. The Far North, North, South West, Littoral regions had respectively the highest number of hotspots, i.e. 73(72%). The North and Littoral regions have the largest number of HP HDs, respectively 11(39%) and 6(20.7%). We recommend taking into account the prioritization of hotspots for the elaboration of the cholera elimination strategic plan of Cameroon.

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DESERT SORES: THE SCOURGE OF THE SAS "ROGUE HEROES" IN NORTH AFRICA, 1941-1943

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"Desert Sores: The Scourge of the SAS 'Rogue Heroes' in North Africa, 1941-1943" Ben Macintyre's 2017 book, Rogue Heroes, has sparked renewed interest in the operations of Special Air Service (SAS) personnel in the North African Campaign. Their unit became famous for swift, highly mobile raids on Italian and German posts along the Mediterranean coast throughout 1942. Their attacks, carried out on twin machine gun-kitted jeep laden with four well-armed men, played a significant role in the defeat of the Axis in North Africa. Desert life, however, took a physical toll on the SAS units. "Desert sores," vividly featured in an episode of the Netflix television series based on Macintyre's historical account, became a particular problem. Unable to bathe with any regularity, many men developed these painful ulcerated lesions. In severe cases, they became physically debilitating. Their precise aetiology, however, remained unclear. Was it a pathogen? If so, was it a bacterium or a parasite of some kind? Perhaps it was virtual absence of personal hygiene and chronic skin irritation the sand caused? What therapy worked best? It was not until the end of WWII that these puzzling questions were satisfactorily solved. This presentation, relying heavily on biomedical sources and historical accounts from WWII, will trace the evolution of the desert sores debate among British troops in North Africa. More specifically, it will examine their impact on SAS operations. The evolution of this debate reveals as much about competing schools of thought in tropical medicine as it does about the ever-expanding field of 20th-century microbiology.

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MULTIFACETED REALITIES OF SCRUB TYPHUS: A CASE SERIES FROM SOUTHERN INDIA

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Scrub typhus is an acute febrile illness caused by Orientia tsutsugamushi, a gram-negative bacillus commonly occurring in Asia- Pacific region. It is transmitted to humans by the bite of an infected Leptotrombidium mite which then causes vasculitis with endothelial dysfunction resulting in widespread vascular damage. Scrub typhus is a serious disease that can cause a range of complications, including thrombocytopenia, meningitis, acute respiratory distress syndrome, and, rarely, myocarditis, underscoring the importance of early diagnosis and prompt treatment. We examine four cases of scrub typhus and review the literature to emphasize the importance of considering scrub typhus in patients of all age groups from endemic areas presenting with fever, thrombocytopenia, or transaminitis, regardless of typical clinical features. The characteristic lesion at the site of mite feeding, eschar, was present in two cases. Fever and thrombocytopenia or transaminitis were commonly noted. One of the cases involved a middle-aged woman who was diagnosed with typhus-induced myocarditis. ECHO showed global hypokinesia of the left ventricle, grade 3 left ventricular diastolic dysfunction and an ejection fraction of 30%. Post-treatment ejection fraction improved to 64%. In addition, a 23-day-old neonate with poor feeding and seizures was diagnosed with late-onset sepsis with meningitis due to bacteremia, confirmed by a lumbar puncture showing neutrophilic predominance. In all cases, scrub typhus was confirmed with a positive qualitative IgM ELISA. Though quantitative and paired titers are preferred, due to resource limitations, single qualitative titers were performed at the time of hospital admission. This case series demonstrated marked responses to doxycycline. It is important that healthcare providers evaluate the patient's exposure history, along with clinical presentation, to diagnose scrub typhus. Confirmation of the diagnosis is typically done through serological testing.

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THE UNIVERSAL VITAL ASSESSMENT SCORE PREDICTS MORTALITY IN PATIENTS WITH COVID-19 IN RWANDA

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COVID-19 ranges from asymptomatic infection to the acute respiratory distress syndrome (ARDS). There are few data regarding clinical outcomes from COVD-19 from low income countries (LICs), including Rwanda. Accordingly, we aimed to determine 1) outcomes of patients admitted to hospital with COVID-19 in Rwanda, and 2) the ability of the Universal Vital Assessment (UVA) score to predict mortality. We conducted a retrospective study of patients aged ≥ 18 years hospitalized with laboratory confirmed COVID-19 at the University Teaching Hospital of Butare (CHUB), Rwanda from May-October 2021. For each subject, we calculated the UVA mortality risk score, which has been previously validated in patients hospitalized in sub-Saharan Africa. We used logistic regression to determine predictors of mortality and considered $P<0.05$ to be significant. Of the 150 patients included, 83 (55%) were female and the median (IQR) age was 61 (43-73) years. The median (IQR) of length of stay was 6 (3-10) days. Hypertension was identified in 36 (24%) of 150 and was the most common comorbidity. Respiratory failure occurred in 69 (46%) of 150 including 34 (23%) who developed ARDS. The case fatality rate was 44%. Factors independently associated with mortality included acute kidney injury (aOR 7.99, 95% CI 1.47-43.22, p=0.016), COVID-19 severity status (aOR 3.42, 95% CI 1.06-11.01, p=0.039), and the UVA score (aOR 7.15, 95% CI 1.56-32.79, p=0.011). The UVA score at admission had good discrimination for mortality with an area under the receiver operating characteristic curve of 0.85 (95% CI 0.80-0.92). At a UVA score cut-off of 4, the sensitivity, specificity, positive predictive value, and negative predictive value for mortality were 57.58%, 92.85%,86.36% and 73.58% respectively. Patients admitted to CHUB with COVID-19 had high mortality, which was predicted by the UVA score. Calculation of the UVA score in patients with COVID-19 in LICs may assist clinicians with triage and other management decisions.

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THE PREVALENCE OF MENSTRUAL DYSFUNCTION FOLLOWING COVID-19 INFECTION IN THAILAND

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There is a lack of information in the literature describing menstrual dysfunction following infection with COVID-19. A recent systematic review found 12 studies evaluating menstrual cycle changes during the pandemic; only 3 specifically assessed the impact of infection. This case series aims to assess the prevalence and nature of menstrual changes following COVID-19 infection in Thailand. Ninety-six participants were recruited to the study. All had received inpatient care for COVID-19 at MedPark Hospital in Bangkok, Thailand. They completed a survey including menstrual history before and after illness. Basic demographic data and COVID-19 test results were collected from electronic patient records. To analyse menstrual disruption, we reviewed a subset consisting of female patients under the age of 50. Of 96 patients, 60 (62.5%) were female, of which 44 (73%) were under 50 years old. Mean age under 50 was 31.8, with a range of 15-47 years. Six (13.6%) reported menstrual dysfunction prior to COVID-19 infection; 38 (86.4%) reported no previous dysfunction. After infection, 11 (25%) reported a change in their menstruation, 6 of whom had

previously regular periods; 25 (56.8%) reported no menstrual dysfunction; and 8 (18.2%) were pregnant. Reported changes include irregular cycles or missed periods (n=5); shorter duration (n=3); heavy bleeding (n=2); and longer duration (n=1). This observational study found that while the majority of participants reported no menstrual disturbance following covid-19 infection, a proportion (11, 25%) reported a change. The nature of menstrual dysfunction was varied, with irregular/missed cycles and shorter cycles most common. Other studies with larger sample sizes have indicated that lighter bleeding and a prolonged cycle are commonly reported. Eight (18.2%) participants reported pregnancy. Although a small sample size, this suggests that short-term fertility was not affected in these women. Larger samples and prospective data collection will be valuable to further explore the impact of COVID-19 infection on menstruation patterns and its implications for patients.

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PATTERNS AND PREDICTORS OF MORTALITY WITHIN THE FIRST 24 HOURS OF ADMISSION AMONG CHILDREN AGED 1-59 MONTHS AT A REGIONAL REFERRAL HOSPITAL IN SOUTH WESTERN UGANDA

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Most deaths among children under 5 years occur within the first 24 hours of hospital admission from preventable causes such as diarrhea, pneumonia, measles, malaria, and HIV/AIDS. This is worsened by socioeconomic factors such as delays seeking health care, delayed interventions, financial limitations, unavailability of life-saving equipment, and inadequate support services. The demographic and clinical predictors of death within 24 hours of hospital admission are not yet well documented in our setting. This study aimed to describe the patterns and predictors of mortality within the first 24 hours of admission among children aged 1-59 months admitted at Mbarara Regional Referral Hospital. We conducted a prospective cohort study among 208 children aged 1-59 months admitted at the Mbarara Regional Referral Hospital. Participants were consecutively enrolled and pre-hospital, clinical, and laboratory factors that predicted their mortality within 24 hours of in-hospital admission were studied. Patterns of mortality were described using proportions, means and median and statistical analysis of predictors of mortality was done using multivariate regression. The mortality rate within the first 24 hours of admission was 7.7% (16), the median time to death was 7 hours and death was higher among infants. Severe pneumonia, severe acute malnutrition, and malaria accounted for 26.4%, 23.5%, and 11.5%, respectively of deaths. Admission during the night (p-value 0.047, AHR 3.7 (95% CI 1.02-13.53)) and having an abnormal neutrophil count (p-value 0.034, AHR 3.5 (95% CI 1.10-11-31) were predictive of mortality. The most common causes of death within 24 hours of admission are pneumonia and severe acute malnutrition. The mortality rate was higher among infants <12 months (9, 56.2%) than older children (7, 43.8%). Children who are admitted at night or have an abnormal neutrophil count should receive extra monitoring and interventions due to a higher risk of mortality within 24 hours of admission.

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RECONSTRUCTIVE SURGERY FOR THE NEGLECTED TROPICAL DISEASES (NTDS): GLOBAL GAPS AND FUTURE DIRECTIONS

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Several neglected tropical diseases (NTDs) are highly disfiguring, particularly those in resource-poor countries that lack access to basic surgeries. There has been a push to integrate surgeries into treatment programs for NTDs. In this paper, we provide an overview of the major disfiguring NTDs and discuss the processes and barriers that impede access to reconstructive surgical treatments or their integration into health systems. A review of the literature was conducted using the online database PubMed from 2008 to 2021 with the specific diseases listed as neglected tropical diseases either on the World Health Organization (WHO) or the PLoS Neglected Tropical Disease Web sites. Reference lists of identified articles and reviews were also searched, as were databases from the WHO's Weekly Epidemiological Record. Success in the surgical treatment and post-operative care of disfiguring NTDs would benefit from standardization and harmonization of surgical approaches and procedures. In some settings, reconstructive surgery should be used cautiously, emphasizing appropriate use of antibiotics, partnerships with global and local surgical teams, and local capacity building. Preventative hygiene approaches remain paramount in resource-poor areas. In conclusion, surgery is a promising treatment for NTDs that result in disfigurement and disability. The expansion of local capacity building, with medical trips and surgical training of local health workers, together with the development of universal surgical protocols remain essential cornerstones for NTD reconstructive surgery. Antibiotics and drug management should comprise key first steps before turning to surgery.

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PATTERN OF OCCURRENCE, CLINICOPATHOLOGICAL PRESENTATION AND MANAGEMENT OF SALIVARY GLAND TUMOURS AMONG PATIENTS ATTENDING MUHIMBILI NATIONAL HOSPITAL, TANZANIA

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Tumours of salivary glands form one of most heterogeneous groups of lesions accounting for 2.8% and 10% of all head and neck tumours. The tumours have overlapping clinical and histological characteristics of benign and malignant salivary gland tumours which results in difficulty in diagnosis which mostly require experienced personnel. Delay in presentation has led to challenging management and poor outcomes. Authors set out to investigate pattern of occurrence, clinicopathological presentation and management of salivary gland tumours in Tanzania. A descriptive prospective hospital-based study was conducted at Muhimbili National Hospital between May 2021 and April 2022. Patient interview was conducted by investigator enquired about the socio-demographics main complaint(s), associated symptoms and examination findings. Tissue biopsies which were taken from all patients for histological investigation for diagnosis confirmation. Surgical and post-operative histology details were recorded. Data entry, cleaning, coding and analysis were done by using the SPSS 23.0 software. Ethical clearance was sought from the Ethical Board of MUHAS. A total of 597 patients with head and neck tumours were seen and among these, 63 patients were diagnosed with salivary gland tumours making prevalence of 10.56%. Majority (68.3%) of patients had salivary gland cancers, and most of patients (73%) first sought health care more than 3 months after initial symptom. Main reason for delay was neglect (41.3%). All benign salivary gland tumours were pleomorphic adenomas while adenoid cystic carcinoma was most common salivary gland cancer (39.5%). Patients with salivary gland cancers presented with ulcerated lesions, bleeding, tender, indurated, fixed to underlying structures, paraesthesia and facial nerve paralysis. Surgery was done on 46.5% of patients and the remaining were treated by palliative chemoradiotherapy. In conclusion, salivary gland cancers presented in late stages associated with patient's poor healthcare-seeking behaviour leading to treatment delays more palliative than curative therapy

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AETIOLOGY OF ACUTE UNDIFFERENTIATED FEBRILE ILLNESS AT A TERTIARY CARE CENTRE IN EASTERN UTTAR PRADESH, INDIA

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Acute undifferentiated febrile illness (AUFI) a common presenting complaint, can cause significant mortality and morbidity if left undiagnosed. There is a regional variation in the aetiology of AUFI. Moreover, similarity in the symptoms makes an accurate clinical diagnosis difficult without laboratory confirmation. Thus, this study was done to identify the common aetiology of AUFI at a tertiary care centre in Eastern Uttar Pradesh, India. This cross-sectional study was conducted in SSL Hospital, Banaras Hindu University, Uttar Pradesh, India, between May 2021 and May 2022. All adult patients presenting with fever <14 days without any localizing sign were included in this study. ELISA tests were performed on all samples by Leptospira IgM ELISA, Chikungunya IgM ELISA, Scrub Typhus IgM ELISA , DENV IgM Capture ELISA, as per the manufacturer protocol. During the study period, 121 patients admitted with AUFI were included in the study. The most common aetiology found was Dengue comprising 41 (33.88%) of the total AUFI patients whereas 22/41 patients were found positive for dengue alone and rest were having co-infection in which Scrub Typhus was the most common co-infection. Second most common aetiology were Leptospirosis and Scrub Typhus comprising 29 (23.96%) patients each whereas 8/29 patients were positive for Leptospirosis alone and Scrub Typhus alone was positive in 10/29 patients. Remaining 21/29 patients of Leptospirosis had co-infections majorly of scrub typhus. Whereas in the remaining 19/29 patients of Scrub typhus, the most common co-infection was Leptospirosis. The patients found positive for Chikungunya were 9(8.49%) whereas only 6 were positive for Chikungunya only. Remaining 3 patients were having double co-infection of Scrub Typhus along with Leptospirosis. There were 13(10.74%) patients not found positive for any of the aetiology stated above and needed further clinical investigations. The most common cause of AUFI was viral. Availability of cost-effective serological test for dengue, scrub typhus and leptospirosis at primary health care setting would lead to early diagnosis and effective management of AUFI in this region.

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IMPROVING THE REPEATABILITY OF A QUANTITATIVE G6PD POINT-OF-CARE DIAGNOSTIC THROUGH VARIATION OF TEST PROCEDURES

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymopathy worldwide and the main risk factor for 8-aminoquinoline (8AQ) induced haemolysis. The introduction of novel, short course, 8AQ-based treatment regimens for the radical cure of Plasmodium vivax (P. vivax) presents a good opportunity for more effective P. vivax control, however, widespread use will require stringent G6PD testing at the point-of-care (PoC). Diagnosing heterozygous women with intermediate G6PD activity at the PoC requires a quantitative G6PD measurement. In a controlled laboratory setting, the quantitative PoC diagnostic G6PD Standard (SD Biosensor, ROK) has good repeatability, however, anecdotal evidence suggests that this may not be the case in real-life settings. We assessed whether the repeatability of the G6PD Standard in real-life settings can be improved by varying test procedures. In a pilot study conducted in Australia, G6PD activity was tested in three volunteers using four different test procedures and the standard method; two methods used capillary blood, and three methods used venous EDTA blood. Each volunteer was tested ten times pairwise with each method. The pilot study found that using venous blood with a modified pipetting method (blood is absorbed from the pipette to the test membrane rather than dispensed) improved the repeatability of the G6PD measurements. The median difference between paired readings was 0.3U/gHb (IQR: 0.2-0.4) for the novel method compared to 0.5U/gHb (IQR: 0.2-0.9) for the manufacturer-recommended method. However, subsequent field studies in Indonesia (n=60) and Nepal (n=120) found no significant improvement compared to the standard manufacturer-recommended method. The field study in Nepal is ongoing with more than 60% of participants enrolled to date. We found that the repeatability of the G6PD Standard can be improved by using venous instead of capillary blood. The use of venous blood rather than capillary blood may improve repeatability since the variation in blood collection procedures is reduced, though we could not consistently replicate this improvement in field settings.

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MISSED OPPORTUNITIES: SCREENING FOR CHAGAS DISEASE AND STRONGYLOIDIASIS IN LIVER AND KIDNEY TRANSPLANT RECIPIENTS BORN IN LATIN AMERICA

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Strongyloides stercoralis and Trypanosoma cruzi are common chronic parasitic infections in U.S. residents born in Latin America. Although immunocompetent individuals are often asymptomatic, patients receiving iatrogenic immunosuppression can develop life-threatening complications from disseminated strongyloidiasis and T. cruzi reactivation. We evaluated pre-transplant screening practices in liver and kidney recipients with epidemiologic risk factors for both parasites. We retrospectively identified all Hispanic/Latinx adult liver or kidney transplant recipients at MedStar Georgetown University Hospital in Washington, DC from January 1,2019 to December 31,2021. We included only patients born in Mexico, Central or South America. We recorded demographics, transplant characteristics, diagnostics, antiparasitics, and whether infectious disease (ID) consultation was performed. Sixty-five Latin-American born patients received transplants, including 8 (12%) from Mexico, 45 (69%) from Central America, and 12 (19%) from South America. Recipients from El Salvador accounted for 63%. Thirteen patients (20%) received Strongyloides screening, of which 2 (15%) tested positive. Liver recipients were more likely to be screened than kidney recipients (p<0.001). Eosinophilia was not associated with Strongyloides screening (p=0.09). Nine patients (14%) received T. cruzi screening, all with normal tests. There was no difference in screening based on the presence of EKG changes (p=0.1). All patients screened for T. cruzi or S. stercoralis had received pre-transplant ID consultation for an unrelated reason, most commonly latent tuberculosis infection. Despite epidemiologic risk factors, the majority of Latin-American born recipients of liver and kidney transplants at our institution did not receive pre-transplant Strongyloides or T. cruzi testing. Improved screening protocols based on geographic exposure history are needed to identify chronic parasitic infections prior to immunosuppression. Routine ID consultation for transplant candidates with prolonged residence abroad could increase screening uptake.

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RETROSPECTIVE EPIDEMIOLOGICAL STUDY ON THE EFFECTIVENESS OF VISCERAL LEISHMANIASIS TREATMENT PROTOCOLS AND RISK FACTORS FOR RELAPSE IN TIATY EAST AND TIATY WEST SUB-COUNTIES, KENYA

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This project seeks to determine the effectiveness of current treatment protocols for visceral leishmaniasis (VL) in Tiaty East and Tiaty West Sub-counties, Kenya, and identify risk factors for relapse. The 2017 Republic of Kenya Ministry of Health's Guidelines for Prevention, Diagnosis, and Treatment of Visceral Leishmaniasis require patients to undergo follow-up examination six months after completing treatment to determine final cure, relapse, death, or loss to follow-up as well as assess for Post Kala-azar Dermal Leishmaniasis (PKDL). However, due to situational difficulties including lack of transportation, distance to health facilities, poverty, and low health-seeking behavior, follow-up is rarely done leading to a large gap in long-term treatment effectiveness data. Few studies have been done on VL relapse, but the rate has been shown to be between 1.4% and 14.4% globally with much higher rates in Eastern Africa. No study has been done on VL follow-up in Kenya with current treatment protocols. This study was conducted at Chemolingot Sub-county Hospital (CSCH) in Baringo, Kenya during February and March 2023 on patients living in Tiaty East and West that were treated before August 2022 at CSCH and Kimalel Health Centre. Patients were tracked down using contact information from medical records and Community Health Volunteer searches and referrals. Patients received a follow-up examination from a clinician including history taking, physical examination, and hemoglobin level to assess for the above outcomes. Compensation for the cost of travel to the health facility was provided. Preliminary results of 18 patients show all patients as fully cured. Preliminary analysis of relapse cases from medical records at CSCH show a low relapse rate as well, but further conclusions about relapse rate and risk factors cannot be drawn before formal analysis. From preliminary data, current treatment protocols in Kenya appear to be effective. Given the upcoming change to a new drug combination and shorter treatment period, study results should be compared to future treatment protocol follow-up data.

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IMPLEMENTING LABORATORY QUALITY MANAGEMENT SYSTEMS IN GHANA - A BASELINE QUALITY AUDIT OF ACCREDITATION READINESS IN LOWER-TIER HEALTH FACILITIES

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In the last decade, the implementation of the Stepwise Laboratory Improvement Process Towards Accreditation (SLIPTA) in Africa has targeted laboratory performance to characterize error and improve patient safety but often targets the highest-tier laboratories. The current study implemented a SLIPTA quality audit in a representative sampling of Ghanaian health facilities. An audit using a modified SLIPTA checklist was carried out in health facilities randomly selected within districts stratified by ecological zone, remoteness from zonal Laboratories, and population density. The audit was conducted in regional and district hospitals, polyclinics, and sub-district facilities from February 2021 to July 2022. The Wilcoxon rank sum test and quantile regression were used to characterize the associations between laboratory characteristics and SLIPTA scores. Forty-nine health facilities were audited with the majority in the public health sector (81.6%). Laboratories performed a median of 30 (Interquartile range: 10 – 90) tests daily, with 40.8% of facilities only performing point-of-care testing. The median SLIPTA score was 44.1% (Interquartile range: 24.0% – 56.7%) with hospitals recording the highest (55.9%). Of the 12 SLIPTA quality systems essentials, performance was highest in Organization & Personnel, and poorest in Client Management and Occurrence Management & Process Improvement. In multivariable regression, the median SLIPTA scores reduced for facilities located in the Northern zone [-21.5(95% CI=-31.7- -11.3; p<0.001)], compared to those in the Southern zone and also for facilities that performed only point-of-care testing [-18.2(95% CI=-31.6- -4.7; p<0.01)] compared to moderate to high complexity testing. The majority of the laboratories audited were yet to attain international accreditation readiness. Quality compliance was equivalent to 1 star for hospitals but lower for the other facility tiers. There is a need to conduct a root cause analysis for laboratory quality with commensurate policy changes to enhance performance.

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ASSESSMENT OF TREATMENT OUTCOMES OF HUMAN IMMUNODEFICIENCY VIRUS POSITIVES TRANSITIONED FROM TENOFOVIR/LAMIVUDINE/EFAVIRENZ TO DOLUTEGRAVIR REGIMEN COMBINATION IN A NIGERIAN TERTIARY HOSPITAL

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Due to the introduction of dolutegravir as a replacement for nevirapine or efavirenz in a fixed dose combination with Tenofovir/Lamivudine, as the preferred first-line option for the prevention and treatment of HIV infection, there is a need to assess the treatment outcomes of the new Tenofovir/Lamivudine/Dolutegravir (TLD) regimen in a Nigerian tertiary hospital. This retrospective study used data drawn from the treatment register of patients who transitioned from Tenofovir/Lamivudine/Efavirence (TLE) to TLD between January 2016 and January 2018. The data extracted were analyzed using SPSS statistical software version 20. Descriptive statistics were used to describe categorical and continuous variables. Chi-square test statistics was done to test for association between categorical variables and treatment outcomes and the level of significance was set at $p<0.05$. A total of 358 cases were reviewed. Their mean age was 44.29 ± 11.5 years and the majority 267 (74.6%) were females. Viral load suppression of ≤1000 copies/ml was achieved in 313 (87.4%) of cases while on TLE but increased to 339 (94.7%) when transitioned to TLD within the period of study. In addition, 36.3% had a high CD4 count while on TLE and this increased to 67.3% of those with high CD4 within the period of study. There was a statistically significant difference between the mean CD4 count while using TLE and then when transitioned to TLD (t=31.601; p-value-0.001). Treatment outcome was greatly improved in terms of virologic, immunologic, and clinical presentation among patients who transitioned from TDF/3TC/EFV to TDF/3TC/DTG in this study. The outcome of this study supports and encourages the use of TDF/3TC/DTG as the preferred first-line regimen in HIV treatment for the patient's maximum clinical benefit. This should be communicated to all stakeholders and policy-makers involved in the provision of effective healthcare service delivery in HIV management.

5575

IMPACT OF THE INTRODUCTION OF A PACKAGE OF DIAGNOSTIC TOOLS, DIAGNOSTIC ALGORITHM, AND TRAINING AND COMMUNICATION ON OUTPATIENT ACUTE FEVER CASE MANAGEMENT AT THREE DIVERSE SITES IN UGANDA: RESULTS OF A RANDOMIZED CONTROLLED TRIAL

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Increasing trends of antimicrobial resistance are observed around the world, driven in part by excessive use of antimicrobials. Limited access to diagnostics particularly in low- and middle-income countries contributes to diagnostic uncertainty which may promote unnecessary antibiotic use. We investigated whether introducing a package of diagnostic tools, clinical algorithm, and training and communication messages could safely reduce antibiotic prescribing compared with current standard of care for febrile patients presenting to outpatient clinics in Uganda.This was an open-label, multi-center, two-arm randomized controlled trial conducted at three public health facilities (Aduku, Nagongera, and Kihihi health center IVs), between September 2020 to August 2021, comparing the proportions of antibiotic prescriptions and of clinical outcomes for febrile outpatients aged one year and older. The intervention arm included a package of point-of-care tests, a diagnostic and treatment algorithm, and training and communication messages. Standard-of-care was provided to patients in the control arm. A total of 2400 patients were enrolled with 49.5% in the intervention arm. Overall, there was no statistically significant difference in antibiotic prescriptions between the study arms; relative risk (RR 1.030, 95% CI 0.958-1.108). In the intervention arm, patients with positive malaria test results had a higher RR of being prescribed antibiotics (1.742 [1.517-2.000]) while those with negative malaria results had a lower RR (0.683, [0.625-0.748]). There was no significant difference in clinical outcomes. This study found that a diagnostic intervention for management of febrile outpatients did not achieve the overall desired impact on antibiotic prescribing at three diverse and representative health facility sites in Uganda.

5576

PREVALENCE OF CHRONIC KIDNEY DISEASE IN A COHORT OF GUATEMALAN AGRICULTURAL WORKERS 2020-2022: THE AGRICULTURAL WORKERS AND RESPIRATORY ILLNESS IMPACT (AGRI) STUDY

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Chronic kidney disease (CKD) has recently been identified as a major public health concern in Central American agricultural workers and has been linked to physically stressful working conditions and dehydration. We measured estimated glomerular filtration rate (eGFR) annually from 2020-2022 among banana plantation workers in southwest Guatemala enrolled in the longitudinal AGricultural workers and Respiratory Illness impact (AGRI) study. The cohort is primarily comprised of otherwise healthy young workers (mean age 30 (range 18-62) years; 84% male) who are economically vulnerable (58% report food insecurity) and live within a geographically broad (2,600 km2) catchment area in southwest Guatemala. eGFR screening was completed for 1,879 workers in 2020, 1,085 workers in 2021, and 602 workers in 2022. The prevalence of eGFR < 90 ml/min/1.73m2 was 33.0%, 26.6% and 30.9% (2020, 2021, and 2022, respectively) within which the prevalence of eGFR < 60 was 2.3%, 1.9%, and 2.3% (2020, 2021, and 2022, respectively). Of the 1,233 workers that received at least two annual eGFR screenings in this period, 237 (19.2%; mean age 37.0 years, range 18-60 years) were "at risk" for CKD (defined as eGFR < 90 at least twice), and 13 (1.1%; mean age 37.5 years, range 23-59 years) also met the definition for moderate/severe CKD (defined as eGFR < 60 at least twice). Regression models adjusted for sex showed that age was associated with moderate/severe CKD (Relative Risk = 1.07, 95% Confidence interval: 1.01 – 1.12), indicating a 7% increase in risk with each increasing year of age. Comorbidities and modifiable risk factors are being collected and will be examined in expanded regression models. The high prevalence of CKD in this relatively young population suggests the need for regular screening and follow-up in agricultural workers in similar work environments, which can then lead to programs to reduce modifiable risk factors of disease. Ongoing assessments include follow-up testing of those workers with moderate/severe CKD screening and continued annual screening of workers enrolled in the AGRI study.

5577

IMPACT OF IMPROVED DIAGNOSTIC TOOLS, PRACTICES, TRAINING AND COMMUNICATION ON ACUTE FEVER CASE MANAGEMENT AND ANTIBIOTIC PRESCRIPTIONS FOR PATIENTS PRESENTING AT OUTPATIENT FACILITIES IN UGANDA

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Antibiotic prescribing practices is one of the main causes of antimicrobial resistance. The study explored the key drivers and barriers to adherence to prescribing instructions by patients/caregivers.As part of a randomized trial, a qualitative assessment was done. This involved three arms of the study: pre-intervention, intervention and post-intervention. The intervention involved randomization of patients to either the intervention or control arm. A training and communication package was developed guided by the findings. Health workers were trained on the package for use with the intervention patients. It was pretested for clarity with sample patients. Meetings were held with policy makers to discuss the capacity, opportunity and motivational COM-B/TDF framework and behavior change techniqueThis study was conducted at three Health centres in Uganda; Aduku in Northern region, Kihihi in Western region, and Nagongera in the Eastern region.Focus groups discussions were conducted with patients who sought care from the health facility and in-depth interviews were conducted with health workers based on their role as clinicians and laboratory attendants. Content analysis identified two themes namely key drivers and barriers and the COM-B/TDF behaviour frameworks approach identified four themes.Results: 1) Key drivers included: drug availability, health worker knowledge and communication 2) Barriers included: use of treatment resorts and inability to buy drugs. Findings from the COMB-B/TDF showed that an opportunity like 1) good support network, 2) capability of the health workers with good knowledge, 3) cognition and interpersonal skills, 4) motivation and awareness from the training and communication package increased positive social and environmental factors to tackle poor adherence.

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A SIMPLIFIED CAREGIVER DERIVED DIARRHEA SEVERITY SCORE (14DCODA) FOR USE IN SURVEYS WITH 14-DAY RECALL PERIODS: A VALIDATION STUDY NESTED WITH IN A VIRAL DIARRHEA SURVEILLANCE PROJECT IN AMAZONIAN PERU

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Diarrhea is a frequent syndrome in children in low- and middle-income countries (LMICs). While most diarrheal episodes are mild, some are severe and fatal, and the syndrome remains a leading cause of death in young children in LMICs. Nationally representative household surveys such as those conducted by DHS and MICS estimate diarrhea prevalence by asking caregivers about occurrence of diarrheal episodes in their children in the two-week preceding the interview. However, doubts have been raised about the reliability of illness recall over this period, leading to the exclusion of survey questions about the specific symptoms that might delineated severe from mild episodes. We address these questions by nesting a recall validation study within a larger diarrhea etiology study being carried out in Iquitos, a city in the Peruvian Amazon. Caregivers seeking care for children presenting with diarrheal illness were asked about symptoms for the 7 days prior to enrollment. At home visits 14 days later, they were then asked to recall the same illness features present on the day the child presented for care and on the days prior to presentation. CODA diarrhea severity scores were calculated for baseline ("gold standard") and at 14 day follow up (dCODA) and the latter compared for accuracy using ROC analysis. A dCODA score of 8 had an accuracy of 79.3% in classifying moderate to severe disease from mild disease as defined by the CODA score. Three symptom-specific questions that had a high accuracy included the maximum number of unformed stools in a 24-hour period (79.4%), days spent with fever (80.8%) and days of illness with vomiting (84.1%). We suggest that incorporating these three questions into household surveys may allow differentiation of episodes by severity across diverse contexts. This will be useful to improve estimates of health care coverage and understand the differential impact of disease specific interventions in reducing severe diarrheal disease.

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HUMAN EXPOSURE TO ONCHOCERCA VOLVOLUS IN HIGH AND LOW RISK ONCHOCERCIASIS TRANSMISSION SETTINGS

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Onchocerciasis caused by Onchocerca volvulus is transmitted by blackflies. Simulium damnosum are primary vectors in Africa. Onchocerciasis is the second leading cause of blindness after Trachoma. Community-directed treatment with ivermectin (CDTI) is the strategy for onchocerciasis control. A recently published modelling study shows that onchocerciasis elimination time depends on connectedness between villages either by human mobility or migrating flies. This study was therefore conducted to generate data to substantiate/improve findings from the study by investigating onchocerciasis infection in mobile individuals at low (5 km from breeding sites) and high risk (15 km from breeding sites) communities frequenting both settlements. The study was conducted in three villages each in onchocerciasis low and high risk areas in the Nkwanta North District of Ghana. A total of 539 participants from low risk (225) and high risk (314) communities had questionnaire administered to them to obtain biodata, movement, CDTI history, etc. Dried blood spots and skin snips were collected for OV 16 testing and microfilariae detection respectively. The overall serological prevalence for the six communities was 29.1%, (high risk: Kone=52.63%, Abunyanya=50.0% and River View=22.86%; low risk: Lancha=14.94%, Badule=17.72% and Gborsike=8.77%). This was significantly higher (P<0.0001) in high-risk (41.50%) than in low risk (14.35%) areas. Skin snip prevalence was (high risk: Kone=5.15%, Abunyanya=6.25% and River View=5.71%; low risk: Lancha=4.5%, and Badule/Gborsike=0.00%). Prevalence in high risk (5.73%) was significantly higher (P<0.0001) than in low risk (0.92%). Overall skin snip prevalence was 2.9%. Negative skin snips are currently being screened for parasites using RT PCR. Questionnaire data shows skin snip positive participants from Lancha spend ample time in high risk communities and their farms where they experience blackfly bites. During onchocerciasis elimination mapping phase, information on human movements (questionnaire) and diagnostics with high sensitivity (PCR) must be considered to guide policies and strategies.

5580

COST-BENEFIT ASSESSMENT OF SURGICAL INTERVENTION FOR FILARIAL HYDROCELE PATIENTS AT THE PRIMARY HEALTH CARE LEVEL IN BANGLADESH

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Lymphatic filariasis (LF) is the 2nd leading cause of disability, affecting 120 million people and endemic in 72 countries worldwide. One of the complications of chronic LF is hydrocele which reduces mobility, induces social stigma and depression, and drastically decreases the ability to work. Surgical correction of filarial hydrocele with minimal complications can help these people return to a socioeconomically productive life. The study evaluated the hydrocele-related lifetime economic loss and the surgical benefits compared to its cost based on the 838 hydrocelectomy surgeries conducted between March to June 2021. The data were collected before and one year after surgery. Assumptions included financial losses and gains for the patients. Area-based daily wage rates were used to determine average lifetime earning gain and discounted value from surgery to age 64 - the end of working life. We estimated the total costs and compared them with the benefit of the work capacity restored to determine the cost-benefit ratio. Further Incremental Cost-effectiveness ratio (ICER) was calculated to determine the intervention program's cost-effectiveness level. The total monetary benefit of the surgery was 3,892,118 USD (without discounting) and 2,700,505 USD (with discounting). The average lifetime income gain per patient was USD 4644 (without discounting) and USD 3222 (with discounting) and approximate cost-benefit ratio is 1:15. The ICER value (71 USD) makes the intervention highly cost-effective, as it is substantially lower than the per capita GDP of Bangladesh (1961 USD). The sensitivity analysis demonstrates that the results are robust to surgery cost variations. The colossal patient burden in Bangladesh warrants significant investment to reinstate these patients to a normal life. However, the study findings show that the required investment is minimal compared to the lifetime impact of the surgery on the patients, their families, and the country. Governments and international aid organizations should prioritize investing in similar projects to eliminate LF and help thousands by improving disability and averting poverty.

5581

BASELINE EVALUATION OF ONCHOCERCIASIS TRANSMISSION IN FOUR DISTRICTS OF NORTHERN GHANA

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Onchocerciasis, a filarial disease transmitted by blackflies, is targeted by the World Health Organization (WHO) for elimination. The WHO-recommended serologic threshold for stopping MDA is Ov16 seroprevalence <0.1% in children <10 years; however, models suggest that a higher seroprevalence of ≤2% may be sufficient to indicate interruption of transmission. We sought to evaluate the 2% threshold using paired entomological and serological studies in 4 districts in Northern Ghana where transmission may have been interrupted. If the Ov16 seroprevalence in children 5–9 years is ≤2% and blackfly O-150 PCR positivity meets WHO stopping criteria, then MDA will be stopped, and the area monitored annually. Vector control began in Ghana in 1974 followed by mass drug administration (MDA) with ivermectin in 1998; baseline prevalence in the study area was 5–89%. In 2022, a baseline serosurvey of children 5–9 years was conducted. The districts were stratified by endemicity status and villages selected through probability proportionate to estimated size methodology. In villages, a multi-stage random sample of children were enrolled with parental permission. A separate convenience sample of children was selected from 5 first-line villages. Dried blood spots (DBS) were prepared from venipuncture specimens, then eluted for analysis with Ov16 IgG4 rapid diagnostic tests (RDT). Results were available for 2,087 children from 65 villages. RDT results were positive in 31 children from 18 villages. When adjusted for survey design, the overall positive percentage was 1.3% (95% CI 0.6%–2.0%) for the districts. District positive percentages ranged from 0.5% (95% CI 0.1%–1.7%) to 2.2% (95% CI 0.8%–4.6%). Mapping of the positive villages did not reveal clustering. Study results show the Ghana program has significantly reduced transmission and met the study serologic criteria for stopping MDA. Results from the ongoing Ov16 ELISA of DBS and O-150 PCR testing in blackflies will be needed for a stop-MDA decision. Demonstration that a higher serologic threshold is consistent with interruption of transmission would facilitate progress toward WHO 2030 goals.

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EVALUATION OF HIGHER SEROLOGIC THRESHOLD FOR STOPPING MASS DRUG ADMINISTRATION IN ONCHOCERCIASIS ELIMINATION IN THE TUKUYU FOCUS, TANZANIA

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Mass drug administration (MDA) with ivermectin is the primary elimination strategy for onchocerciasis. MDA may be stopped if programs meet World Health Organization (WHO) entomological and seroprevalence (<0.1%) criteria, the latter of which is challenging and may be lower than necessary. A multi-year study to evaluate a serologic threshold of ≤2% for stopping MDA was conducted in Tukuyu focus, Tanzania. If seroprevalence was ≤2% and WHO entomological criteria were met, then MDA would be stopped, and annual follow-up would begin. We present baseline and year 1 follow-up results. In the baseline study, 2000 children 5–9 years old were randomly sampled in villages stratified by prevalence concurrent with an entomologic study. Additional 1st-line villages were added so that one associated with each breeding site was evaluated, but the results were excluded from the overall seroprevalence. In year 1 of follow-up, 800 children 5–9 years old were sampled in eight 1st-line villages and entomologic evaluation was repeated. After parental permission and child assent were obtained, questionnaires were administered, and dried blood spots (DBS) were collected. DBS were analysed by Ov16 enzyme-linked immunosorbent assay (ELISA) and Ov16 rapid diagnostic tests (RDT). Entomology results will be presented separately. In the baseline study, 2,561 children (51% male) were enrolled: 2,070 children (52% male) from randomly selected villages and 491 children (47% male) from purposively selected villages. The seroprevalence among the children in randomly selected villages was 1.21% by ELISA and 0.045% by RDT. In 1st-line villages, the seroprevalence was 0.61% by ELISA and 0% by RDT. In year 1 follow-up, 809 children (47% male) were sampled with seroprevalence 0.12% by RDT; ELISA results are pending. Demonstrating that MDA can be stopped at a threshold >0.1% is important to help countries achieve WHO 2030 roadmap goals. New diagnostics are being developed assuming that 1% will be the threshold. Serologic data presented here are consistent with the hypothesis that it is safe to stop MDA at a higher threshold, but more follow-up data are needed to demonstrate this.

5583

PROVIDING EVIDENCE ON THE STATUS OF TRANSMISSION OF ONCHOCERCIASIS IN 5 COUNTIES IN LIBERIA

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In 2018, the Ministry of Health-Liberia conducted its first programmatic Ov16 serological survey (pre-stop) to provide evidence on the status of transmission of onchocerciasis in the Southwest Regions (five counties; Bomi, Cape Mount, Margibi, Grand Bassa and River Cess). These five counties had received 14th years of MDA with ivermectin. Specifically, the objective was to determine the village level sero-prevalence of Ov16 in children 5-9 years old. A target convenience sample size of 100 children from each of 30 frontline communities within 5km of a blackfly breeding site or onchocerciasis river basin was selected in line with WHO onchocerciasis technical subcommittee guidelines. All enrolled consented children were tested for Ov16 using RDT in the field, and DBS were collected to allow subsequent ELISA testing. Of children testing negative for rapid test, 10% was randomly selected for confirmatory testing using SD Ov16 ELISA (Abbott, South Korea). Out of the target sample size of 3,000, a sample size of 2,468 was achieved. 91 of these children tested positive for Ov16 via RDT in the field. Out of 30 communities tested with RDT, 19 communities had positive cases while 11 reported all negative tests. The overall seroprevalence rate of 3.7% (91/2432) was found in five counties (Bomi, Grand Bassa, Grand Cape Mount, Margibi and Rivercess) with rate of 3.7% (21/572) in onchocerciasis endemic county only. In addition, rates of 3.2% (10/314), 0.5% (3/595), 0.7% (3/455) was observed in onchocerciasis and lymphatic Filariasis co-endemic counties with a high rate of 10.9% (54/496), respectively. According to WHO, to proceed to a full stop MDA survey, the prevalence threshold for IUs to “pass” pre-stop is <2%. We realized only two counties have crossed this benchmark, onchocerciasis transmission is still ongoing in one of the counties (Rivercess) and there is a need for support to conduct similar testing in the remaining 10 counties.

5584

HIGH PREVALENCE OF LOA LOA AND MANSONELLA PERSTANS IN NORTHERN GABON

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Loa loa infection is endemic in central African countries, such as Gabon, and in West Africa. In regions where onchocerciasis is co-endemic with loasis, L. loa infection represents a major obstacle to control of onchocerciasis. Subjects with Loa loa hypermicrofilaremia more than 8000 mf/mL are at risk of developing severe and/or serious adverse effects following treatment with ivermectin. In 2011, the distribution of filariasis due to L. loa and Mansonella perstans has been carried out in Gabon. Ten years later, we are interested in evaluating the evolution of the prevalence of these filariasis in a northern of Gabon. Participants were recruited in northern Gabon, from November 2021 to April 2022. Venous blood was collected in an EDTA tube for microfilaria detection using blood direct examination and leukoconcentration techniques. Sociodemographics, hematological and parasitological parameters have been recorded. During the study, 1342 participants over the age of 18 were screened for the L. loa and M. perstans detection in 36 villages. Prevalences were 30.0% (403/1342) for L. loa, 4.9% (66/1342) for M. perstans and 1.9% (25/1342) for the coinfection. A hypermicrofilaremia was found in 12.9% (52/403) of participants with L. loa infection. Age and gender were risk factors associated with Loa loa and M. perstans microfilariae carriage: men were twice more infected than women (OR = 1.9, 95% CI [1.49 - 2.41] ; pγ0.001) and older people (>55) (p=0.0012, OR = 1.48, IC95% [1.16; 1.90]) than age group varying between regarding loiasis. For M. perstans, same findings were observed for M. perstans for men (OR = 2.4, 95% CI [1.40; 4.20]; p<0.001) and older people (p= 0.003, OR = 2.15, IC95% [1.25; 3.74]). The filariasis distribution according to villages differed significantly for L. loa (p=0.0034) and M. perstans (p<0.001). In conclusion, the prevalence of L. loa in northern Gabon is higher than the global rate of 22.4% reported, 10 years ago unlike M. perstans, found two times less than the 10.0% of 10 years ago. There was heterogeneity between villages.

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DIROFILARIA SP. HONG KONG AND BRUGIA SP. SRI LANKAN GENOTYPE ARE THE PRIMARY CAUSES OF FILARIAL INFECTION IN DOGS IN SRI LANKA

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The mosquito-borne Dirofilaria repens, Brugia malayi, B. ceylonensis, and flea- and louse-borne Acanthocheilonema reconditum are historically known to be endemic among dogs in Sri Lanka. Despite this, limited information on the prevalence, diversity, and predictors of filarial infections in dogs in Sri Lanka have resulted in suboptimal control and prevention of these parasites, some of which are known to be zoonotic. To address this, whole blood and metadata were collected and analysed from 423 pet dogs across three geo-climatic zones within Sri Lanka. Blood samples were screened using the Modified Knott's Test (MKT) and PCR followed by Sanger sequencing. Multivariable logistic regression models were used to assess predictors for canine filarial infections. Two novel genotypes, Dirofilaria sp. Hong Kong (Dirofilaria HK) and Brugia sp. Sri Lankan genotypes were identified infecting dogs. The overall prevalence of filarial infection in pet dogs by PCR was 37.1% (95% CI 32.5 - 41.9%, n=157), compared to 18.6% (95% CI 15 - 22.6%, n=78) detected using the MKT. More than 80% of filarial-positive dogs were infected with Dirofilaria HK, while the remaining dogs were infected with Brugia sp. SL genotype. Increasing age (p<0.001) and residing in the low-country wet zone (p<0.001), which include regions that were endemic for human filariasis in Sri Lanka were associated with filarial infections in the study subjects. No clear pathognomonic signs for filarial infection were identified, indicating that dogs may act as reservoirs for these potentially zoonotic pathogens. Given the morphologic similarity of Dirofilaria HK and Brugia sp. Sri Lankan microfilariae with those of D. repens and B. malayi, respectively, it is likely that these species have been misidentified in the past. Therefore, it is necessary to take measures to prevent and control canine filarial infections to safeguard both canine and human health.

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DIFFERENCES IN VACCINE-SPECIFIC RESPONSES BETWEEN URBAN AND RURAL ENVIRONMENTS AND MEDIATORS OF THESE DIFFERENCES AMONG UGANDAN ADOLESCENTS: THE POPVAC TRIALS

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Geographic and urban-rural variation in vaccine immune responses has been observed. Helminth and malaria infections, more common in settings where immune responses are impaired, have been implicated due to their immunomodulatory roles. We aimed to assess urban-rural differences in vaccine responses in Uganda and to identify mediators (with a focus on parasites) of these differences. We conducted three linked randomised trials: POPVAC A assessed effects of intensive vs standard praziquantel treatment on vaccine responses in a high schistosomiasis burden rural area, POPVAC B effects of intermittent preventive malaria treatment vs placebo in a high malaria burden rural area, and POPVAC C effects of BCG re-vaccination in a low infection urban area. BCG, yellow fever (YF-17D), oral typhoid (Ty21a), HPV and tetanus/diphtheria (Td) vaccines were administered to the same schedule in each trial. Outcomes were BCG-specific IFN-γ 8 weeks post-BCG vaccination and antibody responses to vaccine-specific antigens 4 weeks post-vaccination (YF-17D, S. typhi lipopolysaccharide (LPS), HPV) and 24 weeks post-Td. Schistosomiasis and malaria infections at baseline were determined using CAA assay and PCR, respectively. Regression analysis adjusting for age and sex assessed differences in responses between studies, with comparisons restricted to standard treatment and placebo arms for POPVAC A and B, respectively. Vaccine responses from 239 (POPVAC A), 171 (B), and 151 (C) participants were compared. There were differences in responses between settings for all vaccines: tetanus IgG (p=0.004), yellow fever titers (p=0.005) and oral typhoid IgG (p<0.001) were lower in both rural settings compared to urban. However, diphtheria IgG (p<0.001) was lowest in POPVAC A (high schistosomiasis) but highest in POPVAC B (high malaria) and BCG-specific IFN-γ differences varied over time with POPVAC A participants having lower peak responses but higher waning responses. Differences were observed for all vaccines; causal mediation analysis to quantify the contribution of parasitic infections to these differences will be presented at the meeting.

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HOW DOES THE PROPORTION OF NEVER TREATMENT INFLUENCE THE SUCCESS OF MASS DRUG ADMINISTRATION PROGRAMMES FOR THE ELIMINATION OF LYMPHATIC FILARIASIS?

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Mass drug administration (MDA) is the cornerstone for the elimination of lymphatic filariasis (LF). An important driver for achieving this goal is the proportion of the population that never received treatment (NT). We employ two individual-based stochastic transmission models to assess the maximum level of NT with which the 1% microfilaria (mf) prevalence threshold can still be achieved under different scenarios for coverage of annual MDA, the drug combination used and transmission settings. For Anopheles-transmission settings, we find that treating 80% of the eligible population annually with ivermectin + albendazole (IA) can achieve the target within 10 years of annual treatment when baseline mf prevalence is 10%, as long as NT is below 10%. Higher proportions of NT are acceptable when more efficacious treatment regimens are used. For Culex-transmission settings with a low (5%) baseline mf prevalence and DA or IDA treatment, elimination can be reached if treatment coverage among eligibles is 80% or higher. For 10% baseline mf prevalence, the target can be achieved when the annual coverage is 80% and NT is 15% or lower. Higher infection prevalence or levels of NT would make achieving the target more difficult. The proportion of people never treated in MDA programmes for LF can strongly influence the achievement of elimination and the impact of NT is greater in high transmission areas. This study provides policy-relevant quantitative insights into what levels of NT may be acceptable to achieve elimination in different epidemiological and programmatic settings. In addition, our results provide a starting point for further development of criteria for the evaluation of NT.

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ASSESSING IMPACT OF IVERMECTIN AND ALBENDAZOLE MASS DRUG ADMINISTRATION ON TRANSMISSION OF LYMPHATIC FILARIASIS IN 24 DISTRICTS IN SENEGAL

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Mapping of lymphatic filariasis was conducted in Senegal in 2003-2010 and found 51 of 79 districts endemic with Wuchereria bancrofti parasite antigenemia prevalence in sentinel sites of 1.0 to 78%. Annual mass drug administration (MDA) with ivermectin and albendazole was initiated in 2007. In 2018-2021, 17 districts passed transmission assessment survey (TAS) for the first time and have since stopped MDA. In 2021, 24 districts with an average baseline antigenemia prevalence of 14% became eligible for pre-transmission assessment survey (pre-TAS) to assess impact of MDA on prevalence of W. bancrofti infection after achieving the required five effective annual MDA rounds with at least 80% program coverage. In the pre-TAS conducted in 2021, 300-350 persons over 5 years old were assessed for W. bancrofti antigenaemia in sentinel and spot-check sites in each district. W. bancrofti antigenaemia prevalence was fund to have reduced from 1-78% in sentinel sites and 3-32% in spot-check sites to ≤ 0.3% in all 24 districts. Subsequently, transmission assessment surveys were conducted in 24 districts in 2022 to determine if transmission of the parasite has been interrupted and MDA could be stopped. The 24 districts were grouped into 19 evaluation units (EU) based on similarity of baseline prevalence, ecological factors, proximity and population for the TAS. Between 1320 and 1548 randomly selected children in grades 1 and 2 (as proxy for 6-7-year-olds) were assessed for antigenaemia in 30 randomly selected clusters (primary schools) in each EU. In both pre-TAS and TAS, filarial test strips (FTS) were used to detect presence of W. bancrofti antigens in 75µl of finger stick blood. Two out of 19 EU recorded one positive case, significantly below the critical cut-off value of 18 positives, no positive case was found in the remaining 17 EU indicating that parasite transmission has been interrupted in all EU. MDA has consequently been stopped in the 24 districts and they are currently under post-treatment surveillance.

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SIGNIFICANT ACHIEVEMENTS IN LYMPHATIC FILARIASIS ELIMINATION IN NORTHWESTERN ETHIOPIA

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Lymphatic filariasis (LF) was historically endemic in 104 (9%) of Ethiopia's districts. Efforts to eliminate LF as a public health problem started in three districts of West Gondar zone in Northwestern Ethiopia in 2012 with integrated annual mass administration (MDA) of ivermectin and albendazole for onchocerciasis and LF. Following the WHO guidelines, after five rounds of effective mass treatment with >65% epidemiological coverage and successful Pre-transmission assessment surveys, the first Transmission Assessment Survey (TAS-1) was conducted in 2016 in the three districts with total population of about 330,000 at the time: Metema, Gendewuha, and Quara, which were independent, contiguous implementation units combined into one evaluation unit. The TAS-1 tested 1899 children aged 6 and 7 sampled from randomly selected communities, only 3 of whom (0.2%) were positive for circulating filarial antigen (CFA), which was less than the critical cut-off of 18. Following the halt of MDA for LF and onchocerciasis in 2017, LF post-treatment surveillance surveys found zero CFA-positive children among 1877 tested in the second of the TAS series, TAS-2, in 2019. Finally, only 1 (0.06%) CFA-positive child (a 7-year-old lifelong resident) was found among 1611 children tested in the final TAS-3 in November 2022. This indicates that over 360,000 people are no longer at risk for LF transmission in these three districts of northwestern Ethiopia. Continued post-"elimination" surveillance should continue until surrounding areas also interrupt transmission as migration from endemic areas is common. The successful completion of the TAS series is the first of its kind in Ethiopia and has motivated other parts of the country to achieve LF elimination success.

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NATIONWIDE RE-MAPPING SURVEY FOR LYMPHATIC FILARIASIS ELIMINATION IN THE DOMINICAN REPUBLIC

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The Dominican Republic aims to eliminate lymphatic filariasis (LF) as a public health problem and demonstrate elimination of transmission. Nationwide baseline mapping (1999-2003, 2007) using lot-quality assurance sampling for LF identified three endemic foci in need of mass drug administration (MDA). These foci are currently in post-treatment surveillance. Recognizing the gap since baseline mapping, the Ministry of Health (MSP) conducted an LF re-mapping survey in 2022 to confirm that active transmission does not exist in historically non-endemic areas. A nationwide cross-sectional household (HH) survey was conducted in 40 provincial and health area directorate evaluation units (EU). Within each EU, 30 communities were randomly sampled; within each community, 16 HHs were selected where one member ≥6 years of age was asked to participate. A blood sample was tested for circulating filarial antigen (CFA) by Filariasis Test Strip (FTS). The prevalence and spatial distribution of LF antigenemia and LF morbidity was evaluated. Case investigations, treatment, and night blood sample collection were conducted per MSP guidelines. Provisionally, 19 of 15379 participants tested were CFA-positive (age range: 21-68 years). All 14 of

those tested to date for microfilaremia by night blood sample were negative; follow-up testing is pending for 5 individuals. Lymphedema was self-reported by 166 of 15358 adults and hydrocele by 19 of 6001 adult males. Weighted CFA prevalence estimates by EU ranged from 0-3.6%, with five EUs having an upper confidence limit &gt2%, the proposed threshold for starting MDA in re-mapping assessments. Additional investigation is needed to determine whether these results represent evidence of past or current transmission and if interventions such as MDA or focal MDA are needed. This re-mapping approach contributes to the conversation and possible methodologies for establishing verification of elimination of LF transmission.

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MOLECULAR EPIDEMIOLOGY OF CIRCULATING DIROFILARIA IMMITIS AND D. REPENS IN CULICIDAE MOSQUITOES FROM REYNOSA, TAMAULIPAS

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Dirofilariasis is a disease caused by a nematode of the genus Dirofilaria, as D. immitis and D. repens. This disease affects both dogs and other vertebrate hosts and involves the parasite lodging in the heart or other organs. The parasite is transmitted to another host by mosquito bites. The aim of this study was to assess the prevalence of D. immitis and D. repens in dogs and mosquitoes in Reynosa, Tamaulipas, Mexico. An assay was performed to identify the presence of Dirofilaria in dog blood samples and mosquito abdomen to determine the prevalence of both filaria's species. For the capture of mosquitoes, 25 colonies distributed in Reynosa city were sampled using Sentinel traps, whereas for dog blood samples we had the support of veterinaries that treat dogs from different parts of the city and adjacent areas. An nested PCR assay was performed for the detection of species of Dirofilaria. In addition, a second PCR assay was performed to determine the mosquito species that fed on human blood to determine a possible zoonosis. A 2.64% prevalence of D. immitis infection was found in dogs from 188 samples tested, while no presence of the parasite was found in female mosquitoes from 250 specimens. Four of the five dogs positive for the presence of Dirofilaria spp. belonged to another US cities whose neighboring areas have a higher prevalence, specifically localized in the Rio Grande Valley; only one was found to be from Reynosa. Two hundred fifty engorged Culicidae mosquitoes were captured, of which 98.5% were fed with human blood. The mosquito's species with the highest population density are Aedes aegypti and Culex quinquefasciatus and both species are competent as a vector for Dirofilaria. All samples of Ae. aegypti and most samples of Cx. quinquefasciatus reveals at least having fed on humans' blood, making this finding a possible risk of Dirofilaria zoonosis towards humans in the city of Reynosa. Another culicid species was identified were An quadrimaculatus (not showing human blood feeding), and in the case of Cx. erraticus and Ae. epactius, not exist too much information regarding their vector competence for Dirofilaria.

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GENETIC DIVERSITY WITH THE EMERGING ZOONOSIS OF AN ONCHOCERCA SPECIES OF HUMAN POPULATIONS IN TARABA STATE, NIGERIA

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A better understanding of Onchocerca population genetic processes in a specific biogeography is needed to support the onchocerciasis elimination goals. The study investigated the genetic diversity of Onchocerca microfilariae using a fragment of 16S rDNA genes in some onchocerciasis endemic communities of Taraba State, Nigeria. The investigation was in eight selected communities comprising six endemic communities with a high prevalence of infection despite receiving mass drug administration with ivermectin for between 10 and 16 years of annual treatments and two non-endemic areas. Skin snips were obtained from 321 consenting participants after community engagement and who were more than five years of age and had resided within the communities for more than ten years or since birth. DNA was extracted from the microfilariae that emerged from the normal saline and the residual skin snip samples and preserved in RNAlater® in a 1.5 ml centrifuge tubes. A Polymerase Chain Reaction (PCR) amplification with generic and species-specific primers targeting the 16S gene of the DNA extracted. The PCR product was eluded and cleaned for sequencing, while the resultant sequences were analysed to identify the Onchocerca species. The multiple sequence alignment protocol showed the distinct diversity of two sequences G49_O.v. Gashaka and Y02_O.v. Yorro samples with 100% similarity that matched sequences of O. volvulus from Cameroon that has been deposited in the GenBank, indicating the emergence of a new polymorphic strain of O. volvulus species. Similarly, two O. ochengi sequences isolated from human samples, O. ochengi G44_Gashaka; O. ochengi G01_Gashaka and O. ochengi Y04_Yorro, matched with an O. ochengi sequence in the GenBank from Cameroon and is being reported from the study communities for the first. The study has identified O. volvulus as the cause of onchocerciasis and O. ochengi with the potentials of an emerging zoonotic onchocerciasis in the cattle (animal)-Simulium(vector)- human interface characteristic of the communities.

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BENCHMARKING AN ACCESSIBLE METHOD FOR GENERATING COMPLETE GENOMES FROM PARASITIC NEMATODES

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Parasitic nematodes, including filarial worms and soil-transmitted helminths, are etiological agents of both acute and chronic disease. Recent technological and methodological advances in genomics have revolutionized the study and treatment of parasitic nematodes. Though remarkably impactful, these advances have also underscored a critical issue: Generating short-read DNA sequence data (and building and maintaining the infrastructure needed to do so) is expensive, making genomic resources largely inaccessible. The Oxford Nanopore Technologies (ONT) MinION is an inexpensive and portable next-generation sequencing platform capable of producing ultra-long DNA sequences ideal for whole genome assemblies; however, poor read level accuracy has hindered widespread adoption of the platform. Recent advances in ONT chemistries have produced more accurate and reliable read level data. To determine if whole genome assemblies using only ONT data reflect current gold standard hybrid assemblies, we generated complete genome assemblies for the parasitic nematodes Brugia malayi and Trichuris trichiura using only ONT MinION Q20+ sequence data. We compared each ONT MinION assembly to reference genomes generated using a hybrid assembly approach, and assessed contiguity, completeness, and accuracy using QUAST, BUSCO, and MUMmer4, respectively. For B. malayi, we generated an 88 gigabase (Gb) assembly in 85 contigs that covers 99.8% of the reference genome. The two assemblies both contain >99% of BUSCOs known for the phylum Nematoda and are >99.9% identical when considering only single base pair (bp) mismatches. For T. trichiura, we generated a 71 Gb assembly in 158 contigs that covers 99.4% of the reference genome. The two assemblies both contain ~46% of BUSCOs known for the Nematoda and are >97.8% identical when considering only single bp mismatches. These results highlight the ONT MinION and its Q20+ platform update as an accessible stand-alone alternative to traditional sequencing approaches for the generation of whole genome assemblies for parasitic nematodes.

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BMA-LAD-2 AS A NOVEL ANTIBODY TARGET FOR THE TREATMENT OF LYMPHATIC FILARIASIS

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Efforts to control the global burden of Lymphatic Filariasis focus primarily on Mass Drug Administration (MDA). While highly effective against microfilariae, current MDA regimens have little to modest effects on adult worms. Thus, MDA typically has to be repeated over several years. Additionally, the most efficacious MDA regimen is contraindicated in areas co-endemic with Loa loa and Onchocerca volvulus infections due to adverse effects caused by rapid killing of microfilariae. The long-term goal of this study is to develop a novel macrofilaricidal agent that would allow for fewer MDA treatments and safe use in areas with L. loa and O. volvulus. Previously, we showed that Bma-LAD-2, an intestinal protein in Brugia malayi likely involved in tight junction formation, is essential for adult worm fecundity, metabolism, and motility. In this study, we are testing whether antibodies targeting Bma-LAD-2 can function as macrofilaricidal agents. We have recombinantly expressed a soluble form of the outer binding Ig domains of Bma-LAD-2 (Bma-LAD-2 Ig1-4) and have created stably transfected HEK293 cells expressing full-length transmembrane Bma-LAD-2 protein. Bma-LAD-2 transfected cells were found to have higher electrical resistance across a monolayer than non-transfected HEK cells by TransEpithelial Electrical Resistance (TEER) assay. Addition of polyclonal rabbit antibodies against Bma-LAD-2¬ Ig1-4 to the transfected cell line decreased TEER values to those of non-transfected cells. Finally, we have found that anti-SARS-CoV-2 antibodies in human sera cultured with adult B.malayi worms were still functional after ingestion by adult worms. Together, these results suggest that adult filarial worms ingest antibodies into their intestinal tracts, and that antibodies against Bma-LAD-2 have the potential to interrupt intestinal tight junctions of filariae. We are currently working to determine the effect of treating adult B.malayi worms with anti-Bma-LAD-2 antibody. It is possible that if the binding domains of the Bma-LAD-2 are conserved across filarial species, these antibodies could be used as a pan-filarial macrofilaricide.

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IMPACT OF WUCHERERIA BANCROFTI INFECTION ON CERVICAL MUCOSAL IMMUNITY OF WOMEN IN LINDI, TANZANIA

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Lymphatic filariasis is a mosquito-transmitted parasitic infection in tropical regions. Our group had previously described an increased HIV incidence in individuals infected with Wuchereria bancrofti in Southwest Tanzania. Most HIV transmissions in sub-Saharan Africa occur through heterosexual contact. However, W. bancrofti is not known to cause lesions or ulcers in the genital mucosa as other diseases are known to do. The aim of this work is to analyze cervical mucosal T cell phenotypes in women infected with W. bancrofti and compare the results with uninfected women from the same area. Women (aged 18-45) from the Lindi region of Tanzania were screened for W. bancrofti infection using filarial test strips (FTS, Abbott). HIV status was determined using HIV 1/2 3.0 (Standard Diagnostics Inc) and positive results were confirmed using Uni-Gold Recombigen HIV - ½ (Trinity Biotech). From each woman, a cervical mucosal sample was taken for T cell phenotyping and Pap smear and HPV typing were performed. Samples were stained for flow cytometric measurement of activation, cell lineage and maturation markers, as well as HIV receptor and facilitator markers (HLA-DR, CD38, Vdelta2, CD45, CD27, CD25, FoxP3, CCR5, beta7) on CD4 and CD8 T cells. Between October and December 2020, 38 HIV-uninfected female study participants (mean age 24.6 years) were recruited; 26 of them were infected with W. bancrofti. None had abnormalities in the Pap smear and 12 women were found to have high-risk (HR) HPV types. Two of 12 filarial-uninfected women had HR HPV (17%) detected in the mucosal sample versus 10/25 (40%) HR HPV in W. bancrofti infected women (p=0.2). An increased expression of HIV co-receptor CCR5 on memory CD4 T cells as well as increased number of gamma-delta2+ T cells (p=0.0042) were found in the cervical mucosa of W. bancrofti-infected women. The systemic infection with W. bancrofti infection, which, unlike other helminthic infections, has no known genital lesions, was associated with T cell changes of the cervical mucosa in a small number of women. We additionally found an augmented prevalence of HPV in W. bancrofti infected women.

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EFFECTS OF WUCHERERIA BANCROFTI INFECTION ON CD4 T CELL RESPONSES TO SPECIFIC AND NON-SPECIFIC ANTIGENS

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Lymphatic filariasis, primarily caused by Wuchereria bancrofti, is a mosquito-transmitted disease, which is affecting people living in tropical regions. Infection with W. bancrofti is associated with chronic inflammations that may cause lymphedema and hydroceles. The adult worm of W. bancrofti lives for many years in the human host and even without disfiguring consequences leads to modulation of the adaptive immune response. This study aims to determine whether chronic W. bancrofti infection affects CD4 T cell responses to specific and non-specific antigens. Blood samples were collected from 141 participants living in two W. bancrofti endemic regions in Tanzania: Kyela district in Mbeya region, n=106 and Lindi district, n=35. Samples were stimulated with the whole lysate of Mycobacterium tuberculosis (Mtb), Staphylococcus Enterotoxin B (SEB) or PBS (control) for 16 hours. The frequency of CD4 T cells responding to stimulation by secreting interferon gamma (IFN-γ) or interleukin 2 (IL-2) cytokines was measured by flow cytometry. W. bancrofti-infected individuals had significantly fewer Mtb specific IL-2 producing CD4 T cells compared to uninfected individuals (p =0.010), while IFN-γ responses to Mtb specific stimulation were comparable between W. bancrofti infected and uninfected individuals. Interestingly, W. bancrofti infection showed significant reduced frequencies of IFN-γ (p<0.0001) and IL2 (p<0.0001) CD4 T cells responses upon stimulation with SEB compared to uninfected individuals. Our findings show diminished CD4 T cell responses to SEB in W. bancrofti infected individuals. Stimulation with Mtb showed differences for only one cytokine, IL-2, otherwise comparable results between the infected and the control group. These results indicate that chronic infection with W. bancrofti suppresses CD4 T cell responses, most likely as part of the immune evasion strategy of the parasite. These reduced immune responses might have a deleterious impact on the capability of the host to fight other infections.

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MULTIPLEXED HIGH THROUGHPUT POINT-OF-CARE BIOSENSING OF ONCHOCERCIASIS ANTIBODY MARKERS

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Neglected tropical diseases (NTDs) disproportionately affect marginalized populations, often in resource-poor settings. The critical lack of cost-effective diagnostic tests devices for NTDs was highlighted in WHO's 2021-2030 Road Map. Current serological tests for onchocerciasis, which aid diagnosis and are important for disease mapping and mass drug administration decisions, detect only one antigen-specific antibody, limiting their sensitivity and specificity. Here, we report inexpensive yet multiplexed and high-throughput optical and electronic biosensing methods for point-of-care (POC) detection of antibodies against several onchocerciasis antigens from a single drop of serum. The optical method uses enzymatic silver metallization on standard glass slides and a custom cellphone app that measures the optical readout. The electronic method uses similar assay chemistry, but on microelectrode chips and generates a direct electronic readout. Recombinant onchocerciasis antigens are immobilized using laser-cut polydimethylsiloxane microwells. After sample incubation with onchocerciasis-positive and control samples, a horseradish peroxidase labeled probe is added. Finally, silver substrates are added to generate silver metallization related to the measured biomarker concentration. To demonstrate the POC detection, onchocerciasis patient (n=56) and control (n=35) sera were measured for IgG4 against multiple antigens (FABP, OV-16, Ov33, OvMSA) from single drops (3µL) of diluted sera. Onchocerciasis+ samples exhibited dark metallization decreasing with serial dilution, while controls showed low metallization. These findings were cross-referenced against an FABP ELISA, which demonstrated similar results. Multiple logistic regression with the onchocerciasis antigens improved the diagnostic accuracy (AuROC>0.95), indicating the value of multiplexed detection. This inexpensive multiplexed POC diagnostic approach holds promise for onchocerciasis detection as well as other NTDs.

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CYTOKINE IN UTERO PRIMING IS ASSOCIATED WITH DETRIMENTAL BIRTH OUTCOMES AND CHILD INFECTIONS

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Infections during pregnancy are associated with foetal immune imprinting that impacts birth outcomes and susceptibility to childhood infections. This study investigated how anti-parasitic cytokine profiles in newborns' cord blood mononuclear cells (CBMCs) relate to low birth weight (LBW) and childhood infection. A total of 311 Kenyan mothers were followed during pregnancy and were tested for parasitic infections at each ante-natal clinic visit. At delivery, cord blood was collected and newborns' cytokine responses to Plasmodium falciparum, S. hematobium, and W. bancrofti antigens were assessed. The baby's birth weight was also recorded. Infants were followed to 18 months of age and blood, urine and stool samples were collected at every visit and tested for parasitic infections. Cytokine profiles of each child were classified by principle component analysis and termed as positive or negative response. We observed a positive association between IL-10, TNF-a and Th-1 responses in babies born to mothers with maternal malaria infection but negative response in those born to mothers co-infected with malaria and helminths. LBW was associated with IL-5 and IL-10 sensitized babies but not with any maternal infection. We also observed increased risk of malaria infection in children whose CBMCs had a predominant Th-1 profile particularly IL-2. Childhood malaria was also associated with increased risk of having severe anaemia, hookworm infection and any co-infection. This study suggests that maternal sensitization of either Th-1 or Th-2 cytokine profiles may contribute to poor pregnancy outcomes and increased susceptibility to childhood infections. Additionally, differential imprinting trajectories in utero were associated with either mothers were mono- or co-infected.

5599

IMPACT AND COST EFFECTIVENESS OF ANNUAL VS. TWICE ANNUAL MASS DRUG ADMINISTRATION FOR ELIMINATION OF LYMPHATIC FILARIASIS AND CONTROL OF ON CHOCERCIASIS IN COTE D'IVOIRE

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Lymphatic filariasis (LF) and onchocerciasis (oncho) are coendemic in many parts of Cote d'Ivoire, and can cause severe economic and physical burdens on populations and health systems. Mass drug administration (MDA) of ivermectin and albendazole is a key intervention strategy to eliminate these diseases in Africa. While most country programs implement MDA annually, some have posited that a twice per year MDA may be more effective, potentially reducing the time to elimination. Despite these potential benefits, very few studies have examined the costs and program implications for switching to a semi-annual schedule. We compared the relative impact and cost effectiveness of annual versus twice-yearly MDA in the two districts Abengourou (1x MDA) and Akoupe (2x MDA) in south-eastern Côte d'Ivoire. The Ministry of Health and other implementing partners collected cost data associated with the inputs and activities needed to run MDA programs. Data was collected from January - December 2014 and used to project costs for the full 3-year study period. The annual financial costs were 20% higher for 2x/year MDA ($34,012USD vs. $22,839USD). One year after the third round of 1x and the fifth round of 2x MDA, the LF microfilaria (Mf) prevalence decreased from 8.4% to 2.5% in the 1x MDA area and from 8.1% to 2.3% in the 2x MDA area. The oncho skin Mf prevalence decreased from 22.7% to 8.4% and from 23.1% to 7.5% in these areas, respectively. In conclusion, 2x MDA was more costly but no more effective than annual MDA in this study. Based on these results, we recommend that country programs focus limited resources to conduct high quality annual MDA, in accordance with current WHO guidance.

5600

INVESTIGATING KNOWLEDGE, ATTITUDES, AND PRACTICES OF HEALTH WORKERS ON THE MANAGEMENT OF FEMALE GENITAL SCHISTOSOMIASIS IN THE SOUTH REGION OF CAMEROON

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Schistosomiasis is an acute and chronic disease caused by parasitic worms that can take two main forms: intestinal or urogenital. If left untreated, the urogenital form can lead to female genital schistosomiasis (FGS) in women and girls; frequently resulting in severe reproductive health complications which are often misdiagnosed as sexually-transmitted infections. This study assessed healthcare workers' knowledge, attitudes and practices of the management of FGS in the South Region of Cameroon.Using quantitative research methods, a questionnaire was administered to 104 health workers from all levels in the health system (Health facility, district and Region) from all the 10 health districts of the South Region. Over half of the participants

had heard about FGS but very few had clinical knowledge that could enable them to diagnose, treat and prevent FGS. Most healthcare workers did not have any confidence in their ability to effectively manage cases. Healthcare workers in the South Region of Cameroon present significant gaps in knowledge about FGS especially when it comes to its diagnosis and treatment. There is a great need for the National NTDs programme to develop training manuals and organize capacity building workshops to equip healthcare workers with knowledge on FGS. Also, it is important to take advantage of other campaigns like free distribution of Ivermectin and Albendazole in communities against lymphatic filaria to educate the community on FGS and also improve upon water sanitation and hygiene to break the chain of transmission of the infection.

5601

INVESTIGATING THE INFLUENCE OF PATHOGENIC LEPTOSPIRE SHEDDING BY RAT POPULATIONS ON HUMAN LEPTOSPIRA INCIDENCE IN SALVADOR, BRAZIL

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Leptospirosis is a neglected zoonotic disease responsible for 1 million cases and 60,000 deaths annually, making it a major global health concern. Environmental distribution and concentration of pathogenic leptospires shed from rats are speculated to affect infection risk, but little is known on this association. Our objective was to investigate whether variations in leptospire shedding influence human Leptospira infection risk. We explored a novel approach of combining several statistical models to elucidate links between shedding and human Leptospira incidence, and the interplay with other risk factors. We performed eco-epidemiological studies in an urban slum environment in north-eastern Brazil. During 2013-14, we sampled roughly 500 Rattus norvegicus and quantified their shedding status and load, identified 700 unique points for R. norvegicus presence, and performed sequential surveys of residents to evaluate potential environmental and socioeconomic risk factors. We integrated data from these populations by building three statistical models. Models were built based on the Rattus norvegicus data for two outcomes: 1) shedding by individual rats and 2) the relative abundance of rats. The estimated 'total shedding' variable, obtained by multiplying the predictions from those two models, was used in a third model, as a risk factor for human Leptospira infection. Our results suggest that 'total shedding' by rat populations is an important risk factor for human infections (odds ratio [OR]=1.4; 95% confidence interval [CI]: 1.0-1.9), however, rat abundance, rather than shedding by individual rats, is the main driver of this association. Among factors pertaining to surroundings and the environment, infection risk was higher in areas with higher vegetative land cover i.e., more rural areas (OR=2.1; 95% CI: 1.1-3.9), and when rainfall entered the house (OR=1.9; 95% CI: 1.4-2.6). Effective prevention strategies will require control of the reservoir population in addition to addressing the structural features of slum settlements that promote transmission.

5602

MAINTAINING ELIMINATION OF TRACHOMA AS A PUBLIC HEALTH PROBLEM: POST-VALIDATION SURVEILLANCE PLANS IN VALIDATED COUNTRIES

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Trachoma is targeted for global elimination as a public health problem by 2030. Repeated infections with Chlamydia trachomatis lead to inner eyelid scarring, causing the eyelashes to turn in and rub the cornea (trachomatous trichiasis, or TT) which can lead to blindness. The WHO-endorsed SAFE strategy (Surgery, Antibiotics, Facial cleanliness and Environmental improvement) is used to eliminate trachoma. To date, 15 countries have been validated by WHO as having eliminated trachoma. The epidemiological targets for validation are: trachomatous inflammation – follicular (TF) <5% among children 1-9 years and TT <0.2% in adults 15 and above in all districts. National Program submit dossiers to WHO to be validated. In these dossiers, plans to conduct post-validation surveillance (PVS) are described. We conducted a literature review to understand the organic landscape of PVS plans and activities. A search was conducted using the PubMed and Google Scholar databases using the terms "trachoma" and "post-validation surveillance." A Google search using "trachoma elimination dossiers" and country names was conducted. Abstracts were reviewed, and elimination dossiers, documents describing programmatic plans, or operations research on PVS were retained. Three dossiers were found (Ghana, Iran and Mexico). Programmatic documents with PVS plans were available from Oman and Morocco; a peer-reviewed publication was available for The Gambia. All countries plan to use a passive surveillance approach (case reporting via health information systems), though populations targeted and methods vary. Four countries also had an active surveillance approach: sentinel sites, contact investigations, or periodic surveys. All countries rely on clinical indicators; one country is considering syndromic and biological indicators. Two countries (Ghana and Morocco) have conducted operations research on PVS using clinical and biological indicators. In these, clinical signs remained under the elimination threshold. Age-adjusted seroprevalence varied by study site but seroconversion rates were low. Where detected, current infection prevalence was low.

5603

INTEGRATED SURVEILLANCE FOR LYMPHATIC FILARIASIS, VISCERAL LEISHMANIASIS AND DENGUE ARE DIFFICULT PROPOSITION

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Lymphatic Filariasis (LF), Kala azar and Dengue are the public health concerns in India. These diseases are included in 20 identified NTDs. The surveillance of clinically manifested LF cases is done annually and updated once a year whereas, microfilaria prevalence is done in sentinel and random sites @ 1 site per million population as per WHO guidelines. Visceral leishmaniasis or Kala azar case search is also done in endemic areas for both with symptoms or for PKDL ones unlike malaria where surveillance is done routinely from all areas mostly at weekly or fortnightly intervals. Similarly, the surveillance of dengue cases is also institution (hospitals/labs) based. The integration of such type of surveillance would have various challenges like skill of the technicians for all the three diseases, different diagnostic labs and partial verticality in human resource etc. The various challenges including control command of human resource, difference in skill development and vertical implementation specific to surveillance, case detection and management in respect of these three NTDs namely LF, Kala azar and dengue prevalent in India need to be carefully looked into before considering integrated surveillance, however, vector surveillance can be undertaken in an integrated manner so that evidence generated can be used for action.

5604

IMPLEMENTATION OF A SUSTAINABLE AEDES AEGYPTI CONTROL STRATEGY: A COMMUNITY-BASED MODEL

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Dengue, Chikungunya, and Zika viruses pose significant challenges for public health disease management in the tropics. The control of these arboviruses has traditionally relied on strategies focused on the mosquito vector, Aedes aegypti, through insecticides or more recently with the use of suppression or replacement strategies. Traditional efforts have failed to contain arbovirus transmission or control the vector, and while novel technologies have shown promising results they are still being tested. We implemented a sustainable community-focused Participatory Action Research methodology for Ae. aegypti control based on the Care Group and DengueChat programs that have been previously evaluated in high-risk communities for dengue in Managua, Nicaragua. Between 2017 and 2020, house-to-house visits were made to promote container management. These were carried out jointly between a community "brigadista" (volunteer) and a household participant. All containers with water inside and outside of the household were checked to promote resident-led elimination of breeding sites. Our team promoted the implementation without carrying out the removal of positive containers. Subsequently, the "brigadista" coordinated meetings with neighbors to build rapport based on the evidence of the control activities and generate collective achievements with neighbors to avoiding stigmatization. Throughout the study, the Ministry of Health carried out routine control measures in the area. In the baseline wet season of 2017, we found 161 pupae per household, 38 pupae per container, and 0.35 pupae per person. At the baseline of the dry season in 2018, we found 60 pupae per household, 20 pupae per container, and 0.13 pupae per person. After the implementation of our control strategy, we observed a Reduction of 81% for pupae per household, 64% pupae per container, and 81% pupae per person. With a sustained reduction of productive containers in the area. Our results show that the inclusion of communities in the management and control activities of Ae. aegypti can be maintained and run by community members and sustained over time.

5605

COST EFFECTIVENESS OF COMPARATIVE SURVEY DESIGNS FOR HELMINTH CONTROL PROGRAMS: POST-HOC COST ANALYSIS AND MODELLING OF THE KENYAN NATIONAL SCHOOL BASED DEWORMING PROGRAM

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Soil-transmitted helminths (STH) and schistosomiasis comprise the most wide-spread NTDs globally. Preventative chemotherapy is a cost-effective approach to controlling morbidity of both diseases, but relies on large scale surveys to determine and revise treatment frequency. Availability of detailed information on survey costs is limited despite recent methodological surveying innovations. We micro-costed a survey of STH and schistosomiasis in Kenya, and linked results to precision estimates of competing survey methods to compare cost-efficiency. Costs from a 2017 Kenyan parasitological survey were retrospectively analyzed and extrapolated to explore marginal changes when altering survey size, defined by the number of schools sampled and the number of samples taken per school. Subsequent costs were applied to simulated precision estimates of model-based geostatistical (MBG) and traditional survey designs. Cost-precision was calculated for a range of survey sizes per method. Four traditional survey design scenarios, based around WHO guidelines, were selected to act as reference cases for calculating incremental cost-effectiveness ratios (ICERs) for MBG design. MBG designed surveys showed improved cost-precision, particularly if optimizing number of schools against samples per school. MBG was found to be more cost-effective under 87 of 92 comparisons to reference cases. This comprised 14 situations where MBG was both cheaper and more precise, 42 which had cost saving with precision trade off (ICERs; $8,915-$344,932 per percentage precision lost); and 31 more precise with increased cost (ICERs; $426-$147,748 per percentage precision gained). The remaining 5 comparisons represented extremes of MBG simulated site selection, unlikely to be applied in practice.

5606

SEROSTATUS OF ANTI-RABIES TITER VACCINE LEVELS IN IMPOUNDED DOGS IN MUNTINLUPA CITY, PHILIPPINES, 2021

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Rabies is a zoonotic disease transmissible thru bite by an infected rabid animal. It is a vaccine preventable disease wherein a titer of 0.5 IU/ml is considered on protective level based on the WHO and WOAH (World Organization for Animal Health, formerly known as OIE). This study aims to investigate the serostatus of anti-rabies titer vaccine level that is impounded dogs in Muntinlupa city. Two hundred and fifty-two (252) serum samples were collected from dogs that is impounded in Muntinlupa city pound with unknown history of vaccination, out of these 86 (34.13%) dogs showed antibody titer above 0.5 EU/ml. all dogs collected with serum samples were processed and tested using ELISA with manufacturer's graphpad prism software to check all computation of the vaccinal immune response. Out of 252 serum samples, 166 (65.87%) impounded dogs showed anti-rabies antibody titer below 0.5 EU/ml/ indicating susceptibility to rabies infection and thereby posing possible threat to surrounding human and animal population in the area.

5607

ASSESSING HEALTH SYSTEM'S PERFORMANCE FOR NEGLECTED TROPICAL DISEASES (NTDS) THROUGH WHO'S DATA QUALITY ASSESSMENT (DQA) TOOL IN FOUR WEST AFRICAN COUNTRIES

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The WHO's Data Quality Assessment (DQA)for Neglected Tropical Diseases (NTDs) is an important Monitoring and Evaluation (M&E) tool that can be used after Mass Drug Administration (MDA) to analyze data quality. The tool evaluates two parts: 1) Verification of MDA data, which includes verification factor (VF, ratio of recounted and reported numbers) for up to five indicators, and 2) An assessment of data management and reporting system through a. M&E structure, b. Indicator reporting guidelines, c. Data-collection, reporting tools, d. Data management processes, and e. Links with the national reporting system. Act to End NTDs | West is a five-year USAID-funded program that aims to eliminate or control five NTDs (LF, Trachoma, OV, SCH, and STH) in 11 West African countries. It routinely implements DQAs in its portfolio. We summarized data across seven DQAs (84 service delivery points) across four West African countries. The average verification factor was 94.4 (SD-20), demonstrating potential over-reporting for indicators assessed ("Number of pills administered" and "Number of people treated.") The scores were high for all five system assessments, particularly Indicator reporting guidelines (3.0 out of 3.0) and Links with national reporting system (2.9 out of 3.0). We explored the association between system scores and the VF to identify ways of enhancing data quality using DQAs. The VF and total system scores had a moderate positive correlation, r= 0.42. (pr<0.05). Additionally, we built a linear regression model with VF as the outcome variable and five system scores, border districts, and MDA

rounds as independent variables. The analysis showed positive associations between VF and M&E structure, data collection, and reporting tools, where VF increased by 0.10 (95% CI: 0.01, 0.20), and 0.45 (95% CI: 0.27, 0.63) respectively per unit increase in the system score. We observed that the number of MDA rounds and border districts had an inverse relationship with VF. These findings indicate that improving system scores (a & b) would enhance the accuracy of MDA data (VF). The programmatic response could also include focusing on improving MDA at border districts.

5608

MEASURING THE OUTCOME OF THE MASS DRUGS ADMINISTRATION OF LYMPHATIC FILARIASIS THROUGH SENTINEL AND SPOT SITES SURVEYS FROM 2012 - 2021

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The results of the survey show that the disease is endemic in 13 of the 15 counties. The programme began implementing the first LF MDA, using a community distribution method, in 2012 in all 13 endemic counties. The programme has subsequently treated in 2013, 2015-2019 and 2021 in all endemic counties. Based on WHO guidelines to monitor the progress and impact of MDA, Sentinel sites must be identified in each implementation unit for evaluation after every 3 rounds of MDA. The program has conducted 3 destined Sentinel and Spot Check Sites Surveys in the Counties. The objective is to showcase the progress of MDA in reducing micro filarial in the communities through monitoring and Evaluation of Sentinel and Spot sites survey at the county level. To showcase results and data indicating a downward trend of the impact of MDA only lymphatic filariasis with the use of Albendazole in Liberia. To demonstrate the strategies in determining the impact of the Mass Drug Administration in controlling and eliminating Lymphatic Filariasis in Liberia. The Sentinel and Spot Check sites survey were conducted with a cross-sectional approach whereby people ages 5 years and above were sampled. Samples collected from participants were tested with Filarial Test Strips and counting chambers. The method of sample collection and testing were recommended by WHO. The NTD programme has conducted three sentinel site surveys; the first, baseline, was conducted in 2012 in 11 sites and the second was conducted in 2016 in 11 sites across the same 11 counties. The second survey was conducted in 4spot-check sites and 7 sentinel sites. The county of River Gee had an increase from 0% to 0.99%Mf. Maryland, the only county with a MF rate over 1% showed a reduction from 11.37% to 8.36%.The slow rate of reduction is likely attributed to receiving 2 rounds of MDA instead of 3 rounds.

5609

INCIDENCE OF SNAKEBITES IN RURAL POPULATIONS OF REPUBLIC OF CONGO

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Snakebites are a real social, economic and public health problem in the world. Few studies on snakebites have been conducted in Congo. The objective of this study is to report data on the risk and incidence of snakebites in rural populations in the Republic of Congo. A household survey of rural populations was conducted in 5 districts. This household survey was conducted using a questionnaire that took into account the characteristics of snakebite victims, the circumstances of the bite (location, season, time of day, activity) and the victim's recourse to treatment (traditional practitioners, dispensaries, self-medication). For the calculation of incidence, the average age of the respondents was used as a proxy for the period covered by the survey, thus completing the denominator. The collected data were entered into Microsoft Excel 2013, exported, and analyzed using Package for Social Science (SPSS) version 22 software. A total of 133 snakebite cases were recorded during the study period. In Okoyo District, 80 snakebite cases were reported and 2 deaths recorded. In Enyéllé District, 35 cases of snakebites were reported and 5 deaths were recorded. In Gamboma, 13 cases of snakebites were reported and no deaths were recorded. In the districts of Tchiamba-Nzassi and Mokéko, 1 case and 4 cases of snakebites were respectively recorded with no deaths. The incidence measured during this survey was 2857 bites per 100,000 inhabitants per year in Okoyo, 3535 bites per 100,000 inhabitants per year in Enyellé and 1032 bites per 100,000 inhabitants per year in Gamboma. More than half of the victims sought traditional care in Okoyo, Enyelle and Gamboma districts. While in Enyelle, 28.57% of cases used traditional-modern care and 7.69 of cases in Gamboma used modern care.This study highlights the need to intensify snakebite surveys throughout Congo by conducting surveys at three levels: health facilities, households and traditional healers in order to have a more general knowledge of snakebite victims. A program to raise awareness among rural populations about the dangers involved should be put in place.

5610

UTILITY OF THE LOOP-MEDIATED ISOTHERMAL AMPLIFICATION ASSAY FOR THE DIAGNOSIS OF VISCERAL LEISHMANIASIS FROM BLOOD SAMPLES IN ETHIOPIA

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Rapid and accurate visceral leishmaniasis (VL) diagnosis is needed to initiate prompt treatment to reduce morbidity and mortality. Here, we evaluated the performance of loop-mediated isothermal amplification (LAMP) assay for the diagnosis of VL from blood in an endemic area in Ethiopia. LAMP was positive in 117/122 confirmed VL cases and negative in 149/152 controls, resulting in a sensitivity of 95.9% (95% CI: 90.69-98.66) and a specificity of 98.0% (95% CI: 94.34-99.59), respectively. The sensitivity of the LAMP assay was 95.0% (95% CI: 88.61-98.34) in HIV-negatives and 100% (95% CI: 85.18-100.0) in HIV-positives. Compared with microscopy, LAMP detected 82/87 (94.3%, 95% CI: 87.10-98.11) of the microscopy1 cases and was negative in 11/27 (40.7%, 95% CI: 22.39-61.20) of the microscopy2 cases. Compared with the rK39 serology, LAMP detected 113/120 (94.2%, 95% CI: 88.35-97.62) of the rK391 cases and was negative in 149/154 (96.8%, 95% CI: 92.59-98.94) of the rK392 cases. However, when compared with microscopy only, rK39 detected 83/87 (95.4%, 95% CI: 88.64-98.73) of the microscopy1 cases and negative in only 12/27 (44.4%, 95% CI: 25.48-64.67) of the microscopy- cases. There was an excellent agreement between rK39 and LAMP (Kappa 5 0.91, 95% CI: 0.86-0.96). Furthermore, an algorithm using rK39 followed by LAMP would yield a sensitivity of 99.2% (95%CI: 95.52-99.89) and a specificity of 98.0% (95% CI: 94.34-99.59). The findings demonstrate that LAMP assay is an accurate and rapid molecular assay for VL diagnosis, including in HIV-1 co-infected patients, in an endemic setting.

5611

VISCERAL LEISHMANIASIS: IMPROVED MOLECULAR DIAGNOSIS USING THE MINI DIRECT ON BLOOD PCR NUCLEIC ACID LATERAL FLOW IMMUNOASSAY (DBPCR-NALFIA)

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Accurate and early diagnosis of Visceral Leishmaniasis (VL) is important to install proper treatment, because of the fatality of the condition and the high toxicity of available treatments. Current diagnostic methods include parasitology and serology (with rK39 dipstick test and direct agglutination test). These methods do have limitations (patient safety or diagnostic accuracy), and molecular testing is proposed to improve diagnosis. Current molecular tools, in particular PCR, have high accuracy for detecting VL, however their complexity and high costs make their use

unsuitable for endemic areas with limited resources. Consequently, there is a need for a simple molecular diagnostic test that can be implemented in resource limited setting. We have developed a miniaturized direct-on-blood PCR nucleic acid lateral flow immunoassay (mini-dbPCR-NALFIA) as an innovative, easy-to-use molecular assay for the diagnosis of VL in these particular settings. Unlike other simplified molecular methods, such as LAMP, the mini-dbPCR-NALFIA does not require DNA extraction and utilizes a handheld, portable thermal cycler powered by a solar-charged power pack enabling to perform the test without any laboratory infrastructure. Reading of results is done using a rapid lateral flow strip. In the present study we have conducted a laboratory evaluation on the mini db-PCR-NALFIA to determine its diagnostic accuracy. Patient samples (N=146) with suspected VL were tested using the mini db-PCR-NALFIA and compared to conventional PCR (reference test). Sensitivity and specificity represented the accuracy. Cohen's k determined the degree or agreeableness between the mini db-PCR-NALFIA and other diagnostic tests (PCR and rk39 rapid test). Compared to qPCR, the mini db-PCR-NALFIA for VL had a sensitivity of 95.83% (95% CI, 88.30%-99.13%) and a specificity of 97.22% (95% CI, 90.32% - 99.66%). The agreement between both tests was excellent (k-value: 0.93). The Limit of Detection of the platform is around 10 parasites per microliter of blood (spiked with promastigotes).

5612

COST EFFECTIVENESS ANALYSIS OF CONGENITAL CHAGAS DISEASE SCREENING METHODS IN BOLIVIA

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Of the 6 to 7 million global cases of Chagas disease, Bolivia is the country with the highest prevalence, many due to congenital transmission, which is one of the routes of transmission of Chagas disease. The WHO calls for the elimination of congenital Chagas disease by 2030. This study compares the cost-effectiveness of three methods for a national screening intervention: qPCR, Western Blot, and microhematocrit (all utilized at ages zero, one, and nine months). We used decision tree analysis to compare the cost effectiveness of three screening methods: i) microhematocrit, ii) qPCR, and iii) Western blot, considering microhematocrit as the standard of care. Transition probabilities were taken from previous studies or derived as assumptions. Previous studies and primary data collection from Bolivia provided cost data. We performed one-way sensitivity analysis to test the model's uncertainty, represented through a tornado diagram. Parameters included were the methods' respective sensitivities; the probability of being tested at zero, one, and nine months; and the costs of the microhematocrit, qPCR, and Western Blot tests. The model indicates that screening intervention using qPCR is more cost-effective than using microhematocrit, considering a willingness to pay (WTP) threshold of three times the GDP per capita of Bolivia. National implementation of qPCR would result in earlier diagnosis of congenital Chagas disease, resulting in effective treatment for infants and prevention of future costs. We continue to develop our model, comparing Western Blot data with that of qPCR and microhematocrit. We also continue to analyze the effectiveness of these interventions, using DALYs to consider long-term effects. The most common method to diagnose congenital Chagas disease in Bolivia, microhematocrit, has low sensitivity: more than 40% of infected infants are misdiagnosed due to false negatives. qPCR's high cost and Western Blot's long learning curve have resulted in less frequent use. Considering the direct and indirect costs for Chagas disease patients, the two methods' overall cost-effectiveness must be re-evaluated.

5613

POTENTIAL BIOMARKERS FOR ASYMPTOMATIC VISCERAL LEISHMANIASIS AMONG DEPLOYED U.S. MILITARY PERSONNEL

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Visceral leishmaniasis (VL) is caused by infection with Leishmania (L.) donovani or L. infantum (syn. L. chagasi) parasites. Despite infection, most individuals immunologically control the parasite and remain asymptomatic. However, some people progress to symptomatic VL, potentially leading to death if untreated. Although several immune biomarkers of symptomatic VL have been described; our objective was to determine new biomarkers capable of identifying asymptomatic visceral leishmaniasis (AVL), in addition to interferon gamma. Levels of chemokines/cytokines in supernatants of peripheral mononuclear blood cells (PBMC) from 35 AVL+ healthy Iraq-deployed participants, stimulated in vitro with soluble Leishmania antigen (SLA) for 72 hours, were assessed by a bead-based assay that allows the measure of multiple analytes. Additionally, we evaluated the chemokine/cytokine levels in supernatants from whole blood of 18 subsequently-immunosuppressed AVL+ Iraq and Afghanistan deployers (tumor necrosis factor α inhibitor users, n=7; renal transplant, n=4; or HIV infection, n=7), stimulated in vitro with SLA for 24 hours and tested by the same assay. We also studied blood of AVL negative controls, both healthy (n=14) and immunosuppressed (n=22). Three biomarkers: monokine induced by gamma interferon (MIG) (AUC 0.87, 71% sensitivity), monocyte chemoattractant protein-1 (MCP-1) (AUC 0.79, 91% sensitivity) and interleukin (IL)-8 (AUC 0.80, 66% sensitivity) were detected at high levels in AVL+ supernatants from stimulated cultures from healthy deployers compared to uninfected controls. MCP-1 was detected at high levels in AVL+ persons living with HIV (AUC 0.92, 100% sensitivity). In conclusion, chemokine profiling is a useful strategy for identifying cellular immune responses in AVL+ individuals. Our results show that MCP-1 is a candidate biomarker in assessing AVL in stimulated whole blood of persons living with HIV and in PBMC of healthy adults and MIG (and IL-8 to a lesser extent) is also possible biomarkers in assessing AVL+ in healthy deployers.

5614

OPTIMIZATION AND VALIDATION OF RECOMBINANT ANTIGEN BASED INDIRECT ELISA FOR CUTANEOUS LEISHMANIASIS

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Cutaneous leishmaniasis (CL) in Sri Lanka is caused by Leishmania donovani, a parasite having a potential for visceralization. Even though CL is not generally considered as a disease that induces humoral responses, several recent studies have reported antibody responses against CL. This study was designed to assess the antibody responses of CL patients in Sri Lanka by optimizing and validating a recombinant rK39 and KMP11 antigen-based ELISA. Optimization of the ELISA included the checkerboard titration method to determine the optimum antigen concentration and sample dilution. The ELISA was conducted using a standard protocol after optimization. The optimum antigen concentration of rK39 ELISA was 3.0 µg/ml and the optimum sample dilution was 1:400. The optimum antigen concentration for KMP11 ELISA was 2.0 µg/ml and the optimum sample dilution was 1:50. The optimized ELISAs were conducted for 140 serum

samples from confirmed CL patients (both treated and non-treated) and for negative samples taken from healthy individuals from non-endemic areas. The established ELISA protocol using parasite crude antigen was also performed for comparison. The results were analyzed using SPSS V26.0 software and cut-off values for each antigen were determined by Receiver-Operator-Characteristic (ROC) curve. ELISA for rK39 showed 51.4% sensitivity and 60% specificity. ELISA for KMP11 showed 71.4% sensitivity and 52% specificity. ELISA for parasite crude antigen showed 84.3% sensitivity and 85.7% specificity. Therefore, the parasite crude antigen ELISA was a better assay than recombinant antigen based ELISAs for the detection of ani-leishmania antibodies. The low sensitivity and specificity of the tests are the major limitation when developing these into a reliable diagnostic tool for CL.

5615

EVALUATION OF NOVODIAG® STOOL PARASITES TEST, A HIGH-PLEX STOOL TEST, AGAINST TRADITIONAL METHODS IN A HIGH-RISK TRAVELLER AND MIGRANT POPULATION AS A POTENTIAL FOR QUICKER AND MORE ACCURATE IDENTIFICATION OF INTESTINAL PARASITES

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Introduction. Identification of intestinal pathogens via stool microscopy requires highly trained personnel, multiple samples and is labour intensive. Early identification is key to limiting spread and informing treatment to prevent clinical complications. We aimed to compare traditional methods with the Novodiag® Stool Parasites test (Mobidiag, Espoo, Finland), a CE-marked high-plex test that combines real-time PCR (rt-PCR) and microarray assays for the identification of 25 pathogens. Methods. Stool samples from traveller and migrant populations were run on the Novodiag® Stool Parasites test (NSP) and a Giardia intestinalis in-house rt-PCR assay. Positive samples were analysed using traditional microscopy staining of formalin-ethyl acetate faecal concentrates for ova, cysts and parasites (OCP). Results. Between September 2022 and February 2023, 454 tests for 448 patients were run on the NSP. One assay failed due to sample inhibition. 48 patients had positive results; 4 patients had dual infection (3 on NSP and 1 on OCP). Stool OCP was performed on 46 samples, results were concordant in 25 out of 46 samples. Hymenolepis nana was identified in two OCP samples which were not identified by NSP and on two NSP samples not seen on OCP. NSP detected more Enterobius vermicularis, Schistosoma spp, Strongyloides stercoralis, Ancylostoma duodenale, Enterocytozoon bieneusi, Necator americanus and Taenia spp than OCP. Detection of Giardia was similar between standard rt-PCR and NSP; there were 19 positive Giardia samples in NSP, 17 of which were also detected by rt-PCR. One sample was detected by rt-PCR and not detected by NSP. Discussion. NSP had a greater detection rate for a wider range of pathogens than OCP and is equivalent to rt-PCR for detection of Giardia. However, as it cannot identify all intestinal parasites, it cannot replace standard microscopy, but can provide an appropriate additional diagnostic tool for identification of common pathogens with a more rapid turn-around time, greater number of pathogens identified and requires less skilled personnel.

5616

A SEROLOGICAL 'TEST OF TREATMENT RESPONSE' FOR CHAGAS DISEASE

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Chagas disease, caused by the protozoan Trypanosoma cruzi, is the most prevalent parasitic disease in the western hemisphere. Treatment with available antiparasitics is lengthy, often with adverse events, and efficacy varies depending on age and stage of disease. Determining if treatment is effective is critical, as ~30% of infected individuals will develop cardiac or gastrointestinal complications that can be fatal. There is currently no standardized assay to measure treatment response and guide clinical decision-making. Accordingly, we sought to develop a 'Test of Treatment Response' (TTR) to measure post-treatment serological decline as an accepted surrogate for decreasing parasite burden. To identify potential biomarkers, we probed a peptide array comprising ~8000 sequences from 41 known T. cruzi antigens with IgG from Chagasic subjects and healthy controls. Four peptides were selected based on sensitivity against a geographically diverse panel of Chagasic sera and on responsiveness to serological decline in post-Rx samples. A prototype ELISA using the 4 peptides was tested on a longitudinal treatment cohort from São Paulo, Brazil that included samples pre-Rx and 6,12, and 36-months post-Rx. When tested on samples collected 12m post-Rx, each peptide biomarker detected serological decline (defined as ≥20% decline in IgG titer) in a larger proportion of individuals (45-71%) than conventional ELISA (22%). Using a simple algorithm to combine individual peptide results, the peptide ELISA detected serodecline in 72/76 patients at 36m post-Rx compared to 16/76 by conventional ELISA. Our results demonstrate that synthetic peptides may be more sensitive serologic indicators of treatment response than full-length recombinant or native proteins, revealing serodecline faster and to a greater magnitude than conventional ELISA. However, further studies are needed to determine the exact relationship between serodecline and parasite burden. Development and clinical evaluations of the peptide TTR assay are ongoing with the ultimate aim to provide commercial ELISA and point-of-care versions.

5617

EVALUATION OF TOXOPLASMA GONDII EXCRETORY/SECRETORY AND MEMBRANE ANTIGEN FOR THE DETECTION OF INFECTION IN ACUTE PHASE BY WESTERN BLOTTING

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One of the most common zoonoses affecting humans is toxoplasmosis, which is caused by Toxoplasma gondii and represents a danger because of the significant morbidity and mortality levels in at-risk populations: immunosuppressed patients and pregnant women. Since at-risk populations need to be constantly monitored, a confirmatory test that is sensitive and specific enough to detect and differentiate the different stages of the disease is needed. To meet this objective, 25 Holtzman rats of 30 days old were infected intraperitoneally with 105 T. gondii tachyzoites of the RH strain and followed up to 90 days post infection. Blood was collected and used for disease detection using immunological tests to detect proteins and antibodies generated during infection (acute and chronic phase). The antigens used were total antigen lysate (TLA), excretory secretory antigens (E/S) and membrane antigens. Western blot results showed that using the excretory secretory (E/S) antigens, 25 kD and 30 kD bands were recognised that only appeared in the rats of the 30 and 60 day post infection (chronic phase) group. When the antigens of the membrane fraction were confronted against the sera of rats from the 60 days post infection group (chronic phase), the most significant bands detected were 80 kD, 19 kD, 15 kD, as these bands were not evident in the cytoplasmic fraction when confronted with the same sera. The T. gondii total antigen lysate (TLA) showed too many bands when confronted with rat sera from the chronic and acute group, and it was not possible to establish significant

differences between the two phases. This study concludes that excretory secretory antigens (E/S) and membrane antigens are the most optimal to differentiate the chronic and acute phases of infection because the bands can be observed better separated and with higher specificity (30 and 60 kDa in the E/S antigen) compared to TLA, where too many and in many cases non-specific bands are reported, making the diagnosis of the phase more difficult. These results will serve as a basis for studies in at-risk human populations to differentiate between chronic and acute phases of infection.

5618

DRIED BLOOD SPOTS: A SUITABLE ALTERNATIVE TO USING WHOLE BLOOD SAMPLES FOR DIAGNOSTIC TESTING OF VISCERAL LEISHMANIASIS IN THE POST-ELIMINATION ERA

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Serum or whole blood collection, processing, transport and storage still represent a significant challenge in low resource settings where mass surveillance is required to sustain disease elimination. Therefore, in this study, we explored the diagnostic efficacy of dried blood spots (DBS) as a minimally invasive and potentially cost-effective alternative sampling technique to whole blood sampling procedures for subsequent detection of Leishmania donovani antibodies or DNA. Archived serum, DNA samples from whole blood of visceral leishmaniasis (VL) cases and healthy controls, and DBS from corresponding cases and controls, were used. Both molecular and serological assays were optimized to detect L. donovani antibodies or DNA in DBS elute and results were compared against those obtained with whole blood. Serological assays (both rK28 ELISA and rK39 ELISA) of DBS samples showed sensitivity and specificity of 100% and had excellent agreement with results from whole blood samples (kappa value ranged from 0.98-1). Bland-Altman analysis of OD values from rK28-ELISA with DBS elute and patients' serum showed an excellent agreement (ICC=0.9) whereas a good agreement (ICC=0.8) was observed in the case of rK39-ELISA. However, qPCR and RPA of DBS samples had a diminished sensitivity of 76% and 68 %, respectively, and poor agreement was observed with the whole blood samples.Our results demonstrate that DBS offer excellent diagnostic efficiency for serological assays and represent a viable alternative to whole blood sampling procedures.

5619

ACCURACY OF THE "TESA-BLOT RAPID TEST" FOR THE DIAGNOSIS OF CHAGAS DISEASE

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A common form of Trypanosoma cruzi transmission is vertical mother-to-child transmission, which is the main form of transmission in nonedemic countries in addition to being a significant -but neglected-contributor in endemic regions. Lack of awareness and timely diagnosis in rural endemic areas, exacerbate high infection rates, with more than one million Latin American women of childbearing age are infected with Chagas disease. Only approximately 10% of these women are aware of their infection leaving thousands of newborns at risk of being born infected. The lack of access to rapid and accurate diagnostic assays makes it difficult to detect positive mothers, especially since many of these women have limited contact with healthcare workers prenatally and only come to the hospital for delivery and then return to a rural area. Conventional diagnostic tests- such as HAI, IFA, and ELISA-. lack reproducibility and reliability of results and take hours to process. Therefore, the test results are often not available until after the mother has left the health centre. In order to address this issue, we developed a rapid Western blot (using the trypomastigote excretory-secretory antigen), which has a sensitivity of 100% and a specificity of over 94%. For the evaluation of the standardized "TESA Blot rapid test", 35 samples from mothers and samples from their babies (34 samples) were tested, comparing the standard TESA to the new reapid TESA. In conclusion, it was possible to detect patients in the acute phase in 25 minutes and the chronic phase in 35 minutes, compared to the 14 hours needed for the original TESA blot. This allows for timely follow-up and treatment for the mother and newborns.

5620

EVALUATION OF TRYPANOSOMA CRUZI AMASTIGOTE ANTIGENS IN CARDIAC TISSUE AT DIFFERENT POST-INFECTION TIMES

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Chagas disease is caused by Trypanosoma cruzi and affects between 6-7 million people mainly in Latin America. Many people in the acute phase have no symptoms and in some cases only general symptoms are present, which makes diagnosis difficult. It is known that 30% of infected persons develop cardiac manifestations after 20-30 years of infection. The development of chronic cardiomyopathy in infected persons increases the risk of death by 20% compared to other types of cardiomyopathy. Currently, government programs are not efficient in monitoring and diagnosing the disease. Therefore, it is important to develop better tools in in vivo models to understand the development of the pathogenesis of the disease. It is difficult to identify the presence of amastigotes when tissue parasitism begins to decline. The availability of specific polyclonal antibodies, conjugated with fluorophores or HRP, against amastigote would be a good alternative to identify them in a more efficient way. Therefore, axenic amastigotes, free of cells and other stages, were obtained by amastigogenesis from trypomastigotes of strain Y, cultured in LL-CMK2 cells and RPMI medium at 2% SFB. Trypomastigotes were incubated in medio Dulbecco's Modified Eagle's medium alto en glucosa (hgDMEM) with 20 mM MES buffer at pH 5 with 0.4% BSA (condition I) and without BSA (condition II). The evaluation of the transformation kinetics was performed by counting in Neubauer hemocytometer where it was observed that at 4 h of incubation 75% and 95% of the incubated parasites were transformed to amastigotes, in condition I and II, respectively. While at 8 h of incubation 97% and 100% were observed for condition I and II respectively, however with condition I at 12 h, 100% transformation was also observed. According to these results, successful amastigogenesis was obtained in both conditions, with faster transformation in condition II. These results contribute to the production of polyclonal antibodies from immunizing rabbits with the lysate of these amastigotes. In order to identify more specifically, by immunofluorescence or immunohistochemistry, the presence of tissue amastigotes in animals.

5621

COMPARATIVE ANALYSIS OF A CHAGAS DISEASE RAPID DIAGNOSTIC TEST (RDT) FOR THE DETECTION OF ANTI-TRYPANOSOMA CRUZI ANTIBODIES AMONG SERUM COLLECTED FROM MULTIPLE REGIONS OF COLOMBIA

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Chagas disease (CD) is known to effect those living in impoverished and vulnerable circumstances, placing those at risk for vector-borne and oral transmission of Trypanosoma cruzi within endemic regions. Rapid Diagnostic Tests (RDT) for CD can be utilized in the field, local clinics and health facilities with limited access to a laboratory which requires specialized equipment and trained technicians. Serum collected and stored (-80C°) from individuals living within the CD endemic regions of

Sierra Nevada de Santa Marta (SNSM), Urabá, Boyacá, and Chocó, regions of Colombia from 2003 until present day, were tested with a lateral flow immunochromatographic assay (DPP® Chagas System; Chembio Diagnostic Systems, Inc.) and compared with confirmed positive and negative stored samples. Among these serum samples, CD was confirmed positive (n=102) with positivity to both T. cruzi IgG ELISA and Immunofluorsecence Antibody (IFA) assays developed at the Universidad de Antioquia (UdeA) in MedellÍn, Colombia, from a T. cruzi isolate cultured from SNSM region of Colombia. Sensitivity and specificity of the UdeA T. cruzi IgG ELISA and IFAT among Colombian serum samples is 98% and 97%, respectively. DPP® Chagas System RDT utilizes a Micro Reader to interpret the immunochromatographic results with either, non-reactive, indeterminate, or reactive. Following manufacturer's protocol, 5µl of serum from both positive and negative serum samples were tested with DPP® Chagas System and results were available within 15 minutes. Results of testing reveal sensitivity of 98.88% [95% CI 93.96-99.97% (n=89/90)] were true negative and specificity of 97.05% [95% CI 91.65-99.39% (n=99/102)] were true positive. Failure rate of testing was 1.04% (n=2/192) in which testing had to be repeated due to non-functioning cartridge or invalid result. The DPP® Chagas System RDT was easy to use and provided both highly sensitive and specific results among those living with CD from these regions of Colombia. The use of RDTs for CD screening and diagnostics can help reach populations with limited resources in Colombia and other endemic regions.

5622

DETECTION OF A TOXOPLASMA GONDII ANTIGENIC PROTEIN AND ITS POTENTIAL USE IN THE NONINVASIVE DIAGNOSIS OF TOXOPLASMOSIS

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Toxoplasma gondii is an intracellular parasite that can infect all warm-blooded living beings, including man. In immunocompetent patients the process is asymptomatic, however cysts persist for life in tissues, when the individual is immunosuppressed (transplants, pregnancy, HIV) reactivation of the active stage of T.gondii can become fatal. Non-invasive and confirmatory techniques are needed in order to detect active T.gondii infection in immunosuppressed individuals. A total of 20 urine samples from HIV patients separated into 2 groups were used: Group I: 10 HIV patients with suspicion of active toxoplasmosis with Cq values (35-20) in CSF samples in the amplification of a REP529 fragment, IgG positive and with a clinical diagnosis of Toxoplasmosis, Group II: 10 HIV patients negative for T.gondii. Hydrogel nanoparticles will be used in order to concentrate small proteins ≤30kD in urine, followed by dot blot detection of a dense granule protein (GRA1) of T.gondii. In GRA1 positive patients, a black spot was observed on the PDVF membrane, detecting GRA1 in 40% (4/10) patients in Group I, and in 0% (0/10) of patients in Group II. The use of nanoparticles in urine samples allowed the detection of GRA1, a dense granule protein of Toxoplasma gondii involved in the development of an active stage or reactivation stage due to immunosuppression, making this technique a promising tool for the non-invasive diagnosis of toxoplasmosis.

5623

ASSESSING THE TSETSE FLY MICROBIOME COMPOSITION AND THE POTENTIAL ASSOCIATION OF SOME BACTERIA TAXA WITH TRYPANOSOME ESTABLISHMENT

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Tsetse flies are biological vectors of trypanosomes which cause African trypanosomiasis. No vaccine is available, and drugs are toxic with increasing emergence of resistance. Reducing vector competence can be additive tools to stop disease transmission. Some bacteria have been shown to be used as paratransgenic organisms capable of blocking trypanosome's development in flies. Understanding the role of tsetse microbiome in disease transmission could improve knowledge in initiatives to develop new vector control strategies. We aim to determine the microbiome composition of tsetse flies and their association with trypanosome establishment. Tsetse flies were collected from Campo, southern Cameroon and total DNA was extracted from fly bodies and heads separately. Trypanosome species were identified by PCR. Amplification of the V3-V4 region of the 16S rRNA gene followed by sequencing on Illumina miseq with subsequent metagenomic analyses were performed to identify the different bacteria communities. PCR analysis of 2186 Glossina p. palpalis revealed 20.08% trypanosome infections with Trypanosoma congolense (13.73 %,) the predominant species; 0.17 % were T. b. gambiense. 21.27% of infected flies produced mature infections. From 192 samples randomly sequenced, a total of 31 bacteria genera were identified with the primary symbiont Wigglesworthia displaying 47.29% abundance. Globally, significant differences were observed in the microbiome diversity among tsetse species, between teneral and non-teneral flies and between flies displaying or not displaying mature trypanosome infections. In addition, differential abundance testing showed several bacteria taxa such as Dechloromonas, Ralstonia and Serratia associated with trypanosome maturation in tsetse flies.This study has shown some bacteria associated with trypanosome infection maturation in flies, which therefore need further studies to investigate an understanding of their mechanism of action and alternatively, transformed and used to block trypanosome development in tsetse flies.

5624

SIMILARITIES BETWEEN GENES FOR TRYPANOSOMA CRUZI MICROTUBULE ASSOCIATED PROTEINS AND HUMAN INTERFERONS

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Trypanosoma cruzi Microtubule Associated Proteins (MAPS) are encoded by a family of homologous genes. We have previously shown that one of these genes, coding for the T. cruzi human serodiagnostic antigen Ag36, is similar in gene sequence to human immune Tripartite Motif (TRIM) proteins, such as TRIM21. Since TRIM proteins are intrinsic to human innate immunity, we examined several cytokines key to innate immunity; for example, human Interferon and Interleukin genes. The Needleman-Wunsch Algorithm, which measures and scores the extent of similarity of two gene sequences, was used to compare Genbank M21331 (the Ag 36 gene) with these two genes, respectively. The tools and gene sequence analysis were performed and the results stored at https://usegalaxy.eu. Human Interferon gamma showed 17.9% identity, Human Interferon alpha displayed 13.6% identity, and Human beta Interferon indicated a 12.6% identity to M21331. Human Interleukin genes showed no significant similarity to M21331. The possible implications during T. cruzi infection and manifestation of Chagas' disease of these similarities to human Interferon genes and the 33 T. cruzi MAP genes will be discussed.

5625

HYBRID ASSEMBLY OF THE LEISHMANIA (VIANNIA) PERUVIANA GENOME

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Leishmania (Viannia) braziliensis complex encompasses two closely related species (L. (V.) braziliensis and L. (V.) peruviana) with different geographical distributions and disease phenotypes. Unlike L. (V.) braziliensis which has been extensively studied, L. (V.) peruviana is still largely uninvestigated. Furthermore, this latter species lacks a reliable or complete reference genome which is key for population genetics, functional studies, and surveillance. In this study we report a high-quality genomic sequence of L. (V.) peruviana obtained from combining long and short reads generated by high-throughput sequencing. For this purpose, genomic DNA from the MHOM/PE/87/PAB2880 L. (V.) peruviana strain was sequenced on

MinION nanopore and Illumina NovaSeq. The resulting Nanopore reads were used for de novo assembly using Flye 2.9.1 to generate contigs and chromosome scaffolds. Then Illumina reads were aligned onto these scaffolds with Minimap 2 2.17 to perform error correction, close gaps, reduce sequencing errors, and generate a consensus sequence. Nanopore sequencing resulted in 84.33Mb estimated bases contained in 19.24K unpaired reads (Length N50=10.89K) whereas Illumina sequencing resulted in 3.56Gb paired reads contained in 23.5M reads (Length N50=151bp). A BLAST search against the NCBI database showed that all reads aligned with at least one species of the Leishmania (Viannia) braziliensis complex. The kinetoplast genome (kDNA) was contained in a single 23.1Kb scaffold whereas the nuclear genome was contained in 197 scaffolds with a total length of ~35Mb (N50=36Kb). This version of the genome constitutes an improved assembly compared to the one previously reported for this species which was limited to 25Mb fragments into 27,873 scaffolds (N50=1.3Kb). Referenced-based, de novo gene annotation and a deeper analysis of chromosome structure, copy number, and single nucleotide polymorphisms are currently being conducted on this improved assembly. Our results will provide a foundational backbone for comparative genomics, phylogenetics, and surveillance of Leishmania (Viannia) peruviana.

5626

MECHANISM OF INTESTINAL BARRIER REPAIR IN GIARDIASIS

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The protozoan parasite Giardia duodenalis is the cause of the common diarrheal disease, giardiasis. Diarrhea is one of the most severe acute symptoms, however, infections can be subclinical. It is transmitted via ingesting infectious cysts in contaminated water or food. Giardiasis is one of the main causes of growth stunting in children under the age of two in developing countries. It has been demonstrated that alterations in intestinal barrier integrity contribute to reduced nutrient absorption, which leads to growth stunting in children. Although intestinal barrier abnormalities have been associated with infection, nothing is known about how the intestinal barrier repairs itself after an infection. Previous studies have demonstrated that Giardia infection is associated with intestinal dysbiosis in humans and animals. We are investigating the function of aryl hydrocarbon receptor (AHR) in barrier repair after a Giardia infection because AHR signaling has been demonstrated to promote intestinal repair in other systems. We measured the levels of particular AHR ligands originating from the microbiome in the plasma of infected C57BL/6 mice and saw a decrease in indole-3-ethanol and indole-3-pyruvic acid after 21 days of infection. As IL-22 signaling can also enhance barrier repair, we quantified IL-22 transcripts by RT-PCR and found significantly elevated levels of IL-22 mRNA in infected animals. Our findings suggest that Giardia can inhibit barrier repair by altering the microbiome's ability to produce AHR ligands, but that in some situations, IL-22 can reverse this defect. This study will give better insight into developing effective dietary interventions to prevent growth stunting in infected children.

5627

GENOMIC ANALYSIS DEMONSTRATES EXTENSIVE DIVERSITY AND SUBTLE POPULATION STRUCTURE IN PLASMODIUM VIVAX ACROSS 9 DISTRICTS OF ETHIOPIA

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Ethiopia suffers the greatest burden of Plasmodium vivax in the African continent with infections contributing as much as 40% of malaria morbidity. Efforts to contain and eliminate P. vivax are constrained by limited knowledge of the major adaptations and epidemiological drivers sustaining local endemicity. We conducted genomic analysis of 155 P. vivax genomes across 9 districts in Ethiopia. The genomic data was generated within the MalariaGEN P. vivax Community Project, using isolates sourced from cross-sectional surveys conducted in Ethiopia from 2012-2016. Measures of within-host and population diversity and structure were conducted using scikit-allel, ADMIXTURE, hmmIBD and custom scripts. Signatures of selection were detected using REHH software with cross-country comparisons against MalariaGEN data from sites in Thailand (n=129) and Indonesia (n=191) with respective low and high levels of chloroquine resistant P. vivax. A high proportion of Ethiopian infections were polyclonal (26%), with 44.7 % comprising clones with high relatedness (identity-by-descent >25%), indicating frequent co-transmission and superinfection. Several infection networks comprised isolates from neighbouring as well as more distal districts, indicating complex patterns of infection spread between communities. Amplification of the Duffy binding protein gene (pvdbp1) was observed at high frequency in 8 districts (range 16%-75%), with up to 5 copies, suggestive of an important local adaptive function. Cross-population comparisons of haplotype homozygosity found evidence of positive selection in a region proximal to the chloroquine resistance transporter gene (pvcrt-o), which has been implicated in chloroquine resistance. The genomic patterns in Ethiopia highlight adaptations of potential public health concern in an endemic setting with moderately high and stable transmission within and between districts.

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IN VITRO TRANSCRIPTOMIC REMODELING OF CARDIOMYOCYTES CAUSED BY TRYPANOSOMA CRUZI

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Chagas disease can lead to cardiac dysfunction or fatal arrythmias. while these manifestations occur more frequently in geographic areas more prevalent with the TcI/II circulating genetic strains of Trypanosoma cruzi; strain-specificity in the expression of disease is influenced by yet-to-be-determined factors. To define the cardiomyocytes differential transcriptomic responses resulting from infection with different T. cruzi strains and explore their relationships with pathogenesis, HL-1 cardiomyocytes were infected with TcI/II or TcVI T. cruzi trypomastigotes. RNA was serially isolated post-infection for microarray analysis. Enrichment analyses of differentially expressed genes highlighted the most affected biological pathways. We found that Oxidative stress-related GO terms, 'Hypertrophy model', 'Apoptosis', and 'MAPK signaling' pathways (all with $p < 0.01$) were upregulated as a common response to all T. cruzi strains. 'Glutathione and one-carbon metabolism' pathway, and 'Cellular nitrogen compound metabolic process' GO term (all with $p < 0.001$) were upregulated exclusively in the cardiomyocytes infected with the TcI/II strains. Upregulation in the oxidative stress-related and hypertrophic responses are shared hallmarks with myocarditis caused by Coxsackie virus, another inflammatory cardiac pathology. Nitrogen metabolism upregulation and Glutathione metabolism

affection may represent the relation of nitrosative stress and poor oxygen radicals scavenging in the pathophysiological events that lead of chagasic cardiomyopathy.

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GENOME ASSEMBLY OF TRYPANOSOMA CRUZI TULAHUEN STRAIN REVEALS HIGHLY ABUNDANT TRANSPOSABLE ELEMENTS ASSOCIATED WITH VARIABLE SURFACE PROTEINS

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Trypanosoma cruzi is the causative agent of Chagas disease, which causes 10,000 deaths per year. Despite the high mortality caused by the disease, there is very little whole genome data available for the parasite. T. cruzi has a highly repetitive genome with multiple copies of variable surface proteins, as well as large scale structural genome rearrangements, which makes resolving whole genomes incredibly challenging. Even laboratory strains frequently used in biomedical research do not have publicly available genomes. Using long read Nanopore sequencing, we have generated a high-quality, partially phased whole genome assembly of the hybrid Tulahuen strain, a Type VI strain commercially available from ATCC. Using automated tools and manual curation we have annotated transposable elements in our newly assembled genome. We report a genome with 35% simple repeats, 24% surface proteins, and 22% transposable elements. Moreover, we find that regions with transposable elements are significantly enriched for surface proteins, and that on average surface proteins are closer to transposable elements compared to other coding regions. This finding supports an interesting possible mechanism for diversification of surface proteins that involves mobile genetic elements such as transposons.

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ZOONOTIC HEPATITIS E VIRUS GENOTYPE 3 STRAIN DETECTED IN A CAPYBARA (HYDROCHOERIS HYDROCHAERIS) FECAL SAMPLE, BRAZIL

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Hepatitis E virus (HEV) is an emerging zoonotic pathogen associated to relevant public health issues. HEV was reported infecting wild rats worldwide; however the importance of wild rodents as potential HEV reservoirs or their zoonotic role is still unknown. Capybara (Hydrochoerus hydrochaeris) is the world´s largest rodent species distributed throughout South America and known to carry potentially zoonotic agents. The aim of this study was to investigate the HEV species Paslahepevirus balayani's presence in free-living capybaras inhabiting urban parks in São Paulo state, Brazil. Molecular characterization and phylogenetic analysis of positive samples was also undertaken. A total of 337 fecal samples collected during 2018-2020 were screened for HEV using RT-qPCR and confirmed by conventional nested RT-PCR targeting ORF1 and ORF2 regions. HEV genotype and subtype was determined combining Sanger and next generation sequencing. HEV was detected in one specimen (0.3%) collected in 2019, and assigned as HEV-3f. Phylogenetic analysis of ORF1 and ORF2 regions revealed that Brazilian capybara HEV-3f strain are closely related to European swine, wild boar and human strains (90.7%-93.2% nt), suggesting an interspecies transmission. Molecular epidemiology of HEV is poorly investigated in Brazil and so far, subtype 3f has only been reported in swine, hampering that more robust conclusions could be drawn from the phylogenetic analysis. This is the first detection of HEV in capybaras stool samples. Nevertheless, this data must be treated with caution once identification of HEV in these mammals may not necessarily be associated with natural infection and not indicate that these animals play a role in the HEV transmission. Capybaras are continuously exposed to fecal-borne viruses as these animals display semi-aquatic habit and are living in human-animal interface environments. The implementation of systematic molecular surveillance of HEV in the One Health concept, including human, wildlife, domestic pigs, wild boars and environment samples are vital to elucidate HEV-3 subtype's role and circulation in the country.

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ASYMPTOMATIC VISCERAL LEISHMANIASIS PREVALENCE IN MILITARY WORKING DOGS COMPARED TO SOLDIERS DEPLOYED TO IRAQ

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Visceral leishmaniasis (VL) is a zoonotic, vector-borne disease that poses a significant health risk to canines and humans. We previously reported 19.5% of American Soldiers deployed to Iraq had asymptomatic visceral leishmaniasis (AVL). Canines are the main reservoir of Leishmania infantum, a cause of VL. Military Working Dogs (MWDs) deploy worldwide and work closely with Soldiers. The aim of this study was to determine the rate of AVL in MWDs that deployed to Iraq to assess their infection and transmission risk. This retrospective study examined records of 104 MWDs that deployed to Iraq from the Remote Online Veterinary Record database and the Federal Records Center between 2005-2022. Banked pre- and post-deployment serum and whole blood samples were obtained from the Department of Defense Food Analysis and Diagnostic Laboratory. Leishmania diagnosis was confirmed using the canine rk39 Rapid test, Indirect Fluorescent Antibody (IFA) Assay and quantitative polymerase chain reaction (PCR). The prevalence of canine VL was 2.9% (n=3/104); 2 were PCR positive, one seroconverted. Sand fly prevention was documented in 65% of the MWDs. Of the 3 MWDs that tested positive, 66% (n=2) did not receive sand fly prevention and 100% were asymptomatic for VL. The odds of a VL positive test were 4.1 times more likely in a MWD without sand fly prevention compared to MWDs with sand fly prevention. Iraq-deployed human American Soldiers who were tested for AVL responded on a survey that 138/200 (69%) rarely or never used insect repellent, 14 (7%) worked or handled MWDs, 18 (9%) cared for local dogs, and 75 (37.5%) reported others had local dogs in their unit. Despite canines being the main host and reservoir for L. infantum, MWDs deployed to Iraq had a considerably lower VL prevalence than their human counterparts. Increasing the use of sand fly prevention in leishmaniasis endemic areas may better protect Soldiers deployed to these regions."The opinions and assertions expressed herein are those of the author(s) and do not reflect the official policy or position of the Uniformed Services University of the Health Sciences or the Department of Defense."

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DOES CAVE USE POSE A RISK FOR PATHOGEN SPILL? A CASE OF CHEKWOPUTOI CAVE IN MT ELGON EASTERN UGANDA

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Bats are increasingly singled out as a source of disease pathogens, what is not very clear though, is how the pathogens cross over to humans. Using camera traps in caves with known bat colonies, we monitorg the inner cave usage by bats and other vertebrates to establish if there may be a possible connection that could provide an avenue for dispersal of bat borne pathogens to humans or human environments.Our preliminary results suggest continuous bat activity in their cave day roost, which we suspect is a result of presence of some other vertebrate in the cave roost that stirs the bats to fly around.From camera trap data so far our results show: --The continued presence of bats in the cave during the day but not in the night.-A total six other vertebrate species (including humans) present in the cave when the bats were also in the cave.-No direct depredation on bats by the other vertebrates in the cave.We continue to monitor the cave use by the bats and the other vertebrates to understand what the potential risk for pathogen (if ever they are determined to be in the bats) spill could be. Two of the species (genet and civet are carnivores that could potentially eat bats). The porcupine and giant rats could potentially feed on guano while all species are exposed to aerosols in the cave. Two species the Porcupine and the Giant rats are species commonly hunted for meat by some members of the local community.

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ACTIVITY PATTERNS OF INSECTIVOROUS BATS IN THE MT. ELGON REGION-UGANDA: IMPLICATION FOR DISEASE SURVEILLANCE

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Uganda is home to over 110 bat species, including 77 species of insectivorous bats playing critical roles of economic importance including pest insect consumption, pollination and fertilizer production. However, some bat species are associated with highly pathogenic viruses such as coronaviruses, paramyxoviruses and filoviruses which pose public health concerns. It has always been a suppositional debate on how these viruses spill-over to humans. In Uganda, humans visit caves to collect manure, minerals and use caves as shelter for both humans and their animals. This poses a spill-over risk of potentially infectious agents. We are currently undertaking a five-year project in Kapchorwa district for bio-surveillance of potential zoonotic pathogens in bats. Where we also investigate the ranging patterns of bats in this region using LOTEK GPS tags to understand how far bats move from their cave roosts to forage and how this behaviour can predispose human communities to disease outbreak should a bat be carrying pathogens; this method has proven useful in providing insightful information on bat species' movements. However, the small size of some insectivorous bats makes it impossible to have a GPS tag mounted on their back. Furthermore, the nocturnal and elusive behaviours of bats make it difficult to capture them for tagging. Using SM4+ bat Detectors we passively monitored the presence and activity of the insectivorous bats species to inform our understanding of the bat community composition in the region. Our results so far point to over 14 species recorded in human occupied landscapes; two of which species have previously shown positive tests for infectious pathogens. We continue collecting long term acoustic data to enable our understanding of seasonal bat activities to enable us draw inferences on the potential risk of spill over of pathogens to humans. Overall, our research underscores the importance of continued research into bat ecology and zoonotic disease surveillance, and will also lead to generating a national library of acoustic for insectivorous bats which shall be point of reference for further studies of bats in Uganda.

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FACTORS INFLUENCING BAT BORNE VIRAL PATHOGENS PREVALENCE AND SPILL OVER IN UGANDA: IMPLICATIONS FOR ONE HEALTH INITIATIVES

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Although bats have been implicated as one of the key reservoirs for various viral pathogens, and also reported to participate in spill over of pathogens; there is still no very clear evidence at what critical threshold of events the viral pathogens spill to humans. And yet, like many other vertebrates, bats have lived with several types viruses for a long time. In recent decades emerging diseases such as Ebola, Murburg, SARS and other viral zoonotic diseases linked to bats, continue to pose critical global public health concerns. This research attempts to contribute to the body of knowledge of how and when bat-borne viral pathogens could spill. Using systematic review, predictive modelling approaches, and active sampling of bat species to detect viral pathogens in different cave roosts of Mt Elgon region, Uganda; we seek to identify the critical threshold levels of spatiotemporal, ecological, physiological and anthropogenic determinants that might trigger bat-borne virus spill over. We suggest that an interplay of several factors at given thresholds might be responsible for triggering likelihood for spillovers. We predict the critical level of interaction of environmental factors, seasonal factors, bat community ecology, bat population size, roost characteristics, roost fidelity by bats, human activity in the caves, and bat physiological stress; that would influence the occurrence and spill over of bat-borne viral pathogens. This in turn is linked to the implications for One health initiatives.

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PURCHASE, CONSUMPTION, AND OWNERSHIP OF CHICKENS AND CHICKEN PRODUCTS AMONG HOUSEHOLDS IN MAPUTO, MOZAMBIQUE: A CROSS-SECTIONAL STUDY

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Poultry farming provides an important source of income and nutrition in low- and middle-income countries; however, chickens are also the major reservoir for zoonotic enteropathogens, which are responsible for a significant burden of foodborne illness. Informal food systems pose the risk of transmission of enteropathogens from poultry to humans. To gain a better understanding of the potential exposure to enteropathogens of poultry origin, we conducted one of the first cross-sectional, population-based surveys assessing chicken consumption, purchase, and rearing practices using in Maputo, Mozambique. We surveyed 570 households using a structured questionnaire between May and June 2021. We found that about half of 570 households purchased broiler chicken meat (weighted n=250, 44.8%) and eggs (263, 46.5%) in the week leading up to the survey. The most common location where households purchased broiler chicken meat was corner stores (i.e., small stores on streets) (weighted n=141, 56.7%), followed by informal wet markets (43, 17.5%) and directly from farmers (45, 16.8%). Of 570 households, 97 (16.4%) reported that they raised live chickens at the time of the survey. Chicken feces were observed on the floor or ground at 49 (51%) of these 97 households. Of 39 households with children under five that raised chickens, 11 (28%) reported that their children take care of live chickens. Of 570 households, 58 (10.2%)

reported that they applied chicken litter compost to their gardens. Our study highlights the importance of implementing food safety measures, particularly at informal food systems that often do not have access to adequate hygiene facilities, to control foodborne illnesses resulting from poultry products.

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HIGHLY PATHOGENIC AVIAN INFLUENZA A (H5N1) IN MARINE MAMMALS AND SEABIRDS IN PERU

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Highly pathogenic avian influenza (HPAI) A/H5N1 viruses (lineage 2.3.4.4b) are rapidly invading the Americas, threatening wildlife, poultry, and potentially evolving into the next global pandemic. In November 2022 HPAI arrived in Peru, causing massive pelican and sea lion die-offs. We report complete genomic characterization of HPAI/H5N1 viruses in five species of marine mammals and seabirds (dolphins, sea lions, sanderlings, pelicans and cormorants) sampled since November 2022. All Peruvian viruses belong to H5N1 lineage 2.3.4.4b, but they are 4:4 reassortants where 4 genomic segments (PA, HA, NA and MP) position within the Eurasian lineage that initially entered North America from Eurasia, while the other 4 genomic segments (PB2, PB1, NP and NS) position within the American lineage (clade C) that was already circulating in North America. These viruses are rapidly accruing mutations as they spread south. Peruvian viruses do not contain PB2 mutations E627K, D701N, K702R previously linked to mammalian host adaptation and enhanced transmission, but at least 8 novel polymorphic sites warrant further examination. This report of HPAI A/H5N1 in marine birds and mammals from South America highlights an urgent need for active local surveillance to manage outbreaks and limit spillover into humans of a highly pathogenic avian influenza strain with clear pandemic potential.

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EXPLORING THE HEALTH SEEKING BEHAVIOR OF SNAKEBITE VICTIMS AND COMMUNITY PERCEPTIONS IN THE VOLTA AND OTI REGIONS OF GHANA

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Snakebite envenoming is a neglected tropical disease with incidence growing globally. In Ghana, an average estimate of 9,600 snakebites occur annually ,thus a serious public health concern . Mortality rates due to snakebites are linked to delays in reporting for treatment in health facilities. This study examined health-seeking behavior of snakebite victims and community members perceptions on treatments for victims of snakebites in the Volta and Oti Regions of Ghana. This was a mixed method study conducted in ten (10) selected communities in both the Volta Region (Ho Municipality, Kpando Municipality) and Oti Region (Nkwanta North District, Jasikan District). Communities were selected using purposive sampling techniques, and data were analyzed using the Statistical Package for the Social Sciences (IBM SPSS) version 26.0. Descriptive statistics was used for sociodemographic characteristics. Bivariate and multivariate binary logistic regression analysis was used to assess the factors associated with health-seeking behavior among participants. A total of 397 participants were included in the study, with a snakebite incidence of 15.9% among community members. The mean age of participants was 39.56 (±SD=14.78) with 42.3% being females and 57.7% males. This study found 43% of participants had a family member who had been bitten by a snake. The multivariate logistic regression analysis showed that those whose family members previously experienced snakebites were more likely (aOR=1.93, 95%CI:1.25-2.99) to seek health care than those who had never experienced snakebites. In Kpando,54% of participants attended the traditional healer as their first treatment for snakebites while Jasikan, Kpassa and Ho showed higher attendance to health facilities with the highest (86%) in Ho. There exists high awareness among community members about seeking healthcare from a health facility however they still believe in using traditional remedies or visiting the traditional healer. Culturally appropriate interventions that seek to improve the health-seeking behavior of snakebite victims within the community will be imperative to reduce the burden.

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PREVALENCE AND RISK FACTORS FOR HUMAN LEPTOSPIROSIS IN A PASTORALIST COMMUNITY, ENDULEN, TANZANIA

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Although leptospirosis is suspected to be common in rural Tanzania, data are limited. We sought to determine leptospirosis prevalence, identify infecting Leptospira serogroups, and investigate risk factors for leptospirosis in a rural area of Tanzania where pastoralist animal husbandry practices and sustained livestock contact are common. We enrolled patients at Endulen Hospital, Arusha Region, Tanzania, presenting with a history of fever within 72 hours, or a tympanic temperature of ≥38.0°C. We administered structured questionnaires covering recent symptoms, animal-related activities, and livestock health. Serum samples were collected at enrolment and 4-6 weeks later and were tested using microscopic agglutination testing with 20 Leptospira serovars from 17 serogroups. Leptospirosis was defined as a ≥four-fold rise in antibody titer between acute and convalescent serum samples, or a reciprocal titer ≥400 in either sample. Leptospira seropositivity was defined as a single reciprocal antibody titer ≥100 in either sample. The predominant reactive serogroup was that with the highest titer. We explored risk factors for leptospirosis and Leptospira seropositivity using multivariable logistic regression modelling. Of 229 participants, 99 (43.2%) were male and the median (range) age was 27 (0, 78) years. Participation in at least one livestock related activity was reported by 160 (69.9%). We identified 18 (7.9%) cases of leptospirosis, with Djasiman 8 (44.4%) and Australis 7 (38.9%) the most common predominant reactive serogroups. Overall, 69 (31.1%) participants were Leptospira seropositive and the most common predominant reactive serogroups were Icterohaemorrhagiae 21 (30.0%), Djasiman 19 (27.1%), and Australis 17 (24.3%). Milking cattle (OR 6.27, 95% CI 2.24-7.52) was a risk factor for leptospirosis, and milking goats (OR 2.35, 95% CI 1.07-5.16) was a risk factor for Leptospira seropositivity. Leptospirosis caused nearly one in

twelve hospitalizations with febrile illness in this predominantly pastoralist population. Interventions that reduce risks associated with milking livestock may reduce human leptospirosis.

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CRIMEAN CONGO HEMORRHAGIC FEVER IN TANZANIA: RELEVANCE OF ONE HEALTH APPROACH ON UNDERSTANDING THE EPIDEMIOLOGY OF A PRIORITY ZOONOSIS

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The World Health Organization's Research and Development Blueprint lists Crimean-Congo hemorrhagic fever (CCHF) virus on their priority A list and hemorrhagic fever diseases are on the list of priority pathogens in Tanzania due to high risk to public health. A One Health approach is necessary to study CCHFV, a tick-borne zoonotic virus, that circulates between ticks and several vertebrate hosts without causing overt disease and thus can be present in areas without being noticed. A systematic sampling method is conducted across a gradient of different human disturbance levels such as pristine, pastoral and agro-pastoral areas in northern Tanzania to assess CCHF seroprevalence and prevalence in ticks, small mammals, cattle and people. More than a thousand ticks have been collected and identified thus far for virus detection by polymerase chain reaction (PCR). Five mainly genera of ticks have been collected and identified namely Rhipicephalus, Amblyomma, Hyalomma and Haemaphysalis. This One Health approach to sample people, cattle, small mammal and vector populations simultaneously will strengthen the study's power to identify associations among these populations as well as risk factors for virus exposure and circulation across the gradients of environmental disturbances. By One Health approach from this study we will be able to create research-based data on the epidemiology of CCHF virus in ticks, cattle, small mammals, people and risk factors associated with the virus exposure. Furthermore, with very limited data present on CCHF in Tanzania, findings from the study will be important in improving Tanzania's capacity to manage the risk of CCHF as well as making evidence-based prevention and control recommendations.

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ARPHILAKE CONSORTIUM COMBATING ANTIBIOTIC RESISTANCE IN PHILIPPINES' LAKES: ONE HEALTH UPSTREAM INTERVENTIONS TO REDUCE THE BURDEN

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Lakes are critical aquatic ecosystems and provide essential natural resources for populations in low-middle income countries like the Philippines. A growing concern has been the contamination of lakes with determinants conferring antimicrobial resistance (AMR) from animal and human sources. In particular, a growing literature supports that beta-lactam resistance is a burgeoning issue in Asian lakes and rivers. However, few interventions have been rigorously evaluated to determine if the impact of environmental contamination from hospitals and agriculture and livestock production can be reduced. Here, we propose specific interventions with pre- and post-evaluations to determine their impact on beta-lactam resistance. Following a One Health the ARPHILAKE consortium composed of partners from Canada, Spain, UK, Ireland, and the Philippines will: i) Conduct environmental monitoring to identify antimicrobials and antimicrobial resistance genes in Laguna Lake and surrounding areas for mitigation at point sources; ii) Enable feasible, economic, and effective treatment method for farm effluents and hospital wastewater based on solar light; iii) Determine the AMR profile of bacteria isolated from backyard farms animals in the Laguna Lake area and exame the driver for antimicrobial use and prescription in the veterinary setting; and iv) Implement point of care rapid testing for key antimicrobial resistant organisms and antimicrobial stewardship in selected hospitals. This is the first project following a One Health approach conducted in the Philippines to reduce the risks of AMR in the lake environment. The outcomes of this project will serve as starting points to replicate the interventions in other lakes in the Philippines and other Southeast Asian countries. The scientific data produced will be used to promote awareness on AMR through community participation and develop government policy interventions. Such knowledge and interventions to reduce antimicrobials and AMR bacteria will help preserve the lake that provides economic services to the lakeshore communities.

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PARASITOLOGICAL RISK AT THE INTERFACE WILDLIFE-DOMESTIC ANIMALS IN NAZINGA RANCH, BURKINA FASO

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Changes in land use, habitat fragmentation, habitat loss, climate change and human population growth are modulating the relationships between humans, domestic animals and wildlife. These events have led to the emergence of new infectious diseases. While some of these diseases have their origins in wildlife, wild populations are also exposed to pathogens from humans and their animals. This situation impacts wildlife conservation. This study aim to highlight parasites at the wildlife and domestic animals interface in Burkina Faso. Fresh droppings of wild and domestic animals were collected in the Nazinga Ranch and its surroundings following transects line that cover the conservation zone, the buffer zone, the hunting zone and the interface of the park where wild, domestic animals and humans can meet. Coprological analyses were done to isolate parasites. A total of 76 samples belonging to eight different species of mammals were collected. These animals were Antelopes (Hippotragus equinus), Defassa Cobs(Kobus ellipsiprymnus defassa), Buffon's Cobs (Kobus kob), Domestic Goat (Capra hircus), Bushbuck (Tragelaphus scriptus), the Elephant (Loxodonta africana), Warthog (Phacochoerus africanus), and Ox (Bos taurus). The prevalence of parasites was 75.0% for Nematoda, 13.16% for Trematoda, 68.42% for Cestoda and 26.31% for Protozoans. At the interface, the droppings encountered belonged to Loxodonta africana, Capra hircus and Bos taurus with infection rate of 66.6%, 64.5% and 100% respectively. While Capra hircus carried only Tapeworms, Bos taurus and Loxodonta africana had several parasites in common such as genera of Haemonchus, Cooperia, Taenia, Moniezia, Eimeria. A total of 16 species of parasites were encountered during this study. This parasite richness and the modes of dissemination of these parasites show that there is a high risk of transmission between wildlife, domestic animals and humans in this area. The high prevalence of infection in elephants is therefore, another threat to this species, which is already heavily impacted by human-elephant conflicts.

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CHARACTERISING PSYCHOSOCIAL IMPACT OF TUBERCULOSIS AND THE SOCIAL SUPPORT NEEDS FOR PEOPLE WITH TUBERCULOSIS IN INDONESIA

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Stigma towards people with TB (TB-Stigma) is a crucial challenge to TB elimination and is associated with other TB psychosocial consequences. We evaluated TB-Stigma, depression, quality of life (QoL), and psychosocial support needs among people with TB in Indonesia. In seven provinces of Indonesia, from February to November 2022, we interviewed adults diagnosed with drug-susceptible (DS)-TB (a) receiving treatment at public facilities, (b) receiving treatment at private facilities, (c) lost to follow up (LTFU) to treatment, and (d) receiving TB retreatment. We used our previously-validated Indonesian TB-Stigma Scale to measure TB-Stigma, Patient Health Questionnaire-9 (PHQ-9) to assess depression, EQ-5D-5L to quantify QoL, and additional questions to determine needs for psychosocial support. We applied general linear models and regression analyses to identify factors associated with TB-Stigma and correlations between TB-Stigma, depression, and QoL. Of 612 study participants, 60.6% experienced moderate TB-Stigma. TB-Stigma scores were higher among people receiving treatment at private facilities (adjusted B (aB)=2.48;0.94-4.03), those LTFU (aB=2.86;0.85-4.87), males (aB=1.73;0.59-2.87), losing or changing job due to TB (aB=2.09;0.31-3.88) and living in a rural area. Participants experienced mild-to-moderate (36%) and moderately severe to severe (6%) depression. Experiencing TB-Stigma was associated with moderately severe to severe depression (adjusted odds ratio=1.23;1.15-1.32), and higher combined stigma and depression levels were associated with lower QoL. Participants had a high unmet need of peer support including peer-to-peer emotional support (52%), peer-to-peer education (63%), and peer-led group counselling (78%). In conclusion, there is a sizeable and intersecting burden of TB-Stigma and depression, which is associated with lower QoL. Participants reported a substantial unmet need for psychosocial support from peers. Based on these findings, we are now co-designing a community-based peer-led psychosocial intervention for TB-affected people in Indonesia.

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DIAGNOSTIC ACCURACY OF THE NOVA TUBERCULOSIS TOTAL ANTIBODY RAPID TEST FOR DETECTION OF PULMONARY TUBERCULOSIS AND INFECTION WITH MYCOBACTERIUM TUBERCULOSIS

GIDEON NSUBUGA

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The NOVA Tuberculosis Total Antibody Rapid Test is a commercially available lateral flow serological assay that is intended to be used as an aid in the diagnosis of tuberculosis. We conducted a study to estimate diagnostic accuracy of this assay for diagnosis of active pulmonary tuberculosis disease and for detection of M. tuberculosis infection. This study used existing frozen plasma specimens that had been obtained previously from consenting adults whose tuberculosis status was rigorously characterized. The investigational assay was performed in a single laboratory by laboratory staff specifically trained to conduct the assays according to the manufacturer's procedures. In addition, intensity of the test band was subjectively assessed. Plasma specimens from 150 participants were tested. All testing attempts yielded a determinate result of either positive or negative. For diagnosis of active pulmonary tuberculosis disease, test sensitivity and specificity were 40.0% (20/50, 95% confidence interval [CI] 27.6% to 53.8%) and 85.0% (95% CI 76.7% to 90.7%), respectively. For detection of M. tuberculosis infection, test sensitivity and specificity were 28.0% (95% CI 20.5% to 37.2%) and 86.0% (95% CI 73.8% to 93.0%), respectively. Among the 35 positive tests, no statistically significant band intensity trend was found across participant groups (p=0.17). Study findings do not support a role for the NOVA Tuberculosis Test in current tuberculosis diagnostic algorithms.

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EXPLORING THE POTENTIAL OF A SALIVA-BASED, RNA-EXTRACTION-FREE PCR TEST FOR THE MULTIPLEXED DETECTION OF KEY RESPIRATORY PATHOGENS

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Efforts to control and monitor transmissible infectious diseases rely on large-scale screening initiatives. The use of saliva as a non-invasive sample type could alleviate bottlenecks encountered in mass testing strategies in community settings. Having extensively demonstrated saliva as sensitive for the detection of SARS-CoV-2, we sought to validate this approach for other common respiratory pathogens. From May-July 2022, de-identified saliva samples were collected from consenting adults ≥18 years of age with respiratory symptoms (New Haven, CT, USA). Saliva samples from SARS-CoV-2-negative individuals were stored at -80ºC until further processing in the research laboratory. We modified our RNA-extraction-free SARS-CoV-2 PCR test for multiplexed detection of four additional key respiratory viruses ("SalivaDirect+"): influenza A, influenza B, RSV and hMPV and for singleplex testing for pneumococcus. Sample stability was tested after storage at +4°C, room temperature (~19°C) and 30°C for 72 hours. We confirmed a limit of assay detection at 4 copies/µl for each virus target. From 804 saliva samples tested with SalivaDirect+, 17 (2.1%) tested positive for one of the viruses targeted, with 7 (0.9%) positive for influenza A, 4 (0.5%) positive for RSV, and 6 (0.7%) samples positive for hMPV. No sample tested positive for influenza B. For influenza A and RSV, detection by SalivaDirect+ was comparable to testing following RNA extraction but detection of hMPV was less sensitive. We confirmed that virus detection remained stable at +4°C, room temperature and 30°C for up to 72 hours. In singleplex testing, 87 (10.8%) samples tested positive for pneumococcus. By testing saliva samples from symptomatic, SARS-CoV-2-negative individuals we detected respiratory viruses which were otherwise missed in testing focused solely on SARS-CoV-2. Being less invasive and less resource-intensive than other sample types, saliva-based testing can lead to more equitable and sustainable testing and surveillance programs. As a result, saliva can bolster the public health response, particularly in low-resource and remote environments.

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PREVALENCE OF NASOPHARYNGEAL CARRIAGE OF MACROLIDE RESISTANCE-ASSOCIATED ERYTHROMYCIN RIBOSOME METHYLASE (ERM) GENES AMONG HEALTHY CHILDREN AND ADULTS IN A PERI-URBAN COMMUNITY IN LIMA, PERU

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Erythromycin ribosome methylase (erm) genes, which confer macrolide resistance, are commonly detected in healthcare settings. Yet, their prevalence among healthy individuals in the community is unknown. Here

we provide an initial assessment of erm nasopharyngeal carriage in healthy children and adults. Nasopharyngeal swabs were systematically obtained at enrollment and weekly thereafter from children and adults enrolled in a household-based prospective cohort study in Lima, Peru. Samples were sequenced using the Illumina Respiratory Pathogen/ID AMR Panel to detect common respiratory bacteria and antimicrobial resistance genes. We defined 'any erm gene' (erm) as the detection of at least one of the specific erm gene classes. We compared the prevalence of erm carriage at enrollment among age groups (ages 0-4, 5-17, 18-44, and 45+ years) using the Fisher's exact test. There were 114 individuals were included in this analysis; 74% were female and median age was 24.2 years (IQR 4.6, 41.8). An erm gene was detected in 51 (44.7%) of individuals, most commonly ermC (15.8%) and ermB (7%). The prevalence of erm gene detection was high and similar among age groups: [0-4 years (19/33, 57.6%), 5-17 years (12/20, 60.0%), 18-44 years (11/34, 32.4%) and 45+ years (9/27, 33.3%) (p=0.056)]. These preliminary results indicate that erm genes were commonly detected in healthy community-dwelling children and young adults in Lima, Peru. Future analysis will assess changes in erm carriage over time, transmission among household members, and its clinical relevance.

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VACCINATION FOLLOWING THE EXPANDED PROGRAM ON IMMUNIZATION SCHEDULE COULD HELP TO REDUCE DEATHS IN CHILDREN UNDER FIVE HOSPITALIZED FOR PNEUMONIA AND SEVERE PNEUMONIA IN A DEVELOPING COUNTRY

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Pneumonia is the leading cause of under-five mortality worldwide. An expanded programme on immunization (EPI) is one kind of evidence-based tool for controlling & even eradicating infectious diseases. This study aimed to explore the impact of EPI vaccination among children of 4-59 months hospitalized for pneumonia & severe pneumonia. Additionally, we evaluated the role of 10 valent pneumococcal conjugate vaccine alone on clinical outcomes in such children. In this retrospective chart review, children 4-59 months of age with the WHO defined pneumonia & severe pneumonia, admitted in the Dhaka Hospital of icddr,b between August`2013 & December`2017 who had the information on immunization as per EPI schedule by 4 months of age, were included in the analysis. Comparison was made between the children who were fully immunized & who were not immunized (consists of partial immunization and no immunization). A total of 4625 children had pneumonia & severe pneumonia during the study period. Among them, 2605 (56.3%) had information on immunization. Between them, 2195 (84.3%) were fully immunized by 4 months of age according to EPI schedule & 410 were not immunized. In log-linear binomial regression analysis, it has been revealed that immunization in children 4-59 months of age was associated with lower risk of diarrhea (p=0.033), severe pneumonia (p=0.001), anemia (p=0.026) & deaths (p=0.035). Importantly, the risk of developing severe pneumonia (1054/1570 [67%] vs. 202/257 [79%], p<0.001) and case-fatality-rate (57/1570 [3.6%] vs.19/257 [7.4%], p=0.005) were still significantly lower among those who were immunized with PCV-10 than those who were not. Under-five children immunized as per EPI schedule were at a lower risk of diarrhea, severe pneumonia, anemia & deaths, compared to unvaccinated children. In addition, PCV-10 was found to be protective against severe pneumonia & deaths in such children. The overall results underscored the importance of the continuation of immunization scrupulously adhering to EPI schedule to reduce the risk of morbidities & mortalities in such children, especially in resource-limited settings.

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RESPIRATORY SYNCYTIAL VIRUS INFECTION IN CHILDREN ADMITTED TO A PEDIATRIC INTENSIVE CARE UNIT IN GHANA AMID COVID-19 PANDEMIC

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Respiratory Syncytial Virus (RSV) infection is a seasonal illness that affects about 97% of children by the age of 2 years. Although RSV infection can be life-threatening during the first year of life and is the leading cause of hospitalization in infants, there are limited data available on the burden of RSV in critically ill children to inform on the prevention and treatment of the disease with specific viral therapeutics. The current study assessed the burden of RSV among children aged less than 2 years in a pediatric intensive care unit (PICU) during the COVID-19 pandemic in Accra, Ghana. Children below the age of 24 months with severe respiratory tract infections who were admitted to the PICU of the Korle Bu Teaching Hospital were recruited with parental consent. Nasal swabs were obtained within 72 hours of admission and tested for RSV and Influenza virus using the ID NOW Point of care test machine at the PICU and then confirmed by real-time quantitative reverse transcription-polymerase chain reaction (RT-qPCR) at the Noguchi Memorial Institute for Medical Research. Samples were also investigated for the presence of other viral agents such as the SARS-Cov 2 virus. Twenty-eight children were enrolled from June to November 2021. RSV was confirmed in 9/28 (32%) of the children who were all below the age of 12 months. Among the RSV-positive group, infants <3 months old had a higher incidence of infection (67%, p<0.01). RSV A predominated 7/9 (78%) cases. One (1) patient each tested positive for Influenza virus and SARS-CoV-2. Two patients (22%) were preterm and 5 (56%) had congenital abnormalities. Besides supportive treatment, children were on antibiotics routinely per the PICU protocol. The average length of stay of patients at the PICU was 19.11 days and one (1) RSV death occurred. RSV remained an important cause of severe respiratory illness during the COVID-19 outbreak in Ghana. The PICU burden of RSV was heavy on infants during the first year of life. And there is a need for targeted interventions such as the introduction of vaccines against severe RSV disease.

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MOLECULAR INVESTIGATION OF THE AETIOLOGY OF TUBERCULOSIS-LIKE CLINICAL SYNDROMES IN ADULTS PRESENTING FOR PRIMARY HEALTH CARE AT LIMBE AND NDIRANDE HEALTH CENTRES

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The suboptimal nature of diagnostics leads to empirical broad-spectrum and tuberculosis treatment for most patients with respiratory illness in low-income settings, where also the aetiology is poorly described especially at the primary care level. Our ACT-TB Trial demonstrated that empirical broad-spectrum antibiotics do not add much diagnostic or clinical benefit for patients presenting to primary care. We hypothesized that the bulk of the respiratory symptoms may have been caused by respiratory viruses and atypical bacteria whose diagnostics are not readily available. To investigate the aetiology and prevalence of respiratory pathogens that are not traditionally investigated, we conducted a cross-sectional study including a random selection of patients from the ACT-TB trial participants (trial included: aged ≥18 years, attending primary care, unwell for at least 14 days, with cough, with no immediate indication for hospitalization). Participants provided nasopharyngeal swab samples and we used real-time-Polymerase Chain Reaction (Siemens® FTD 33kit) to detect pathogens. We included 297 participants (45% male), and the most common pathogens were Bordetella (87%), Klebsiella pneumoniae (77%), salmonella species (70%), HCoVHKU1 (57%), Haemophilus influenzae (56%), Chlamydia pneumoniae (54%), Human rhinovirus (49%), Haemophilus influenzae B (46%) Staphylococcus aureus (45%), and ICV (44%). Our preliminary results demonstrate the high prevalence of respiratory viruses and atypical bacteria, all of which are not covered by any of the antibiotics used for empirical therapy. This mismatch highlights the need for National tuberculosis and antimicrobial stewardship programs to improve diagnostic protocols and limit outpatient prescriptions of antibiotics. Future research and investment should focus on strengthening diagnostics for tuberculosis and other respiratory pathogens. At the conference, we hope to present additional analysis by TB status and clinical improvement status.

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PULMONARY-UROGENITAL TUBERCULOSIS: A DELAYED DIAGNOSIS

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Urogenital tuberculosis (TB) is responsible for one-third of cases of extrapulmonary TB and occurs in up to 20% of patients with pulmonary TB. We illustrate a diagnostic challenge in a case of pulmonary-urogenital TB with HIV infection. A 60-year-old woman with HIV infection diagnosed in May 2020 following an initial presentation of Escherichia Coli bacteremia complicated by HIV-related immune thrombocytopenic purpura. Computed tomography (CT)thorax revealed tree in bud in bilateral upper lobes with mild hydronephrosis of the right kidney compared to the left kidney. She underwent bronchoscopy and her TB work-up was negative. She was treated for latent TB with Isoniazid-based regime and commenced on antiretroviral therapy and prednisolone. She presented again in February 2023 following a 3-day history of fever with documented temperatures of 380C but no obvious source of infection. She had thrombocytopenia of 45X109/L but normal white cell count, renal and liver function. Her chest radiograph was normal. She was treated as occult sepsis with intravenous (IV) Ceftriaxone and IV Hydrocortisone with subsequent resolution of fever. She had recurrence of her fever with tenderness at right lumbar region after five days of Ceftriaxone. Her antibiotic was escalated to IV Meropenem. Ultrasound abdomen showed gross right hydronephrosis with pyonephrosis. Contrast-enhanced CT thorax and abdomen revealed multiple tree-in-bud nodules prominent in both upper lobes with multiple lung nodules. There were no cavitating lung lesions and enlarged mediastinal lymphadenopathy. There was right hydronephrosis with dilated pelvic-calyces, stenosed infundibulum and right mid ureteric stricture. She underwent a right nephrostomy with subsequent right ureteral stenting. Direct smear urine for acid fast bacilli was positive and Mycobacterium TB(MTB) GeneXpert was positive with indeterminate Rifampicin-resistant, pending urine MTB culture and sensitivity. Treatment with anti-TB medications was commenced, with steroid replacement. In conclusion, Urogenital TB can be missed in view of asymptomatic manifestation of hydronephrosis

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PREVALENCE OF MALARIA-PNEUMONIA OVERLAP IN RURAL GAMBIA: NINE YEARS OF CLINICAL EXPERIENCE IN ENDEMIC AREA

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Globally malaria and pneumonia account for almost 40% of the mortality in under-five children in sub-Saharan Africa. Respiratory distress is a common feature of severe falciparum malaria in both children (40%) and adults (25%). We aimed to assess the prevalence of malaria and radiological pneumonia (RP) overlap and the proportion of children with these overlapping who truly require pneumonia treatment along with malaria management. The surveillance population included in the Upper River Region (URR) all Basse Health and Demographic Surveillance System (BHDSS) residents aged 2-59 months. Nurses screened all outpatients and inpatients at Basse Health Centre (BHC) of a referral health facility during the surveillance period from May 2008 to December 2016. Clinicians then applied criteria for patient investigation and treatment was provided based on national guidelines. Rapid diagnostic tests (RDT) for malaria were done from August to December during malaria transmission season. During the population-based surveillance, 22061 patients aged 2-59 months were registered at BHC. We found 1178 cases (6.65%, 1178/17705) of malaria positive, and 1649 cases (12.32%, 1649/13389) of RP. We identified 1198 cases (97.6%, 1198/1227) of RP patients had malaria negative, and 29 cases (2.4%, 29/1227) of RP had malaria positive. 472 cases (5.3%, 472/8858) of no RP had malaria positive and 8386 cases (94.7%, 8386/8858) of no RP had malaria negative. A total of 59.1% (696/1178) (95% CI 56 to 62) of malaria cases had respiratory findings. Among malaria positive and negative cases, we identified 106 cases of Invasive Bacterial Diseases (IBD), Streptococcus pneumoniae, 8 cases of Salmonella spp, and 8 cases of Staphylococcus aureus. Radiological pneumonia is uncommon with malaria RDT-positive. An empiric antibiotic is not indicated with respiratory symptoms and malaria RDT positive. Point of care test for radiological pneumonia/bacterial pneumonia is needed to target antibiotic therapy in children with respiratory symptoms and malaria RDT positive.

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DETERMINANTS OF TUBERCULOSIS OUTCOMES DURING THE COVID-19 PANDEMIC AT A REFERRAL HOSPITAL IN RURAL HAITI

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Tuberculosis (TB) is a major public health threat in Haiti, with an estimated annual incidence of 159/100,000. Little is known about determinants of TB outcomes in Haiti since 2020, when multiple events coincided that were likely to impact TB care: the Covid-19 pandemic, progressively worsening national political and security crises, and an earthquake in 2021. To address this, we conducted a prospective cohort study at the St. Boniface Hospital (SBH), a rural referral center in Southern Haiti. Eligibility criteria included: age greater than 18 years, clinically suspected or microbiologically confirmed (by smear, NAAT, or culture) TB, receiving standard first-line TB treatment. We excluded patients with drug-resistant TB and those who had already received at last 7 days of treatment. We administered a baseline

questionnaire, collected baseline and outcome clinical data, and analyzed laboratory samples. We assessed risk factors for unfavorable outcomes (death, treatment failure, loss to follow up) using multivariable logistic regression models. We enrolled 250 patients (37% female) between May 2020 and January 2023, with a median age of 35 years (IQR 25-45). Only 13% had completed secondary education and 20% reported no formal education. Food insecurity was common (55%), and the median probability of poverty (< $1USD/day) was 45% (IQR 28-77). The median time to reach the hospital was 120 minutes (IQR 90-180), the median duration of symptoms prior to presentation was 12 weeks (IQR 4-20), 40% had undernutrition, and 54% met criteria for depression. Of participants with finalized outcome data, 179 (80%) had a favorable outcome, and 10 (4%) died. Independent risk factors associated with unfavorable outcome were age (Adjusted Odds Ratio [AOR] 1.03 per year, 95% CI 1.01-1.06), travel time (AOR 1.07 per 10 minutes, 95% CI 1.02-1.12) and being a smoker (AOR=2.77, 95% CI 1.21-6.32). Our findings highlight factors that can be deleterious in the course of TB, and can serve as a guide to improve intervention strategies (for example, community outreach for patients living far from health facilities) aimed at minimizing the impact of TB.

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SHORT VERSUS LONG DURATION MACROLIDE TREATMENT FOR RESPIRATORY TRACT INFECTIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF EFFICACY, SAFETY, AND ADHERENCE OUTCOMES

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Respiratory tract infections are a cause of death and disability worldwide. Management involves a course of antibiotics for a period of 7-14 days, however prolonged exposure to antibiotics may lead to the development of antimicrobial resistance. We compared the efficacy, safety, and adherence of short-course with long-course macrolide treatment for respiratory tract infections. We conducted a systematic review and meta-analysis by searching the Embase, MEDLINE, and Cochrane Central Register of Controlled Trials for randomized controlled trials published from inception to 25 August 2021. Studies that recruited patients with respiratory infections and reported treatment outcomes of at least two macrolide antibiotics given for different durations were eligible. We used Rob 2.0 to assess the quality of studies and a random effects meta-analysis to estimate effects and 95% confidence intervals. 2695 articles were retrieved. 9 randomized controlled trials published between 1984 and 2005 involving 2900 participants from 27 countries in Africa, America, Asia, Europe, and Oceania were eligible for inclusion. The target respiratory infections were tonsillo-pharyngitis, atypical pneumonia, acute exacerbation of chronic bronchitis, community-acquired pneumonia, sinusitis and upper respiratory tracts infection, community-acquired acute maxillary sinusitis and Group A beta-haemolytic streptococcal tonsillitis/pharyngitis. Short duration treatment did not differ from long duration treatment with respect to efficacy assessed using incidence of treatment failure (RR= 0.88, 95% CI= 0.71-1.09). The proportion of treatment non-adherent participants was also similar between short and long duration macrolide groups (RR= 0.85, 95% CI=0.65, 1.11). The risk of adverse events was lower among patients in the shorter duration group compared to the longer duration group (RR =0.88, 95% CI=0.80, 0.96). We found that short duration treatment is as effective and safe as long duration treatment. This result should inform the design of antibiotic dosages to preserve the lifespan amid the dryness of the product development pipeline.

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PREVALENCE OF EXTRA-PULMONARY TUBERCULOSIS IN AFRICA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Mycobacterium tuberculosis primarily causes pulmonary disease. Disease in other organs is called extra-pulmonary tuberculosis (EPTB). The burden of EPTB is not well quantified in TB endemic countries such as those in sub-Saharan Africa. This study aimed to quantify the burden of EPTB via a systematic review of the prevalence of EPTB in African countries. Studies were retrieved by searching five databases; 84 studies published between 1990 and 2020 were included. The studies described the prevalence of EPTB among TB patients (53 studies) or patients with conditions other than TB including HIV (12), meningitis (3), renal failure (3) and other comorbidities some of which are cancer (9). The focus of the meta-analysis was on EPTB among TB patients (53 studies). Meta-analysis was performed in the 53 studies (198,781 participants) using a random-effects model to estimate pooled prevalence of EPTB. Meta regression was used to explore possible explanations for the heterogeneity observed, according to regions and time period. The pooled prevalence of EPTB among TB patients was 24% (95% CI 21- 28%). There was substantial heterogeneity in prevalence for the five African regions. The Eastern region had the highest prevalence with 30% (95% CI 26-35%) and the lowest prevalence was in Western Africa, 17% (95% CI 10-27%). There was no significant difference in the prevalence of EPTB when compared between 3 ten-year time periods. This systematic review and meta-analysis provides an estimate of the prevalence of EPTB in TB patients in Africa.

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NEUTRALIZING ANTIBODIES TO SARS-COV-2 IN A ONE YEAR CROSS-SECTIONAL STUDY IN KISUMU COUNTY, KENYA

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Neutralizing antibodies (NAbs) to SARS-CoV-2 spike protein are a good predictor of protective immune response to coronavirus disease 2019 (COVID-19). In this cross-sectional study carried out at Kombewa, Kisumu County, Kenya during Alpha, Delta and Omicron waves, total of 1,385 subjects were enrolled, out of which 827 (61.7%) had NAbs. The mean magnitude of NAbs increased over the successive waves (0.90 U/mL at alpha, 1.80 U/mL at Delta and 5.7 U/mL at Omicron), while frequency of SARS-CoV-2 by qPCR progressively declined; 25% at alpha, 3% at Delta and 10% at Omicron. Further analyses are recommended to dichotomize NAbs emanating from SARS-CoV-2 infections and those from vaccinations.

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PREDICTION OF DISEASE OUTCOME USING A DEFINITE CUT-OFF VALUE IN CHEST X-RAY SCORING, OBSERVATION FROM A RESOURCE LIMITED COVID-19 TREATMENT FACILITY

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Evaluation of potential outcomes of COVID-19 affected pneumonia patients using radiological imaging chest computed tomography (CT) scans, may not be conceivable in low-resource settings. Thus, this study aimed to evaluate the performance of chest X-ray (CXR) scoring in

predicting the disease severity and outcomes of adults hospitalized with COVID-19. This was a retrospective chart analysis consuming data from COVID-19-positive adults who had CXR availability and were admitted to a temporary COVID-19 unit in Bangladesh from 23rd April 2020 to 15th November 2021. We reviewed baseline CXR, clinical data, and blood test results of all enrolled patients. At least one clinical intensivist and one radiologist combinedly reviewed each admission CXR for the presence of consolidation, ground-glass opacities, reticular opacities, and pleural effusion. CXR scoring varied from 0 to 8, depending on the area of lung involvement with 0 indicating no involvement and 8 indicating ≥75% involvement of both lungs. The receiver operating characteristic curve (ROC) was used to determine the optimum CXR cut-off score for predicting fatal outcomes. Out of 263 COVID-19 affected adults, a total of 218 (82.9%), with a mean age of 53.52 ± 16 years, were included in the study. The ROC demonstrated the optimum cut-off as ≥3 and ≥5 for disease severity and death, respectively. In multivariate logistic regression analysis, a CXR score of ≥3 was found to be independently associated with disease severity (aOR, 8.70; 95% CI, 3.82, 19.58, p <0.001) and a score of ≥5 with death (aOR, 16.53; 95% CI, 4.74, 57.60, p <0.001) after adjusting age, sex, antibiotic usage before admission, history of fever, cough, diabetes mellitus, hypertension, total leukocytes count, and C-reactive protein (CRP). Using CXR scoring derived cut-off values at admission might help to prompt identify the COVID-19 affected adults with different severity of pneumonia and who are at risk of severe disease and mortality. This may help to initiate early and aggressive management of such patients as well as reduce their fatal outcomes.

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STREPTOCOCCUS PNEUMONIAE NASOPHARYNGEAL CARRIAGE AND SEROTYPES DISTRIBUTION IN URBAN (KIBERA) AND RURAL (ASEMBO) KENYA AMONG CASES WITH SEVERE ACUTE RESPIRATORY ILLNESS 6-9 YEARS POST INTRODUCTION OF 10-VALENT PNEUMOCOCCAL CONJUGATE VACCINE (PCV10)

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Pneumococcus is a leading cause of pneumonia globally. Pneumococcal conjugate vaccines (PCV) protect against vaccine-serotype disease and nasopharyngeal carriage, leading to reduced transmission and herd protection. Kenya introduced 10-valent Synflorix (PCV10GSK: serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) in 2011 and switched to Pneumosil (PCV10SII: 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F) in 2022. PCV13 includes PCV10GSK types plus 3, 6A and 19A. We examined pneumococcal carriage prevalence and serotype distribution among predominantly outpatient severe acute respiratory illness (SARI) cases, to understand persistence of PCV10GSK serotypes 6-9 years after introduction and to assess serotype coverage of PCV10SII and PCV13. We leveraged ongoing SARI surveillance at two sites (Kibera, urban informal settlement in Nairobi and Asembo, rural western Kenya) collecting nasopharyngeal swabs for culture from patients of all ages meeting a standardized SARI case definition. Culture-positive isolates were serotyped by conventional multiplex PCR and/or Quellung. From January 2017 to April 2020, 3,067 patients in Asembo and 838 in Kibera had swabs collected and tested. Pneumococcal carriage prevalence was 43.0% (n=1,320) and 58.1% (n=487) in Asembo and Kibera, respectively; among children aged <5 years it was 63.3% (606/958) and 78.3% (144/184), respectively. Among 1,298 (97.7%) serotyped isolates from Asembo, most common serotypes were 3 (n=148), 6A (n=108), 35B (n=90), 19F (n=69) and 19A (n=58); among 482 (96.7%) serotyped isolates from Kibera, most common were 3 (n=50), 35B (n=29), 11A (n=26), 16F (n=22), 13 (n=20) and 19A (n=18). The prevalence of carriage with PCV10GSK, PCV10SII and PCV13 serotypes was 5.2%, 10.4%, and 15.5%, respectively in Asembo, and 8.9%, 11.8%, and 18.7% in Kibera; among children <5 years it was 8.0%, 16.6%, 21.2% in Asembo and 9.2%, 17.4%, and 26.6% in Kibera. Pneumococcal carriage in SARI is not reflective of etiology yet provides insight into circulating serotypes. PCV10GSK serotypes, most notably 19F, persisted up to 9 years after vaccine introduction. PCV10SII will offer broader serotype coverage.

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HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND DIABETES MELLITUS IN PEOPLE WITH TUBERCULOSIS IN ODISHA, INDIA

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This study evaluated the burden of human immunodeficiency virus (HIV) infection and diabetes mellitus (DM) in tuberculosis (TB) cases from Odisha, India, during 2019, and its impact on the TB treatment outcome. The study utilized data on TB patients of Odisha during 2019, from the NIKSHAY portal, the health management information system of TB in India. This is a retrospective observational registry-based cohort study, which evaluated a linkage between socio-demographic predictors, clinical diagnostic and treatment predictors, time of treatment predictors, and co-morbidity with TB. Data were retrieved electronically in Microsoft-Excel and analysis was done using STATA 16. Data for 47831 TB cases of Odisha was extracted from the Nikshay application for 2019. The highest prevalence (31.1%, 14863/47831) of TB was observed among young participants aged 15-30 years, whereas the prevalence was least among children <14 years (4.4%, 2124/47831). Of the 47831 TB cases, 7.6% (3659/47831) had DM, along with TB. 1.2% (571/47831) had HIV along with TB, while only 0.08% (37/47831) had both DM and HIV along with TB. 88.2% (3148/3569) of cases with DM and TB had a favorable outcome, compared to 82.3% (449/541) of cases with HIV and TB. People with TB who did not have DM had a significantly higher favorable outcome (OR 1.6, 95% CI 1.5-1.8) compared to those with TB and DM. Similarly, TB cases who did not have HIV infection had a significantly higher favorable outcome (OR 2.4, 95% CI 1.9-3.0) compared to those with TB and HIV. In conclusion, our study showed that presence of DM and/or HIV in TB patients had an impact on the TB treatment outcome.

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SCHISTOSOMAL CIRCULATING ANODIC ANTIGEN CLEARANCE IN PRESCHOOL AGED CHILDREN FROM THE PIP (PRAZIQUANTEL IN PRESCHOOLERS) TRIAL

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Circulating Anodic Antigen (CAA) is known to be specific to schistosomiasis and is assessed using the highly sensitive Up-Converting reporter Particle Lateral Flow (UCP-LF) CAA assay. The CAA assay is an important tool in determining worm burden hence is relevant in estimating treatment efficacy and reinfection rates. Limited data on CAA clearance after praziquantel (PZQ) treatment is available in Preschool Aged Children (PSAC). As part of the PIP trial, a phase II trial exploring different PZQ dosing regimens in children aged 12-47 months in Uganda, we present findings assessing clearance by measuring CAA in urine before and four weeks after PZQ treatment. The trial enrolled PSAC infected with Schistosoma mansoni as diagnosed by stool Kato-Katz (KK) living on the shores of Lake Albert,

Uganda. Schistosomal CAA was analyzed at baseline and at four weeks post treatment along with egg count by KK. 348 participants were enrolled to the trial with a median age of 36 months (IQR 28.0 – 42.0) and 51% of the participants were male. KK infection intensities at baseline were categorised as light (56.9%), medium (24.0%) and heavy (19.1%). Median CAA concentration was 154.8pg/ml (IQR 41.3 - 673.8) at baseline and 4pg/ml (IQR 0.2 - 58.0) at four weeks post treatment. Overall, there was a marked reduction in CAA levels at four weeks post treatment with 41% 'antigen cure' (95% CI 35.4 – 46.7). In comparison, parasitological cure based on KK was 91% (95% CI 86.9 – 94.2) for the 300 participants with complete CAA data. Out of those who showed parasitological cure at four weeks, 52.8% (95% CI 46.4 – 59.3) were still CAA positive but with relevantly reduced CAA concentrations. Findings demonstrate expected high egg reduction after PZQ treatment but with poor 'antigen cure', raising concerns of residual untreated infection in this trial setting. The disparity in diagnostic clearance is likely due to the poor sensitivity of KK at low egg burdens.

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GAPS IN BEDSIDE PROTOCOLS AND POLICIES FOR MANAGEMENT OF FEMALE GENITAL SCHISTOSOMIASIS IN ENDEMIC SOUTH AFRICA AND NON-ENDEMIC NORWAY

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Female genital schistosomiasis (FGS) is a prevalent gynaecological disease amongst women and girls in schistosomiasis-endemic parts of Africa. However, it is often misdiagnosed as a sexually transmitted disease or cervical cancer. FGS may cause abnormal vaginal discharge, infertility, paediatric genital symptoms, and may increase the susceptibility to HIV. The diagnosis entails cervicovaginal examination. WHO recommends praziquantel 40-60 mg/kg as a single dose. To adequately serve immigrants and travellers, health professionals in non-endemic countries should also be aware of FGS as a differential diagnosis. This literature study sought to explore current grey literature for FGS and gaps in patient management protocols in endemic South Africa and non-endemic Norway. Healthcare professionals in ten institutions provided access to bedside protocols used in their clinical practice. The heads of the cervical cancer screening programmes in both countries provided National Department of Health policies and protocols. Management protocols from private practitioners and hospitals were not included for practical reasons. Ten management and policy documents from each country, such as the national Standard Treatment Guidelines in South Africa and the regional hospital guidelines in Norway, were examined. This included reading through the relevant chapters, word searching and exploring the references. No guidelines mentioned FGS in the diagnosis or management of abnormal vaginal discharge, bloody discharge, infertility, or cancer. In order to change the current under-diagnosis, misdiagnosis and mismanagement of women it is imperative that the recommendations for diagnosis and treatment of FGS are included in healthcare policies and management protocols. Further research and collective action are needed to address the gaps in national guidelines and bedside protocols in both countries.

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NEXT STEP TOWARDS POINT-OF-CARE MOLECULAR DIAGNOSIS OF FEMALE GENITAL SCHISTOSOMIASIS: EVALUATION OF AN INSTRUMENT-FREE LAMP PROCEDURE

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Detection of Schistosoma DNA in gynaecological samples by real-time polymerase chain reaction (qPCR) is considered to be the reference laboratory test for the diagnosis of Female Genital Schistosomiasis (FGS). However, qPCR is expensive and needs highly trained technicians. Loop-mediated amplification (LAMP) is a more field-friendly isothermal DNA amplification procedure, but it still requires electrically powered equipment. Here we validated an S. haematobium-specific Sh-LAMP procedure and tested a fully instrument-free isothermal DNA amplification and detection procedure by using a novel low-cost and reusable T-cup device. Specific primers were selected based on published assays, targeting the ribosomal intergenic spacer region of S. haematobium. Technical validation of the Sh-LAMP was performed using 20 negative controls, including DNA extracts of soil transmitted helminths and S. mansoni, and a 10-fold dilution series (100-10-3) of DNA extracted from a single S. haematobium egg (n=4). For clinical validation, the Sh-LAMP was used on 125 DNA samples extracted from swabs of cervicovaginal lesions of a previous FGS study in Madagascar. Results were compared with the cycle threshold value (Ct) of the standard ITS-2 targeting qPCR. The T-cup performance was evaluated in a representative sub-selection (n=10) of Sh-LAMP positive clinical samples. Single S. haematobium egg DNA up to a 10-2 dilution and a Ct<35 were all Sh-LAMP positive. The specificity was found to be excellent (100%). In the clinical samples Sh-LAMP showed comparable results with the qPCR, with 35.2% and 33.6% positives, respectively, and a concordance of 79.2% (99/125). Most false-negatives were seen in the qPCR positive samples with a Ct≥35 (5/7), while Sh-LAMP detected 14 additional cases missed by qPCR. The T-cup was found to be a very user-friendly method, but it missed 1 of the 10 Sh-LAMP positive samples. The Sh-LAMP was found to be a suitable alternative to qPCR for the diagnosis of FGS in gynaecological samples, with high potential for the T-cup as a fully instrument-free DNA amplification device for point-of-care diagnosis in low-resource settings.

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POPULATION LEVEL IMPACT OF NOVEL DRUGS TARGETING JUVENILE SCHISTOSOMES ON CONTROL AND ELIMINATION OF SCHISTOSOMIASIS

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Praziquantel (PZQ), the standard drug for schistosomiasis, has minimal activity against juvenile schistosomes (within 6 weeks of infecting humans) and imperfect cure rates. The effect of treatment-resistant juvenile schistosomes and imperfect PZQ clearance on transmission dynamics of Schistosoma is unknown. We model the population level effects of novel drug candidates targeting both juvenile and adult schistosomes on schistosomiasis control programs in various settings, which can guide drug development decisions. We created an individual-based dynamic mechanistic model of S. mansoni transmission that simulates mass drug

administration programs using novel drugs. The model simulates low, medium, and high prevalence settings using data from SCORE trials, and explicitly models juvenile and adult schistosomes for each infected person. We simulated five years of annual mass drug administration with: i) 1-dose PZQ (40 mg/kg; per WHO guidelines); ii) 2-dose PZQ (6 weeks apart); and iii) novel drug with activity against juvenile and adult schistosomes. Treatment parameters for PZQ were calibrated to literature values (84% and 88% egg reduction for 1- and 2-dose PZQ), and novel drug efficacy was varied. We assumed 75% coverage. In a low prevalence setting (baseline 15%), 1-dose PZQ, 2-dose PZQ, and a novel drug (PZQ-equivalent activity against adult worms plus juvenile activity) led to 1.0%, 0.8%, and 0.8% prevalence at year 5, respectively. In a high prevalence setting (baseline 50%), 1-dose PZQ, 2-dose PZQ, and a novel drug led to 9.0%, 8.0%, and 7.4% prevalence at year 5, respectively. Increased efficacy of a novel drug against adult schistosomes compared to PZQ (+25% potency) had larger effects on prevalence reduction than comparable activity against juvenile schistosomes. A novel drug that can kill both adult and juvenile schistosomes with higher efficacy will have measurable public health gains compared to PZQ alone. A novel drug will have larger effects in high prevalence settings and small relative reductions in near elimination settings. Targeting juveniles is generally less important than increasing efficacy against adults.

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DEVELOPMENT OF ANTIGEN-BASED MULTIPLEX IMMUNODIAGNOSTICS FOR TWO PREDOMINANT SCHISTOSOMA PARASITES IN SUB-SAHARAN AFRICA

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Schistosomiasis is a disease of poverty that is highly prevalent in Sub-Saharan African countries. Cross-reacting proteins in Schistosoma mansoni (Sm) and S. haematobium (Sh) have been alluded to pose diagnostic challenges in the development of serological diagnostics. Proteins specific to these two parasites can leverage diagnostic challenges associated with cross-reactivity and the development of a multiplex diagnostic tool for the two parasites. The aim of this study is to identify protein markers from S. mansoni and S. haematobium for concurrent diagnosis of the two parasites. High-quality protein extracts were prepared from the eggs [(soluble egg antigen (SEA) and adult worms (Schistosoma worm antigens (SWA)] of S. haematobium and S. mansoni. The diagnostic performance of the proteins was evaluated using a quantitative ELISA method with sera obtained from S. mansoni-infected mice. The immunoreactive proteins in the helminths were identified by conventional Western blot analyses and the specific protein markers for concurrent diagnosis of the two parasites were confirmed by double-binding Western blot analyses. Sm SEA gave the best diagnostic performance (Sensitivity (SS) = 1.00, Specificity (SP) = 0.96, AUC = 0.96). Sh SEA slightly performed better in diagnosing S. mansoni infection (SS = 0.96, SP = 0.87, AUC = 0.95) compared to Sm SWA (SS = 0.91, SP = 0.95, AUC = 0.93). Diagnostic protein markers of size 100 kDa in Sh SWA, > 250 kDa (Sh SEA), 25-37 kDa (Sm SWA), and 50-150 kDa (Sm SEA) were specific for the concurrent diagnosis of S. mansoni and S. haematobium. This study showed the plausibility of developing multiplex immunodiagnostic tools for S. mansoni and S. haematobium. Ongoing studies with 2D Western blots and LC-MS seek to identify novel biomarkers for operational diagnosis of these two Schistosoma species simultaneously.

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BASELINE SEROPREVALENCE OF SCHISTOSOMA IN ZAMBIAN WOMEN ENROLLED IN A COHORT STUDY (THE ZIPIME WEKA SCHISTA STUDY)

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Schistosomiasis, a disease caused by the waterborne parasite Schistosoma (S.) spp., continues to present a significant public health problem across sub-Saharan Africa. Schistosoma seroprevalence surveys provide an opportunity for the assessment of the burden of schistosomiasis in low-prevalence areas. This study aimed to assess Schistosoma seroprevalence in women as part of an ongoing cohort study and identify potential risk factors across two communities (Livingstone and Kafue) in Zambia using a field-applicable assay. Community health workers recruited women into the Zipime Weka Schista study through home visits and obtained genital self-swabs, urine samples, rapid tests for HIV and Trichomonas vaginalis (Tv), and administered a questionnaire. Venous blood was obtained at a follow up clinic visit. Serological testing was performed for the detection of antibodies to soluble egg antigen (SEA) using the IVD SEA-ELISA. Urine microscopy was conducted for the detection of S. haematobium (Sh) eggs in urine. Testing for High-Risk Human Papillomavirus (HR-HPV) was performed with Gene Xpert. Descriptive statistics were used to analyse sociodemographic characteristics and logistic regression was conducted to explore associations with other infection parameters. A total of 601 serum samples were analysed. Overall prevalence of egg-patent Sh was 5.7% (34/592). Approximately one third of participants (35.8%, 216/601) were found to be Schistosoma seropositive. Seroprevalence was higher in Livingstone than Kafue (40.1% vs. 32.0%, p=0.053). Seropositive participants were more likely to report daily water contact during childhood (p=0.006). Most seropositive participants had no Sh eggs observed in urine (90.0%, 188/209) suggesting chronic exposure. No crude or adjusted associations between Schistosoma seropositivity and any sexually transmitted infection were found including HR-HPV, HIV and Tv. Further visual and molecular genital testing for female genital schistosomiasis is ongoing and will refine our estimates.

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DEVELOPMENT OF AN ELISA TO DETECT ANTIBODY TO SCHISTOSOMA JAPONICUM INFECTION USING A BACTERIAL EXPRESSED RECOMBINANT ANTIGEN SJ10.3

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Schistosoma japonicum is a trematode parasite endemic in China, the Philippines, and parts of Sulawesi, Indonesia. Traditional diagnosis is based on identifying S. japonicum eggs in fecal samples using microscopy; however, diagnosis by microscopy requires trained personnel to make and read slides and has low sensitivity in light infections. Antibody detection for serological diagnosis can be useful to indicate schistosome infections in individuals who have traveled to schistosomiasis endemic areas, for mapping in control programs, and when attempting to assess interruption of transmission or perform surveillance. We selected protein Sj10.3 based on its homology to an S. mansoni antigen (Sm10.3) and S. haematobium antigen (Sh-SAP-1) that were identified by epitope library selection and peptide array screening. Using GenBank to obtain the sequence, we synthesized the Sj10.3 gene and expressed it as a GST fusion protein using a bacterial expression vector. The protein was purified using

glutathione magnetic beads and confirmed as reactive with sera from persons with S. japonicum infection using immunoblot. After optimization of the ELISA, we evaluated the assay performance using an S. japonicum serum panel obtained from WHO that consisted of 242 negative and 340 positive samples. These sera were confirmed positive by S. japonicum adult microsomal antigen immunoblot, the current CDC serological reference assay. Based on this serum panel, the assay's sensitivity and specificity are 91% and 99%, respectively. Planned validation studies include assay evaluation against a panel of potential cross-reactive sera such as other trematode infections, including paragonimiasis, fascioliasis, clonorchiasis, and opisthorchiasis. Availability of a recombinant antigen specific for schistosome infections improves the ability of control programs to map endemic areas, evaluate interruption of transmission, and perform surveillance for schistosomiasis in several Asian countries.

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URINARY HPV ANALYSIS AS A COMPLEMENTARY DIAGNOSTIC TEST AMONG WOMEN AT RISK FOR CERVICAL CANCER AND FEMALE GENITAL SCHISTOSOMIASIS

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The triad of HIV, cervical cancer and Female Genital Schistosomiasis (FGS) is found mainly in Africa. FGS is a neglected disease that is associated with HIV and is often misdiagnosed as cervical atypia. Most at risk are young women, aged 15 and above, constituting almost 3 million of the South African (SA) population. They may have limited access to healthcare and gynaecological investigations, may be reluctant to undergo a gynaecological examination, and are high at risk for this triad of diseases. The present study sought to compare HPV DNA in urine and cervico-vaginal lavage samples and explore their association with cytology results (Pap smears) and urinary Schistosoma haematobium microscopy results. The study was conducted among 220 young women aged 16-23 years of age from rural high schools in KwaZulu-Natal, South Africa. HPV DNA analysis was done in urine and vaginal lavage. Cytology samples were analysed for squamous cell atypia and urine microscopy was used for the identification of Schistosoma ova. The participants reported to have been sexually active from 17 years of age (SD=1.39). Schistosoma ova were found in 46 (20.9%) of the participants and the HIV prevalence was 43 (19.5%). Cervical cell atypia was detected in 120 (54.5%) of these young women. HPV DNA was detected among in 133 (60.5%) of the urine samples and in 168 (76.8%) of the cervico-vaginal lavage samples ($p < 0.001$). Using cervico-vaginal lavage as a gold standard, HPV PCR DNA urine analysis had a sensitivity of 75.15% and a specificity of 88.24%. There was no association between the HPV DNA in urine and cervico-vaginal lavage and cytology or urinary schistosomiasis results, respectively. It was also found that the young women who were HIV positive were 2,5 times more at risk for HPV in urine/vaginal lavage than those who were HIV negative. Urine has the potential of being optimized as a less invasive, alternative test for HPV among this young adolescent population at risk. In light of the diagnostic challenges urinary HPV testing might be a sustainable solution for targeted intervention among this neglected group.

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POPULATION PHARMACOKINETICS OF PRAZIQUANTEL IN PRE-SCHOOL AGE CHILDREN PARTICIPANTS IN THE PRAZIQUANTEL IN PRESCHOOLERS (PIP) TRIAL

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Praziquantel (PZQ) remains the drug of choice for treatment of schistosomiasis, a major neglected tropical disease with over 250 million people infected globally; children bear more than 50% of the disease burden. However, limited pharmacokinetic (PK) data is available to guide dosing of PZQ in children. The objective of this study was to establish and describe the population PK of PZQ in pre-school age children. Children aged 1 to 4 years old with Schistosoma mansoni infection were enrolled into a clinical trial and randomised to receive either 40mg/kg or 80mg/kg dose of PZQ during the study. The doses were split into two and administered 3 hours apart (i.e. 40mg/kg and placebo; 40mg/kg and 40mg/kg). PK samples were collected at four time points; 1.5, 3, 4, and 6 hrs post dose. Plasma concentrations of PZQ enantiomers (R- and S-PZQ) were quantified using a liquid chromatography – tandem mass spectrometry (LC-MS/MS) assay. A hundred and ninety children (54.2% males) were enrolled with a mean age of 33 (± 9.23) months. There was significant variability in the plasma concentration profile of both R and S enantiomers. The plasma concentrations of both enantiomers were quantified up to 6 hours post dose. Praziquantel dosing at 80mg/kg resulted in higher drug exposure than at 40mg/kg. Further PK/PD modelling is ongoing pending trial unblinding.

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PHARMACOLOGIC MONITORING OF PLASMA CONCENTRATION OF PRAZIQUANTEL ON THE INTENSITY OF SCHISTOSOMA INFECTION IN A THERAPEUTIC EFFICACY MONITORING STUDY IN PERSONS TREATED FOR SCHISTOSMIASIS IN ABUJA, FEDERAL CAPITAL TERRITORY, NIGERIA

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Treatment and control of schistosomiasis depend heavily on praziquantel (PZQ) which is administered mainly as a single dose of 40mg/kg body weight based on WHO recommendation. PZQ is the backbone of Mass Drug Administration (MDA), a strategy for the control and elimination of schistosomiasis. PZQ is well tolerated by patients and has few side effects, but there have been concerns of tolerance/resistance/treatment failure. Continuous therapeutic monitoring is critical for successful mass drug administration programme. We monitored therapeutic efficacy of praziquantel in a cohort of 65 participants from whom urine, plasma and stool samples were collected and processed by microscopy for Schistosoma haematobium (Sh) eggs detection by urine filtration technique, while Kato-Katz method was used for stool examination for the detection and quantification of of S. mansoni (Sm) using standard protocol. Of the 65 persons, 5years and above, a single dose of PZQ, using a praziquantel, given as DOT. After about 2weeks of follow up the blood samples of the

cohort were taken again. 51 of them [32males (62.7%) and 19 females (37.3%] with mean age of 14.5years were selected based on intensity of infection for detection and quantification of plasma levels of PZQ using High Profile Liquid Chromatography (HPLC). Plasma PZQ level was recorded in micrograms per milliliter (µg/ml). Of the 51, 44 were positive for eggs (infection group): 15 low infection (1-50 eggs), 22 moderate infections (50-400 eggs), and 6 heavy infection (>400 eggs). 7 had zero egg count (non-infection or control group). Mean plasma PZQ concentration for the non-infection group was 12.84 µg/ml, low infection 4.22 µg/ml, and 2.71ug/ml for moderate infection. Heavy infection (>400 parasites); no PZQ detected. In addition, mean plasma PZQ concentration was higher for S. haematobium infection (3.20 µg/ml), so was ERR as compared with S. mansoni. This study shows differential effect of PZQ for Sh and Sm, thus indicating an association between intensity of infection of schistosomiasis and plasma levels of PZQ and efficacy. It also shows that PZQ is rapidly taken up by schistosomes following its administration.

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THE PREVAILING INFECTION OF SCHISTOSOMA JAPONICUM AND OTHERZOONOTIC PARASITES IN BUBALINE RESERVOIR HOSTS IN THE RICEFIELD OF LAKE ECOSYSTEM: A CASE IN LAKE MAINIT THE PHILIPPINES

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Bovines are important reservoir hosts of schistosomiasis, placing humans and animals in rice fields areas at risk of infection. This study reported the prevailing infection of zoonotic parasites from bovine feces in the rice fields adjacent to Lake Mainit lake scape in the Philippines. Formalin Ethyl Acetate Sedimentation (FEASD) was performed on 124 bovine fecal samples from rice fields and documented eggs and cysts from eight parasites: Schistosoma japonicum, Fasciola sp., Balantidium coli, coccidian oocyst, Ascaris sp., Strongyloides sp., and hookworm species. Among these parasites, Fasciola sp. harbored the highest infection with a 100% prevalence rate, followed by hookworms (50.94%), B. coli (32.22%), and S. japonicum (13.33%) respectively, while Strongyloides sp. (2.83%) reported lowest. The intensity of infection of Schistosoma eggs per gram (MPEG=4.19) among bovines is categorized as “light.” Bovine contamination index (BCI) calculations revealed that, on average, infected bovines in rice fields excrete 104,750 S. japonicum eggs daily. However, across all ricefield stations, bovines were heavily infested with fascioliasis with BCI at 162,700 Fasciola eggs per day. The study reports that apart from the persistent cases of schistosomiasis in the area, bovines in these rice fields are also heavily infested with fascioliasis. The study confirms the critical role of bovines as a reservoir host for continued infection of schistosomiasis, fascioliasis, and other diseases in the rice fields of Lake Mainit and requires immediate intervention to manage the spread of these diseases.

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POOLED PEAKS PIPELINE (P3): AN R-BASED PROGRAM FOR POPULATION GENETIC ANALYSES IN POOLED SAMPLES

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Over 1.5 billion people globally are infected with soil-transmitted helminths, and 230 million are infected with schistosomiasis. Although the primary diagnostic method is the microscopic examination of stool or urine, essential transmission dynamics can be identified using population genetics. Pooled egg samples facilitate the analysis of large parasite and infrapopulation numbers. While using microsatellite markers on pooled samples can measure genetic diversity and differentiation, few methods of batch analysis are currently available, and even fewer are available offline and for free. DNA sequencers and genetic analyzers store fragment analysis data as .fsa files that are read into licensed software requiring internet access, such as Peak Scanner. The Pooled Peak Pipeline (P3) is written in R and builds off the previously published Fragman package. P3 provides added quality control, produces reviewable tracings, formats the output to perform duplicate sample comparison, converts raw peak heights to allele frequencies, and computes population-level measures, including Nei’s GST, Jost D, principal coordinate analysis plot, and phylogenetic tree. P3 was tested using fsa files from Schistosoma haematobium lab strain samples and Schistosoma mansoni samples from infected Brazilians. The P3 results of the S. mansoni samples were compared to a previous analysis using traditional tools and therefore serve as an excellent control for the accuracy of P3. In conclusion, this analysis pipeline will provide free and offline access to genetic analysis following initial download, enhancing the capability to use pooled samples, egg or otherwise, for genetic analysis in low-resource settings. Although microsatellite markers are not a diagnostic tool, they are used in various genetic studies of infrapopulations, including studies of host-parasite coevolution, transmission dynamics, and drug resistance. A link to P3’s beta version will be provided.

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RISK FACTORS FOR HIGHER-INTENSITY SCHISTOSOMA MANSONI INFECTION IN LAKE ALBERT COMMUNITIES, UGANDA: A CROSS-SECTIONAL STUDY

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Schistosomiasis, a chronic trematode disease, is persistent in Lake Albert, western Uganda, the site of the Praziquantel in Preschoolers (PIP) trial. This cross-sectional study aimed to describe the infection and morbidity burden in household members of trial participants and identify risk factors to explain the persistent infection burden. Recruitment was by convenience sampling from four villages and data collection involved a survey, single Kato-Katz (KK) stool examination, hepatic ultrasound and household GPS measurement. Multilevel logistic regression assessed risk factors for moderate-to-heavy infection. Of 243 participants from 66 households, 66% were female and the median age was 22 years (IQR 12 - 33). Participants lived a median of 242m (IQR 178 - 384) from the shore, most (82%) visited the lake at least twice per day and 77% had unimproved sanitation. Despite local campaigns, only 37% reported taking praziquantel in the past year. Most participants (71%) were positive for Schistosoma mansoni on KK and 50% had moderate-to-heavy infection. Twenty-five (11%) participants had periportal fibrosis (image pattern C - F). In multivariable analysis, age and village were associated with moderate-to-heavy infection: adjusted odds ratio (aOR) 5.53 (95% confidence interval [CI] 1.72 - 17.76) for those aged 10 - 19 years vs. <10 years and aOR 0.11 (95% CI 0.03 - 0.46) for the lowest- vs. highest-burden village. There was weak evidence for a negative association with recent treatment and no association with distance to the lake or water contact. There was evidence of household clustering of moderate-to-heavy infection (intraclass correlation coefficient = .13). Schistosome infection and disease is pervasive in lakeshore communities with poor sanitation and low treatment coverage. We found clustering in infection risk which may be targetable by control programmes. Lake proximity was unimportant at the scales studied. High-intensity infections despite recent treatment suggest rapid reinfection or treatment failure. There is an urgent need for more intensive preventive chemotherapy and improved water and sanitation in endemic areas.

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SNAIL-SCHISTOSOME DYNAMICS IN COMPLEX ECOLOGICAL COMMUNITIES

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Schistosomes are transmitted between human and snail hosts via free-living stages in freshwater. Historically, biocontrol of host snail species using predators and competitors has been attempted with mixed success. In this study we investigated the interactions between the ecological community and snail-schistosome dynamics in two settings. We first conducted a mesocosm experiment to investigate the impact of competition by non-host genera Melanoides and Physa on the population dynamics and schistosome transmission in Biomphalaria, host of Schistosoma mansoni. We tracked snail abundance, body size, reproduction, resources, and schistosome production for 16 weeks. Melanoides decreased the abundance of Biomphalaria and algae, suggesting strong resource competition. Physa also reduced Biomphalaria abundance. However, they increased algae and Biomphalaria body size, cercarial production, and reproduction – effects inconsistent with resource competition, but consistent with intraguild predation. Lab experiments confirmed that Physa is a voracious predator of Biomphalaria eggs. Given these strong effects of competition and predation, we surveyed non-host snail competitors and predators of in 57 waterbodies surrounding Mwanza, Tanzania, at 3 time points over the schistosome transmission season. We found significant variation in predator community composition and that community composition impacted host snail size and infection status: waterbodies with a greater abundance of notonectids and Corixidae had larger snails and a greater infection prevalence. We speculate that these smaller predators are limited to consuming small snails, thereby contributing to larger snail size and infection prevalence. Collectively, our work demonstrates that non-host species in the ecological community of host snails may have a great impact on schistosome transmission dynamics. Synthesizing these community-level processes and understanding which traits of predators and competitors matter can yield important insights into schistosome biocontrol.

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A COMPLEX INTERPLAY BETWEEN FOOD, HEALTH AND LIVELIHOODS - LIVE FLUKE (OPISTHORCHIS VIVERRINI) IN NORTHEAST THAILAND

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Transmission of the human-infective and carcinogenic trematode Opisthorchis viverrini (OV), a parasite acquired from eating raw or undercooked fish that causes cancer of the bile duct, is ongoing in Southeast Asia. The resulting cancer mainly afflicts individuals aged 40+ and once progressed is rapidly fatal with limited treatment options. Despite decades of control, this cholangiocarcinoma caused by OV remains one of the leading causes of death in Thailand and Laos and incidence rates in Northeast Thailand remain the highest in the world. Determining which interventions will be most effective requires an understanding of fundamental epidemiological processes, many of which are poorly understood. The communities most heavily affected by the parasite are lower-income rural households around the Mekong River and its tributaries where the main sources of employment are fishing, rice farming and fish farming. There is therefore a close connection between people's livelihoods and infection. Persistent public health campaigns have stigmatised the practise of eating raw fish, which has contributed to a disconnect between reported behaviour and actual eating habits. To better understand this disconnect and the complex interplay between diet, health and livelihoods from the community perspective, a food festival at a well-established food market was conducted in the highly endemic region of Maha Sarakham. Questionnaires, discussion groups and interactive activities, all conducted in the Thai language by staff and students from Khon Kaen University, formed the basis of the comprehensive qualitative and qualitative data collection from this event. This event engaged with previously overlooked community members – such as fisherman and non-risk-group individuals. Novel evidence and metrics were gathered from this festival that will be used to inform intervention methods, surveillance, treatment, and health policy. This project will also be used as a template for community engagement and epidemiological data collection and has informed research and public health policy for the region.

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THE SNAIL-TREMATODE-MICROBIOME TRIPARTITE INTERACTION: FROM LAB MANIPULATIONS TO THE FIELD

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Snail-borne diseases affect over 250 million people worldwide and pose a substantial burden on the livestock industry. A fundamental understanding of the drivers of the epidemiology of these diseases is crucial for the development of sustainable control measures. The microbiome is increasingly being recognized as an important player in the interaction between parasitic flatworms and snail intermediate hosts. In order to better understand this interaction, field and lab-based studies, including microbiome transplant experiments whereby the microbiome is transferred between a donor and a recipient host, are needed. We conducted a transplant and an infection experiment in the lab on Biomphalaria glabrata and collected field data in the Senegal River Basin (SRB) focused on Bulinus spp. First, a multiplex PCR was used to detect flatworm infections in snails. Next, an amplicon sequencing workflow was used to genotype up to 25 infected snails per species per site and their infecting flatworms. Finally, the microbiome of the selected snail specimens was profiled through 16S metabarcoding. We conducted a successful snail microbiome transplant and show that the phylogenetic relatedness between the recipient and donor snail affects the recipient's survival probability. Furthermore, the microbiome changes throughout flatworm infection development in B. glabrata. Moreover, sympatric host-parasite combinations might affect the microbiome differently compared to allopatric ones. Finally, the SRB field dataset showed marked variation in the microbiome between species and across regions but not between infected and uninfected samples. Combined with information on the co-infection status of our samples, these findings could provide further insights into the relationship between infection status and microbiome. Transplant experiments, complemented by field-based studies, could facilitate future research endeavors to investigate the role of specific bacteria or bacterial communities in parasitic flatworm resistance of freshwater snails and might ultimately pave the way for microbiome-mediated control of snail-borne diseases.

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USING MATHEMATICAL MODELS TO UNDERSTAND SCHISTOSOMIASIS TRANSMISSION IN A UGANDAN HOTSPOT

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Schistosomiasis is a neglected tropical disease of profound medical importance, infecting approximately 240 million people, 90% living in Sub-Saharan Africa. Severe schistosomiasis is associated with periportal fibrosis and portal hypertension which can cause death without appropriate disease management. A cornerstone of international efforts to eliminate schistosomiasis as a public health problem is mass drug administration

(MDA) with praziquantel. However, despite nearly two decades of MDA, the prevalence of infection and the incidence of periportal fibrosis remains high in communities along the shore of Lake Albert in Uganda, representing a conspicuous failure of the current intervention strategy. The FibroScHot Consortium is addressing this urgent public health need by conducting a randomised controlled trial to evaluate the effectiveness of delivering MDA at frequencies of up to four times per year. Reporting on research conducted as part of the Consortium, this talk presents progress from mathematical model-based analyses of the historical impact of MDA on the infection and morbidity dynamics of Schistosoma mansoni along the shore of Late Albert and discusses how severe schistosomiasis may be tackled in transmission hotspots.

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MALE GENITAL SCHISTOSOMIASIS AMONG LOCAL FISHERMEN ALONG SOUTH SHORELINE OF LAKE MALAWI IN MANGOCHI DISTRICT

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Male genital schistosomiasis (MGS) is an ignored consequence of urogenital schistosomiasis (UGS) with schistosome eggs and pathologies in genitalia. First reported by Madden in 1911, its epidemiology, diagnostic testing and management are not well described owing to limited research and diminishing focus. Furthermore, expansion of Human immunodeficiency virus (HIV) epidemic across sub-Saharan Africa has renewed interest in MGS owing to their plausible but under-explored interactions. A longitudinal cohort study was set up among fishermen along southern Lake Malawi shoreline in Mangochi district to investigate prevalence and morbidity of MGS. Fishermen aged 18+ years were recruited and administered questionnaires, assessing knowledge, attitudes and practices associated with MGS. They submitted urine and semen for parasitological and molecular diagnostic tests: dipstick, point-of-care circulating cathodic antigen (POC-CCA), filtration, microscopy and real-time PCR. Abdominopelvic and scrotal ultrasonography were conducted for abnormalities in prostate, seminal vesicles, epididymis, testes and other organs. Standard Praziquantel (PZQ) treatment (40mg/kg) was offered to all and follow-up was done at 1, 3, 6 and 12 months. 376 fishermen (median age: 30 years, range: 18-70) were recruited and interviewed. Below 10% reported experiencing MGS symptoms, like genital or coital pain. Baseline MGS prevalence by semen microscopy was 10.4% (n=114, median: 5.0/ml) while real-time PCR was 26.6% (n=64). UGS prevalence was 17.1% (n=210, median: 2.3/10 ml). None of MGS positive participants experienced MGS symptoms. 130 fishermen had ultrasonography and 9 (6.9%) had abnormalities, 1 with prostatic nodule and another a testicular nodule. Subsequent analyses on follow-up indicated variable detection dynamics, with fewer abnormalities observed. MGS is prevalent among local fishermen along southern Lake Malawi, which calls for improved availability and accessibility to advanced diagnostics, PZQ treatment and control interventions to reduce prevalence and better manage MGS.

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PREVALENCE OF SCHISTOSOMIASIS AND IMPLEMENTATION OF SCHISTOSOMA PREVENTION PROJECT IN GEZIRA STATE, SUDAN 2022-23

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In several developing countries, including Sudan, schistosomiasis remains a public health problem particularly in Gezira state. The needs of clear prevalence and testing an effective environmental and social impact methods were essential to eradicate schistosomiasis .This study is composed of two major sections first to measure the prevalence of schistosomiasis in Gezira state -the second part is to implement environmental-social based interventional projects to cover an area of the gap in knowledge and attitude in one of the most prevalent villages after the primary survey result and the total study period was 18 months. The first part of study was done by Descriptive Prevalence Study design [DPS]using a case-counting survey in major health centers in Gezira state .the second part composed of three phases :-pre intervention knowledge and attitude survey . -intervention through health education session .-Post-intervention evaluation survey.The primary survey reveals S.haematobium was found in 32%, while S.mansoni infection was found in 43% of the Gezira state population, and 13% of the total number of cases in Gezira state from Alhafayer village out of hundreds of villages, that's why we choose Alhafayer village for the interventional project, the outcome of 14 months of interventions: The morbidity rate in alhafayer village has dropped from 82% to 24%. Raising awareness among the village population from 13% to 78% after assessing attitudes and practice of schistosoma-preventing methods. Opening spared section in Alhafayer heath center for diagnosis, provide treatment , and scheduling regular health education sessions for all social classes .The need for clean water sources was discussed with the Gezira government and charities .however the clean water project will start soon to cover Alhafayer and two neighboring villages .Collaboration across sectors for water supply, environmental management, and health education an intersectoral approach needed to eradicate Schistosoma. Also an Operational research is essential to develop intervention methods, diagnostic procedures, and human behavior facilitation.

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EVALUATION OF THE BURDEN AND RISK FACTORS ASSOCIATED WITH FEMALE GENITAL SCHISTOSOMIASIS IN TWO ENDEMIC AREAS IN MALAWI AS PART OF THE MORBIDITY OPERATIONAL RESEARCH FOR BILHARZIASIS IMPLEMENTATION DECISIONS (MORBID) STUDY

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Female genital schistosomiasis (FGS), caused by Schistosoma haematobium (Sh) is prevalent in Sub-Saharan Africa (SSA). FGS is associated with sexual and reproductive life morbidity, and increased HIV and cervical precancer prevalence. There are no control programmes for FGS screening and diagnosis in endemic countries, hindering precise disease burden estimation. This study evaluated the burden of FGS by visual and molecular diagnostic methods in two districts in Southern Malawi. Women aged 15-65 years, sexually active, not currently menstruating, or pregnant, were enrolled from the larger MORBID study. A midwife completed a symptoms questionnaire, obtained a cervicovaginal swab and cervicovaginal lavage (CVL), and assessed FGS-associated

genital lesions using hand-held colposcopy. Visual-FGS was defined as the presence of sandy patches, rubbery papules, or abnormal blood vessels. Molecular-FGS was defined as Sh DNA detected by real-time PCR from a cervicovaginal swab. Egg-patent Sh infection was detected by urine microscopy. 950 women completed the questionnaire (median age 27, [IQR] 20-38). Visual and molecular FGS prevalence was 26.9% (260/967) and 8.2% (78/942), respectively. Of the 584 women with available genital and urinary samples, 6.5% (38/584) had egg-patent Sh infection. Multivariable logistic regression showed a positive significant association between molecular and visual FGS (OR=2.9, p<0.01). Self-reported urinary, genital, sexual and reproductive health symptoms were not predictive of FGS (p>0.05). Molecular-FGS was associated with egg-patent Sh infection (OR=7.5, p<0.01). There was no significant correlation between visual-FGS and Sh infection status (p = 0.5). Some villages had high prevalence of molecular-FGS, even with <10% prevalence of urinary Sh in school-aged children (SAC), a common treatment threshold. No significant association between visual-FGS and village Sh prevalence was found (p=0.2). This study highlights the significant burden of FGS in Southern Malawi and importance of using field-deployable screening methods for FGS diagnosis in SSA countries and determining treatment need.

5678

PRESENCE OF SARS-COV-2 RNA IN DIFFERENT SOURCES OF WATER OF NEPAL

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Wastewater-based epidemiology (WBE) has been one of the most promising surveillance tools for monitoring the status, trend of infection, possible future outbreaks of coronavirus disease-2019 (COVID-19), to gather the information on disease surveillance, epidemiological models, genetic diversity, and geographic distribution. This study reports the presence and reduction of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at two wastewater treatment plants (WWTPs) of Nepal, along with river water, hospital wastewater (HWW), and wastewater from sewer lines collected between July 2020 and February 2021. SARS-CoV-2 RNA was detected in 50%, 54%, 100%, and 100% of water samples from WWTPs, river hospitals, and sewer lines, respectively, by at least one of four quantitative PCR assays tested (CDC-N1, CDC-N2, NIID_2019-nCOV_N, and N_Sarbeco). The CDC-N2 assay detected SARS-CoV-2 RNA in the highest number of raw influent samples of both WWTPs. The highest concentration was observed for an influent sample of WWTP A (5.5 ± 1.0 log10 genome copies/L) by the N_Sarbeco assay. SARS-CoV-2 was detected in 47% (16/34) of the total treated effluents of WWTPs, indicating that biological treatments installed at the tested WWTPs are not enough to eliminate SARS-CoV-2 RNA. One influent sample was positive for N501Y mutation using the mutation-specific qPCR, highlighting a need for further typing of water samples to detect Variants of Concern. Furthermore, crAssphage-normalized SARS-CoV-2 RNA concentrations in raw wastewater did not show any significant association with the number of new coronavirus disease 2019 (COVID-19) cases in the whole district where the WWTPs were located, suggesting a need for further studies focusing on suitability of viral as well as biochemical markers as a population normalizing factor. Detection of SARS-CoV-2 RNA before, after, and during the peaking in number of COVID-19 cases suggests that WBE is a useful tool for COVID-19 case estimation in developing countries.

5679

POOR OUTDOOR BATHROOMS DRAINAGE SYSTEMS OF CHING'AMBO RESIDENTS IN MZUZU CITY AS A SAFE HAVEN AND TOOL FOR INCREASED EXPOSURE TO TROPICAL PARASITES

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Bathroom drainage wastewater is a major source of water borne diseases and injuries especially in densely populated communities with a higher water table. However, water sanitation remains one of the neglected areas of research and health promotion in the fight against diseases of poverty. For this project, we aimed at investigating the implications of poor drainage systems of traditional bathrooms among residence of Ching'ambo, in Mzuzu city. We conducted an exploratory survey using quantitative and qualitative data collection methods which included photography of out-door bathrooms drainage systems, observation checklists, and in-depth interview questionnaires. A total of 60 households with traditional bathrooms were identified through random sampling technique and calculated using n=N/1+N (e)2 with 95% confidence interval participated in the study. SPSS version 16 statistical software was used for the generation of descriptive analysis. The results demonstrated that inhabitants were highly exposed to vectors or parasites that transmit neglected tropical diseases of poverty such as mosquitoes, worms, ticks, snails and other insects of medical entomology. In the study, 60% of participants reported to be victims of snakebite and physical injury while 70% perceived themselves as having experienced zoonotic diseases due to close contact with stray dogs that habited these bathrooms as safe havens. The research showed that poor and inadequate spacing for construction of out-door bathrooms wastewater pathways were important contributors for poor drainage systems which were in agreement with the reports of 68% of households respondents. Consequently, the findings of this study provide an impetus for further wastewater epidemiology and related research. Additionally, there is need for intense interventions tailored towards promotion of proper wastewater disposal leadership among residents of Ching'ambo and surrounding semi-urban communities in Mzuzu city.

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SOCIOCULTURAL INFLUENCES ON ACCEPTANCE AND HEALTH RISK OF WATER RESOURCES IN REMOTE COMMUNITIES IN GHANA

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Access to clean water has an important role to play in ensuring good public health and to reduce health risks, so there are clear guidelines and pollution limits to safeguard the health of populations. Water should be free of microbial inputs, chemical inputs (heavy metals), with water quality indices values between 70 and 100. With these requirements met, consumers can accept and utilize water; however, water may be utilized for other reasons. The relationship between rural people and their environment, vis à vis water resources is deeply rooted in socio-cultural values and norms; this can influence utilization and acceptance regardless of vital health risks, but this gap has not been researched particularly in rural, remote communities. Additionally, water quality assessments usually end at comparing concentrations with WHO guideline values, however, this study assessed health risk. Key Informant Interviews were conducted among twelve purposively sampled community leaders, using an interview guide and results analyzed using Interpretative phenomenological analysis method and health risk of heavy metals were also assessed using USEPA models. Cultural norms and History influenced acceptance, utilization and protection of the water resource. Management of water resources is shrouded in Taboos and Beliefs, with little scientific underpinning; meanwhile water quality is compromised by run-off from riparian agricultural activities and some heavy metals potentially having long term effects despite recording

low concentrations. Therefore, water and policy managers need to conduct proper community engagement, to reduce any sociocultural barriers and assess health risks, in water protection interventions.

5681

MOLECULAR DETECTION OF PATHOGENIC LEPTOSPIRA AND HELICOBACTER PYLORI IN ENVIRONMENTAL SPECIMENS COLLECTED FROM THE OPISTHORCHIASIS ENDEMIC AREAS AT KHON KAEN PROVINCE, THAILAND

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Opisthorchiasis is a foodborne trematodiasis common in Thailand. Interestingly, opisthorchiasis endemic areas were found to have substantial incidences of leptospirosis as well as Helicobacter pylori infection. The parasite causing opisthorchiasis (Opisthorchis viverrini) has a complex life cycle involving different intermediate hosts before maturing into the infective metacercariae stage and infecting humans through ingestion of mainly raw fish. O. viverrini infection is the main risk factor for cholangiocarcinoma in humans. Since O. viverrini, Leptospira spp. and H. pylori are present in various aquatic environments, we attempted to elucidate the relationships of these pathogens at the opisthorchiasis endemic areas around the Lawa Lake region at Khon Kaen Province, Thailand. Specimens were collected from ten study sites around the Lawa Lake region at Khon Kaen Province. Mud, water, snail and fish mucus were collected from the study sites. One metacercariae specimen was also included in the study. DNA extracted from the specimens were subjected to PCR assays targeting the LipL32 (pathogenic Leptospira) and cagA (H. pylori) genes. PCR positive products were sequenced and compared using the BLAST database for identification. Sequencing of the PCR positive products revealed that the mud, fish mucus and metacercariae specimens were positive for the presence of H. pylori. Remarkably, the same mud specimens that were positive for H. pylori were also positive for the presence of pathogenic Leptospira, suggesting co-localization of these two pathogens at the same site. Our findings suggest that H. pylori and pathogenic Leptospira are prevalent in opisthorchiasis endemic areas at Khon Kaen Province, Thailand.

5682

ASSESSMENT OF THE MICROBIAL CONTAMINATION OF DELIVERY BOXES OF ONLINE FOOD DELIVERY SERVICES PROVIDERS IN ACCRA

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The sanitary conditions under which the food is transported is vital for safety. This study aimed at enumerating and identifying microbial contaminants of delivery boxes of food delivery service providers in Accra as an indicator of microbial quality and hygiene. Swab samples were randomly obtained from forty (40) food delivery operators at the beginning and end of week. The Total Aerobic, Total Coliform Enterobacteriaceae, Fecal Coliform, yeast and mold counts, were determined as an index of microbial quality and safety. Pathogens from the delivery boxes were isolated, characterized and identified. There was significant level of bacterial and fungal contamination in the delivery boxes. The maximum Total Aerobic count, coliforms, E. coli yeast and mold in the delivery box were 1.03×106cfu/cm2, 1.7×105cfu/cm2, 4.92×103cfu/cm2, 6.57×102 and 5.60×102 respectively at the beginning of the working week. These increased to 9.56×106cfu/cm2, 2.18×106cfu/cm2, 3.51×104 cfu/cm2, 7.61×103 cfu/cm2 and 8.31×102 cfu/cm2, respectively at the close of the week. Bacillus sp., Staphylococcus sp., Acinetobacter and Pseudomonas stutzeri. Saccharomyces cerevisiae, Rhodotorula rubra, Aspergillus niger and Penicillium sp. were isolated from the delivery boxes. The high contamination levels recorded in this study indicates the poor hygienic state and practices of the food delivery service operators in Accra. Foods and other items being transported for delivery in these boxes have a potential and risk of contamination from these pathogens and contagions, posing a public health threat to recipients and unsuspecting customers who patronize food delivery services in the highly urbanized population of Accra. Hygiene training of food delivery service providers is an urgent necessity.

5683

INCREASING THE ACCESSIBILITY AND HANDWASHING PRACTICES THROUGH TIPPY TAPS IN CABO DELGADO PROVINCE, MOZAMBIQUE

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Diarrheal diseases including cholera are responsible for a high mortality and morbidity in humanitarian emergencies due to overcrowding, malnutrition, lack of healthcare access, water and sanitation facilities as well as handwashing stations. The province of Cabo Delgado, Mozambique, has been immersed in a severe humanitarian crisis due to conflict and insecurity since 2017. Hygiene promotion campaigns have been implemented since August 2022 including construction of a simple and low-demanding resource handwashing station, named tippy tap, in Internal Displaced Persons (IDPs) sites and host communities. The aim of this study was to describe the accessibility, use and community ownership of tippy taps. A cross-sectional survey was conducted in 5 districts after 6 months of a hygiene promotion campaign implementation. A total of 409 people participated in the survey. Overall, 63% of participants were females, the largest age group were people between 26 and 35 years old (26%) and 64% of households had at least a person with the primary education level. Thirty-one per cent of households reported to have a tippy tap within 500 meters and 22% of participants reported to use a tippy tap within the last 24 hours. A hundred and fifty-one households (37%) reported at least one case of diarrhea or stomachal pain within the previous month. The use of tippy taps was strongly associated with their accessibility ($P<0.001$) and knowledge of causes of diarrhea ($P=0.006$). Moderately evidence was found between use of tippy taps and self-reported diarrheal cases within the household during the previous month ($P=0.04$). Further construction of 1550 tippy taps in program targeted areas without programmatic support showed the strong uptake of communities demonstrating the sustainability and ownership of tippy taps as a tool to improve hygiene practices. The provision of functional and feasible handwashing stations in humanitarian contexts is crucial to increase handwashing practices for cholera and diarrheal disease prevention.

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WORK RELATED INJURIES: WHAT FACTORS DETERMINE ITS SEVERITY IN A LOW RESOURCE SETTING?

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It is estimated that more than 2.3 million people (both males and females) die from work-related injury or disease; this links to over 6000 deaths daily globally. This study assessed factors influencing the severity of workplace injuries reported to Teaching Hospitals in Ghana. fr The study employed a cross-sectional prevalence survey with a quantitative approach. A simple random sampling method was used to select the study respondents. Data were captured using REDCAP and was exported from REDCap directly into Stata 16 statistical software for analysis. The total number of respondents

involved in this study was 523. Statistical significance for all testing was set as 0.05.ResultsA total of 523 workplace injuries data were extracted at the various teaching hospitals, less than half the number of injured patients (38.43%) were admitted at KATH. The respondents who resided in rural areas were 2.60 more likely to experience severe workplace injuries (AOR=2.60, 95% CI=1.19-5.69). Exposure to burns, blunt and penetrating injuries increased the likelihood of experiencing severe workplace injuries (AOR=20.46; 95% CI=2.25-186.06), (AOR=19.39; 95% CI=2.14-175-27) and (AOR=9.33; 95% CI=1.53-56.99) respectively. ConclusionThe sentinel hospital site, type of settlement, and mechanism of injury were established to be influencing the severity of workplace injuries. The authors recommend the prioritization of stakeholder involvement such a as industry management team to work towards practical steps to address this burden education

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ASSOCIATION OF PRENATAL ENVIRONMENT FACTORS WITH UNDER FIVE NUTRITIONAL GROWTH OUTCOMES IN UGANDA

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Children with nutritional growth failure are more susceptible to infections and may experience cognitive, physical, and metabolic developmental impairments. Many countries in Africa depend on rain-fed agriculture for food security which is reflected in meteorological environment factors. The objective of the current study is to assess meteorological factors associated with village-level rates of child nutritional growth outcomes in Uganda. This was a cross-sectional study of 5219 children ages 0 to 59 months with anthropometric measures using the 2016 Ugandan Demographic and Health Survey. Geostatistical models parameterized by meteorological, land topography and sociodemographic factors were developed to determine their association with height-for age z-scores (HAZ), weight-for-age z-scores (WAZ), and weight-for-height z-scores (WHZ). Of the 5219 children ages 0 to 59 months included in the analysis, 50% were male, and mean age was 33 (SD:16) months. Large disparities in the burden of child growth failure exist within Uganda at smaller and larger spatial scales; villages in the northeastern and southeastern areas of the country bear the highest prevalence of all forms of child undernutrition. Higher SPEI 3 months pre-birth was positively associated with child nutritional growth outcomes. Additionally, higher location mean rainfall 11 months pre-birth was positively associated with HAZ consistent with SPEI findings. Aridity index association with WAZ and WHZ were consistent with findings of SPEI. Slope angle, land surface mean temperature, travel time to the nearest city, and nighttime light emissions were not consistent with nutritional growth outcomes. In conclusion, pre-birth availability of agricultural water was associated with nutritional child growth outcomes.

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BARRIERS OF EFFECTIVE AND SUSTAINABLE WATER, SANITATION AND HYGIENE (WASH) SERVICES AT SCHOOLS IN BANGLADESH

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Considering the potential effect of a poor environment in schools on children, every school requires appropriate WASH initiatives that include provision of WASH facilities and sustainable operation and maintenance (O&M) of those facilities. In Bangladesh, all government schools are mandated to have a School Management Committee (SMC) who are responsible for ensuring WASH O&M. However, in majority of the schools SMCs didn't perform better in sustainably operating and maintaining their WASH infrastructure. We investigated the barriers for successful O&M of WASH services in schools to help inform strategies. We conducted qualitative interviews with 36 SMC members from purposively selected 18 primary schools in three cities in Bangladesh between Feb- Apr 2020. All interviews were audio recorded, transcribed verbatim and we performed thematic content analysis. The major problem identified was economic. Due to low funding from government, lack of private contributions and lack of financial mechanism, SMCs were unable to make investment decision to ensure supplies as well as recruiting a janitor. Inadequate supplies of cleaning products, handwashing agents left toilets unclean and allow students to wash their hands with water only. Moreover, if maintenance is required when facilities were broken or blocked and need the septic tanks emptied, or replacement of tube wells, SMCs were unable to do it as they did not have their own fund. Children were not aware of how to use the facilities properly, and did not have good hygiene practices. Community contribution was poor in terms of proving good hygiene practices to children and in improving WASH facilities at schools. Communication and coordination gaps between SMCs and other stakeholders were also an important barrier. Moreover, there was an institutional lack of planning and adoption of WASH policies or they lack the capacity, time, and resources for appropriate decision making and planning of WASH services for their schools. Providing information and train SMC for capacity building, establishing a strong financial mechanism may be useful for successful O&M of school WASH in a sustainable way.

5687

EVALUATION OF A MULTI-LEVEL, PARTICIPATORY INTERVENTION TO REDUCE ARSENIC EXPOSURE IN AMERICAN INDIAN COMMUNITIES: A CLUSTER RANDOMIZED CONTROLLED TRIAL OF THE COMMUNITY-LED STRONG HEART WATER STUDY PROGRAM

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Chronic arsenic exposure has been associated with an increased risk of cardiovascular disease, diabetes, cancers of the lung, pancreas and prostate, and all-cause mortality in American Indian communities in the Strong Heart Study. The Strong Heart Water Study (SHWS) designed and evaluated a multi-level, participatory community-led intervention to reduce arsenic exposure among private well users in partnership with Northern Great Plains American Indian Nations. A cluster randomized controlled trial (cRCT) was conducted to evaluate the effectiveness of the SHWS program over a two-year period on: (1) urinary arsenic; and (2) reported use of arsenic safe water for drinking and cooking. The cRCT compared the installation of a point-of-use arsenic filter and a mobile health (mHealth) program (3 phone calls; SHWS mHealth & filter arm) to a more intensive program, which included this same program plus 3 home visits (3 phone calls and 3 home visits; SHWS intensive arm). A 48% significant reduction in urinary arsenic (geometric mean 13.2 to 7.0 µg/g creatinine) was observed from baseline to the final 2 year follow-up when both study arms were combined (Geometric mean ratio (GMR): 0.52 (95% Confidence Interval: 0.39, 0.69)). By treatment arm, the reduction in urinary arsenic from baseline to the final follow-up visit was 57% in the mHealth & filter arm and 29% in the intensive arm. There was no significant difference in urinary arsenic levels by treatment arm at the final follow-up visit (GMR comparing the intensive vs. mHealth & filter arms: 1.21 (95% CI: 0.77, 1.90). In both

arms combined, exclusive use of arsenic-safe water from baseline to the final follow-up visit significantly increased for water used for cooking (17% to 50%) and drinking (12% to 43%). Delivery of the community-led SHWS program, including the installation of a point-of-use arsenic filter and an mHealth program on the use of arsenic-safe water without home visits, resulted in a significant reduction in urinary arsenic and significant increases in reported use of arsenic-safe water for drinking and cooking during the two-year study period.

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A CLUSTER RANDOMIZED CONTROLLED NON-INFERIORITY TRIAL TO COMPARE THE PROTECTIVE EFFECTIVENESS OF SULFADOXINE PYRIMETHAMINE AND AMODIAQUINE AND DIHYDROARTEMISININ PIPERAQUINE FOR SEASONAL MALARIA CHEMOPREVENTION AMONG CHILDREN 3 TO 59 MONTHS, IN THE CONTEXT OF HIGH PARASITE RESISTANCE, KARAMOJA REGION, UGANDA

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In areas with highly seasonal malaria transmission, seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine and amodiaquine (SPAQ) is recommended for age groups at high risk of severe malaria. However, due to widespread prevalence of resistance markers associated with parasite resistance to SP and AQ in east and southern regions of Africa, there was need to explore an effective alternative regimen for SMC that could be used if SPAQ starts to lose efficacy. We assessed the effectiveness of SMC for prevention of malaria among 3,853 children aged 3-59 months using a three-arm open-label prospective cluster-randomized controlled trial (cRCT) in Karamoja sub-region in Uganda. A total of 3,749 children were randomized to receive SMC with either SPAQ (1,698) or dihydroartemisinin-piperaquine (DHAPQ) (1,667) while 384 acted as control and relied on standard malaria care over the five-month high transmission period. In total, 554,155 person-days (251,414 in the SPAQ arm, 249,069 in the DHAPQ arm and 53,672 in the control arm) were generated for analysis. There were 464 events of clinical malaria (76 in the SPAQ arm, 66 in the DHAPQ arm and 322 in the control arm). These represent an incidence rate of 8 confirmed malaria events per 10,000 person-days in the entire study population (3 per 10,000 person-days in the SPAQ arm, 3 per 10,000 person-days in the DHAPQ arm and 60 per 10,000 person-days in the control arm). 750 samples were corrected one month before and after implementation of SMC and assessed for markers of resistance for SP, AQ and DHAPQ. Compared with children in the control arm, those in the SPAQ arm had a 94% lower risk of having an RDT-confirmed malaria episode; Hazard Ratio (HR): 0.06 (95% confidence interval [CI], 0.04 - 0.08, p<0.001); while those in the DHAPQ arm had a 96% lower risk; HR: 0.04 (95% CI, 0.03 - 0.06, p<0.001). The hazard ratio for the protective effectiveness of SPAQ was non-inferior to that of DHAPQ. In our setting, DHAPQ was not superior to SPAQ in terms of prevention of clinically significant malaria in SMC-eligible children.

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MATAMAL: A CLUSTER - RANDOMIZED PLACEBO-CONTROLLED TRIAL TO EVALUATE THE ADDITIVE IMPACT OF IVERMECTIN TO DIHYDROARTEMISININ-PIPERAQUINE SEASONAL MASS DRUG ADMINISTRATION FOR MALARIA CONTROL ON THE BIJAGOS ARCHIPELAGO OF GUINEA-BISSAU

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Ivermectin (IVM) is an anthelminthic drug that effectively kills anopheles mosquitoes which blood-feed on treated individuals. Small phase 2 and 3 clinical trials have demonstrated its potential to reduce malaria incidence, and modelling studies suggest that it could be an effective tool to reduce malaria transmission, particularly if given as Mass Drug Administration (MDA) in combination with Dihydroartemisinin-Piperaquine (DP) MDA. The safety and efficacy of IVM and DP in combination has been demonstrated previously. MATAMAL is a cluster-randomised placebo-controlled parallel assignment clinical trial conducted on the Bijagos Archipelago of Guinea-Bissau, testing whether the addition of IVM (300mcg/kg/day for 3 days) to DP MDA each month for three months during the rainy season significantly reduces malaria prevalence compared to giving DP MDA with placebo ((IVM-P), 300mcg/kg/day for 3 days). MDA was given in the context of standard malaria control measures, including insecticide-treated bed nets. MATAMAL is the largest trial to evaluate the additive impact of IVM MDA, and the only trial to evaluate combined IVM/DP MDA versus a placebo control. The trial arms consisted of 24 clusters, with 12 allocated to each of DP+IVM and DP+IVM-P, distributed monthly in July, August and September of 2021 and 2022. The primary outcome is the difference between arms in malaria prevalence, measured by estimating the cluster-adjusted prevalence of Plasmodium falciparum by varATS qPCR in a random sample of individuals of all ages during the endpoint survey, conducted during the peak transmission season. Secondary outcomes include safety and tolerability, clinical malaria incidence, entomological outcomes and the wider impact of IVM on co-endemic IVM-sensitive infectious diseases. Approximately 24,000 individuals received MDA for 2 years. The MDA was well-tolerated with relatively few adverse events that were predominantly mild in severity. 4,305 individuals were sampled in the primary outcome survey. The primary outcome and select secondary outcome data will be presented.

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MONITORING SUSTAINED IMPACT ONE YEAR AFTER MASS DRUG ADMINISTRATION IN A LOW-MODERATE MALARIA TRANSMISSION SETTING OF SENEGAL WITH OPTIMIZED CONTROL INTERVENTIONS

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Mass drug administration (MDA) is not recommended for malaria transmission reduction in moderate transmission settings due to a lack of evidence of sustained impact. Short-term results of an open-label, cluster-randomized controlled trial in a low-moderate malaria transmission setting demonstrated MDA targeting individuals ≥3 months of age was associated with a 53% [95% CI: 29%, 69%] greater reduction in malaria incidence in all ages from baseline compared to standard-of-care which included seasonal malaria chemoprevention (SMC) given to children 3-120 months of age. Here we assessed if the impact was sustained one year after MDA. The study occurred in Tambacounda, Senegal, where district-level annual incidence was 50-200/1000 population in 2016-2019. Prior to the trial, optimized control interventions were introduced (i.e., proactive community case management and mass distribution of pyrethroid-piperonyl butoxide nets) in all 60 study villages. Villages were randomized 1:1 to receive 3 rounds of MDA with dihydroartemisinin-piperaquine+single low-dose primaquine (DP+SLD-PQ) or standard-of-care which included 3 cycles of SMC with sulfadoxine-pyrimethamine+amodiaquine; coverage was 80-84% and 93-94% of the eligible population, respectively. In 2022, the year after MDA rounds were completed, SMC was resumed in all villages. The primary outcome was malaria incidence confirmed by rapid diagnostic test by village health workers and at health facilities during the high transmission season of the post-intervention year, with subgroup analyses by MDA coverage, age (≥ vs. <10 years), and baseline malaria endemicity. Incidence rates in the MDA arm were 188 cases/1000 in 2020, 93/1000 in 2021, and 130/1000 in 2022, compared to 211, 179 and 152 cases/1000 in the control arm. The adjusted rate ratio (MDA:control) in the post-intervention year was 0.81 [95% CI: 0.51, 1.29]. While a substantial reduction in incidence was seen in the intervention year, this was not sustained in the year after MDA. Higher population coverage and/or more rounds and/or years of MDA may be needed to achieve a sustained impact. Subgroup analyses will be presented.

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TREATMENT OF UNCOMPLICATED MALARIA USING ARTEMISININ-BASED COMBINATION THERAPY IN THE FIRST TRIMESTER OF PREGNANCY: EXPERIENCE FROM TANZANIA

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Artemether-lumefantrine (AL) has been the recommended first-line treatment for uncomplicated malaria and has been widely available in retail markets in Tanzania since 2006. The World Health Organization recommended AL for the treatment of uncomplicated malaria in pregnancy (MiP) in the first trimester of pregnancy in November 2022. This decision came two years after Tanzania revised its malaria treatment guidelines in 2020 recommending AL for the treatment of MiP in the first trimester. We describe the Tanzanian experience following this policy change. We reviewed data from public and private health facilities from the Health Management Information Systems (HMIS) in all 26 regions of Tanzania between January 1, 2016 and December 31, 2022. The updated treatment guidelines were disseminated throughout Tanzania to all facilities (>9,000) by December 2021. In Tanzania, all pregnant women are tested for malaria at their first antenatal care (ANC) visit. However, as midwives may not prescribe antimalarials, all women who test positive at ANC are referred to the outpatient department for treatment. The HMIS does not disaggregate malaria treatment by pregnancy status; therefore, the proportion of pregnant women who tested positive during ANC was used as a proxy indicator for MiP treatment. The proportion of pregnant women tested for malaria during ANC increased from 75% 2016 to 98% in 2022. The malaria test positivity rate ranged between 6-7% between 2016-2022. All pregnant women who tested positive regardless of trimester received AL following implementation of the 2020 treatment policy. It was noted that the HMIS did not capture whether cases were uncomplicated or severe, nor was there a way to directly report adverse drug reactions. AL stock remained >95% in both public and private facilities. Our review suggests a high level of adherence in Tanzania to the updated policy recommending AL for treatment of MiP in the first trimester.

5692

ANTI-GAMETOCYTE ACTIVITY AND POST-TREATMENT PROTECTIVE EFFICACY OF ARTEMETHER-LUMEFANTRINE VS. DIHYDROARTEMISININ-PIPERAQUINE FOR UNCOMPLICATED MALARIA: PRELIMINARY RESULTS OF A MULTI-DOSE PHARMACOKINETIC/PHARMACODYNAMIC TRIAL

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Mass drug administration (MDA) for P. falciparum malaria elimination remains a controversial practice. Currently, the favored agent is dihydroartemisinin-piperaquine (DP) due to its longer half-life and its designation in Africa as second-line to artemether-lumefantrine (AL). We conducted a randomized trial of the comparative anti-gametocyte and secondary chemopreventive effects of AL vs. DP to elicit information relevant to their deployment in different contexts. Zambian children <5 years old (n=182) with uncomplicated malaria were randomized to AL or DP, admitted 72 hours for parasite and drug kinetics, and followed for 9 weeks. 173 participants (95%) contributed 1,424 person-weeks of observation time. Participants were similar at baseline across all covariates, including parasite and gametocyte density. From thin smears, asexual clearance did not differ between the groups but gametocyte clearance was more rapid and durable in the AL group. In those with baseline gametocytemia, 100% (8/8) in the AL group were clear by 1 week compared to 62% (5/8) in the DP group (p=0.04). In those with gametocytes at any time, gametocyte density was significantly lower in the AL group (AUC 38 gam.*h/mL (95% CI 13-107) vs. 136 (95% CI 34-550) in the DP group, p<0.001), the proportion with gametocytemia was significantly lower in the AL group at all weeks, and those treated with DP were significantly more likely to have emergent gametocytemia. The overall incidence of recurrent asexual parasitemia was higher in the AL vs. DP group (hazard ratio 1.9, 95% CI 1.3-2.7, p=0.001) but by 9 weeks there was no significant difference in the cumulative prevalence of recurrent parasitemia (AL 58% vs. DP 49%, p=0.31) or clinical failure (AL 19% vs. 18%, p=0.89). Molecular and chemical assays to generate high-resolution gametocyte dynamics and drug pharmacokinetics are underway, but these preliminary results support a differential impact on gametocytes that could have relevance for how these agents are deployed in different malaria contexts, pointing to a need for pairing primaquine with DP to eradicate gametocytes or prioritizing an alternative combination for MDA.

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PHARMACOMETRIC ASSESSMENT AND DOSE-OPTIMIZATION OF PRIMAQUINE IN THE RADICAL CURE OF PLASMODIUM VIVAX MALARIA IN CHILDREN: AN INDIVIDUAL PATIENT DATA META-ANALYSIS

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Primaquine is one of only two registered antimalarials for the radical cure of P. vivax malaria. The main burden of malaria is in young children and yet there is no suitable pediatric formulation. After decades of use, primaquine dosing recommendations in the pediatric population are still ambiguous. Weight-based and age-based dosing have yet to be optimized, resulting in increased variability in drug exposure and under-dosing in young children. Pharmacokinetic studies were identified through a systematic literature review of articles published in PubMed, Google Scholar, Embase, ClinicalTrials.gov, or conference proceedings between 1960 and 2021, following PRISMA guidelines. Investigators were invited to contribute individual-level patient data to the WWARN repository as part of the study group. Primaquine concentration-time data were analyzed using nonlinear mixed-effects modelling, with a particular focus on the impact of body weight and age. A total of 24 studies (15,862 measured primaquine and 10,693 carboxyprimaquine concentrations), including 2,399 adults and 226 children <5 years, were identified and included in this pooled meta-analysis. Primaquine pharmacokinetics were best described by a one-compartment distribution model, with transit absorption. Nonlinear relationships between total drug exposure and body weight and age were observed, highlighting the need for a pharmacometric approach to evaluate and design evidence-based optimal dosing in young children. The final pharmacokinetic model was used to explore different dosing scenarios with the available dose strengths of 5, 7.5, and 15 mg tablets, which demonstrated unacceptably high exposures in young children. Our findings support the development of novel pediatric formulations that can be used more accurately in this specific population. With the current tablet strengths, a tablet needs to be broken or dissolved in water to administer an appropriate dose in young children. An optimized weight-based dosing was successfully derived with current dosing strengths for patients ≥12 kg body weight, comprising five weight-bands.

5694

FDA-APPROVED KINASE INHIBITORS AS POTENTIAL ADJUNCTIVE THERAPY CANDIDATES FOR ENDOTHELIAL DYSFUNCTION IN CEREBRAL MALARIA

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Cerebral malaria is associated with cerebral coagulopathy, breakdown of the blood-brain barrier (BBB), and severe brain swelling in children, but currently there are no adjunctive drug treatments. To identify new therapeutics for inflammatory injury to blood vessels, we first screened in vitro 31 FDA-approved kinase inhibitors (KI) drugs in primary human microvascular brain endothelial cells monolayers challenged with the procoagulant protein thrombin or with Plasmodium falciparum lysates and down-selected promising candidates to evaluate in the experimental cerebral malaria model. From the in vitro screen, the BCR-ABL family of drugs showed diverse endothelial barrier phenotypes ranging from protective, neutral, to barrier disruptive. In addition, BCR-ABL drugs had anti-malaria activity with Nilotinib and Bosutinib preventing Plasmodium falciparum ring-stage parasite progression to trophozoite stage and Imatinib targeting late-stage parasites. From in vivo analysis in the ECM model, Bosutinib and Imatinib had modest protection in an early-stage treatment regimen (days 4 to 7). By comparison, Nilotinib, showed substantial protection against neuropathologic injury and lung injury measured by a rapid murine coma and behavior score, associated with BBB protection and parasitemia control. Moreover, when given as a late-stage treatment, Nilotinib on its own improved animal survival by 40% and reduced vascular leakage at the brain, lungs, and kidneys, and further increased animal survival and accelerated parasite clearance when given as an adjunctive drug with artesunate. Our work demonstrates that kinase inhibitors are an attractive drug-repurposing option to treat vascular leakage at vital organs during malaria infection and to pursue for cerebral malaria adjunctive therapy.

5695

MULTI-OMIC PROFILING OF CUTANEOUS LEISHMANIASIS INFECTIONS REVEALS MICROBIOTA-DRIVEN MECHANISMS UNDERLYING DISEASE SEVERITY

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Leishmania braziliensis infection results in inflammation and skin injury, with highly variable and unpredictable clinical outcomes. Here, we investigated the potential impact of microbiota on infection-induced inflammatory responses and disease resolution by conducting an integrated analysis of the skin microbiome and host transcriptome on a cohort of 62 L. braziliensis-infected patients. We found that overall bacterial burden and microbiome configurations dominated with Staphylococcus spp. were associated with delayed healing and enhanced inflammatory responses, especially by IL-1 family members. Dual RNA-seq of human lesions revealed that high lesional S. aureus transcript abundance was associated with delayed healing and increased expression of IL-1β. This cytokine was critical for modulating disease outcome in L. braziliensis-infected mice colonized with S. aureus, as its neutralization reduced pathology and inflammation. These results implicate the microbiome in cutaneous leishmaniasis disease outcomes in humans and suggest host-directed therapies to mitigate the inflammatory consequences.

5696

REPROGRAMMING EIF4A-DEPENDENT MRNA TRANSLATION TO CONTROL LEISHMANIA INFECTION

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Protozoan parasites of the genus Leishmania are causative agents of leishmaniasis, a spectrum of tropical neglected diseases. The lack of efficient vaccines and failure to control emerging parasite resistance reflect the need to identify novel targets for therapeutic intervention. More specifically, to counteract parasite resistance, a host-directed therapy, boosting and/or modulating host responses to control the infection is desired. Our laboratory demonstrated that one third of protein-coding mRNAs in macrophages are differentially translated upon infection by Leishmania donovani. In silico analysis indicated activated translation

dependent on the mRNA helicase eIF4A upon infection. Notably, pharmacological inhibition of mammalian eIF4A reduced L. donovani and L. amazonensis survival within macrophages. Selective inhibitors of eIF4A, named rocaglates, have immunomodulatory and antimicrobial properties associated with their ability to fine-tune macrophage functions. Hence, we postulate that pharmacological inhibition of eIF4A-dependent translational programs contributes to control Leishmania infection. To begin testing this hypothesis, we assessed the leishmanicidal activity of a panel of 20 synthetic rocaglates with high affinity for mammalian eIF4A1 (i.e., strong eIF4A1 clampers). As negative controls, we included another subset of 20 rocaglates that promote either low or no clamping of eIF4A1 (i.e., weak/dead eIF4A clampers). Our screening identified four strong eIF4A1 clampers (i.e., C26, C29, C37 and C38) that reduce the infection index in bone marrow-derived macrophages (BMDMs) by more than 50% when compared to DMSO-treated control cells. Surprisingly, five eIF4A1 weak clampers (i.e., C3, C7, C11, C18 and C20) were also able to control intramacrophage Leishmania replication. Additionally, selected rocaglates showed an effect in reducing the infection index of infected THP-1 derived macrophages, validating our findings in a human model. In line with these data, the leishmanicidal activity of rocaglates with strong affinity for eIF4A1 was either partially or completely abrogated in BMDMs derived from Elf4A1+/- mice. In contrast, the anti-parasitic action of eIF4A weak clampers was resistant to reduced eIF4A1 levels in BMDMs. As expected, polysome tracing experiments revealed that only strong eIF4A1 clampers inhibit macrophage mRNA translation rates. To further elucidate the mechanism through which rocaglates act in infected macrophages, we performed a time course of infection in treated cells and identified what appears to be stalling of the parasite replication, instead of parasite killing. These stalled parasites, however, can reinfect and replicate in new, untreated BMDMs, hinting at a host-directed effect, with macrophages being the main target of rocaglate treatment. Taken together, our data allow us to conclude that strong clamper rocaglates seem to inhibit the replication of L. amazonensis in a host eIF4A-dependent manner, both in mouse and human macrophages. Weak clampers, on the other hand, are not dependent on host eIF4A1 for their anti-leishmanial effect and do not seem to be affecting the translation rate of the host cells, suggesting a yet-to-be identified translation-independent host or parasite target that is responsible for the observed effect. Currently, we are implementing a host- and parasite-based multi-omics approach to identify changes in the translatome and the proteome of intramacrophage parasites and their host cells associated with the leishmanicidal activity of strong and weak eIF4A1 clampers identified in our screening. Our long-term goal is to provide insight on the mechanistic basis and therapeutic potential of modulating eIF4A-dependent and -independent translational programs to reduce morbidity and mortality associated with visceral and cutaneous leishmaniasis.

5697

BORRELIA BURGDORFERI CO-EXPOSURE ENHANCES IN VITRO HOST CELL SUSCEPTIBILITY TO LEISHMANIA INFANTUM AND INDUCES TH17-LIKE CELL RESPONSES IN L. INFANTUM-SEROPOSITIVE DOGS

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Canine leishmaniasis (CanL), a zoonotic disease caused by Leishmania infantum, is classically transmitted via sand flies from reservoir dogs to nearby people. Dogs with CanL are often coinfected with tick-borne bacteria, such as Borrelia burgdorferi. These co-infections were causally associated with disease progression and mortality, but specific mechanisms affecting microbicidal responses against L. infantum are unknown. We hypothesize B. burgdorferi co-infection impact host and T cell responses, prompting L. infantum replication and survival. Exposure to B. burgdorferi significantly increased L. infantum parasite burden in DH82 canine macrophage cells. Late apoptosis was significantly decreased in co-infected DH82 cells compared to uninfected and L. infantum-single infected cells. Co-infected DH82 cells showed an enhanced inflammatory response, with upregulation of TNFA, IL6, and IL1B, and concomitant release confirmed via ELISA. Ex-vivo stimulation of PBMCs from L. infantum-seropositive subclinical dogs with spirochetes and/or TLA had limited induction of IFN-γ. In L. infantum-seropositive dogs, co-exposure significantly induced expression of pro-inflammatory cytokines known to induce Th17 differentiation and effector functions, such as IL23p19, IL17A, and IL22, compared to unstimulated and TLA-single stimulated cells. Co-stimulation significantly increased the production of IL-17A and chemokines associated with neutrophilic (IL-8 and CXCL1) and monocytic (CCL2) recruitment compared to TLA-single stimulated PBMCs. L. infantum and B. burgdorferi co-infection promoted robust alterations in the host cell immune response and death, contributing to enhancing L. infantum survival and replication in DH82 cells. B. burgdorferi exposure induced pro-inflammatory and Th17-like responses in PBMCs from L. infantum-seropositive dogs. Excessive inflammation has been shown to contribute to the development of visceral leishmaniasis. Preventing tick-borne disease through already available preventatives will make a significant difference in CanL control and prevent spread of L. infantum in dogs and humans.

5698

STAT6-DEPENDENT/IL-5-MEDIATED EOSINOPHILIA PRIMED BY PRE-EXPOSURE TO UNINFECTED SANDFLY VECTOR BITES ENHANCE SUBSEQUENT LEISHMANIA INFECTION

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The immunological environment primed by pre-exposure to uninfected sandfly bites is thought to have a significant impact on infection by the sand fly vector transmitted parasitic pathogen Leishmania. However, the nature of the immune response to uninfected vector bites and how this response changes over the life history of a mammalian host is poorly understood. We investigated the immune response elicited by exposure to the bites of uninfected Lutzomyia longipalpis sandflies. As previously shown, short-term exposure to sandfly bites activated salivary antigen-specific interferon (IFN)-gamma-producing dermal-derived CD4+ Th1 cells. However, upon repeated exposure, the immune response underwent diversification at the population level to include multiple salivary antigen specific CD4+ subsets (Th1, Th2, Th17, and TREG) and enhanced IL-5 production. Analysis of delayed-type hypersensitivity (DTH) at the bite site during ongoing chronic exposure revealed four phases of DTH, the last of which correlated with a high degree of immunoregulation, a local inflammatory cell infiltrate comprised primarily of eosinophils, an alteration in the maturation of inflammatory monocytes, and enhanced disease upon subsequent challenge with Leishmania plus salivary gland homogenate (SGH). Employing mice genetically deficient in T cells (TCR-/-), Th2 immunity (STAT6-/-), or Eosinophils (GATA-1-/-) revealed that long-term exposure to uninfected bites primes a T cell dependant Th2 response characterized by eosinophil infiltration. GATA1-/- and STAT6-/- deficiency resulted in decreased inflammation, decreased generation of M2-like monocytes-derived macrophages, fewer eosinophils, and enhanced IFN-g response. Disease exacerbation mediated by long-term exposure was found to be dependent on IL-5, as anti-IL-5-mediated reduction of eosinophils resulted in improved control of Leishmania infection. These results show that IL-5-induced eosinophilia mediated by T cells/STAT6 following exposure to uninfected bites influences the virulence of a vector transmitted disease.

5699

DISSECTING PROTECTIVE NK CELL RESPONSES TO TRYPANOSOMA CRUZI INFECTION IN THE HUMAN SKIN

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Chagas disease is caused by the protozoan parasite Trypanosoma cruzi. It is mainly prevalent in Latin America and is classified as one of the most neglected tropical diseases. Since T. cruzi parasites are mainly transmitted by blood-sucking triatomine bugs, the skin is the main entry route and the first affected organ. Although homeostasis and immunosurveillance of this important anatomic site are crucial to limit parasite burden, the initiation of the local immune response in the skin, as well as the systemic consequences of these early events, remain elusive. Due to the obligatory intracellular life cycle of T. cruzi, natural killer (NK) cells substantially contribute to the control of parasite spread. Therefore, our study aimed to dissect the response of human NK cells to T. cruzi infected non-immune cells resident in the skin, mainly fibroblast and keratinocytes. For this purpose, we established in-vitro cultures of primary human cells, characterized T.cruzi infections, and performed NK cell co-cultures. Our findings describe for the first time and in a comprehensive manner how NK cells sense T.cruzi infection in the human skin. We found remarkable differences in the expression of NK ligands between infected keratinocytes and fibroblasts. Furthermore, we demonstrate that T. cruzi infected primary human skin cells promote NK cell degranulation and show how NK cells orchestrate the following immune response by differential cytokine release. Finally, we performed transcriptome analysis of infected fibroblasts and identified pathways leading to contact-independent activation of NK cells. Taken together, we established reliable in-vitro models to study mechanisms of the NK cell response to T. cruzi infected human skin cells and identified crucial receptors for NK cell activation, which are presumably responsible for the containment of parasite spread in the skin during acute infection. Understanding the contribution of NK cells to parasite control and the mechanisms affecting NK cell function can contribute to target natural killer cells as enhancers of vaccine responses and to develop new therapeutic options.

5700

INHIBITION OF SRC SIGNALING INDUCES AUTOPHAGIC KILLING OF TOXOPLASMA GONDII INDEPENDENT OF EGF RECEPTOR

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Toxoplasma gondii is an intracellular parasite that can cause severe disease in both immunocompromised and immunocompetent patients, affecting organs such as the brain and eye. T. gondii avoids degradation by the autophagolysosome by manipulating signaling pathways that promote autophagy. Previous studies have shown that the parasite activates EGFR to prevent targeting by autophagy. It is unclear if T. gondii manipulates alternative mechanisms independent of EGFR to avoid autophagic targeting, an important question since various cells in the brain and retina have little to no expression of EGFR. Our study found that T. gondii activates Src and Akt in cells that lack EGFR expression. Genetic or pharmacological inhibition of Src with Saracatinib impaired T. gondii-induced phosphorylation of Src and Akt. Low-dose Saracatinib and knockdown of Src resulted in the accumulation of autophagosomal and lysosomal markers (LC3 and LAMP1, respectively) and promoted killing of T. gondii dependent on the autophagy protein ULK1 and lysosomal enzymes. T. gondii-dependent activation of Src deactivated PTEN promoting PI3K/Akt signaling that prevented autophagic targeting of the parasite. Inhibition of Src disrupts this pathway and allows for autophagic killing of T. gondii. Saracatinib administration to mice with pre-established ocular and cerebral toxoplasmosis reduced histopathology and parasite loads in the eye and brain without altering cell-mediated or humoral immunity. In conclusion, T. gondii can activate Src - Akt signaling to prevent autophagic eradication independently of EGFR. Inhibition of Src may have therapeutic applications against ocular and cerebral toxoplasmosis.

5701

LOSS OF SIGLEC-7 CORRELATES WITH ENHANCED NATURAL KILLER CELL FUNCTION AND PROTECTION FROM MALARIA SYMPTOMS

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An effective malaria vaccine is urgently needed, but progress towards this goal has been hampered by our limited understanding of the factors responsible for effective malaria immunity. Malaria is a parasitic disease caused by the parasite Plasmodium. Natural killer (NK) cells inhibit the growth of Plasmodium in vitro through antibody dependent cellular cytotoxicity (ADCC). We went on to show that a subset of NK cells in malaria endemic subjects, known as adaptive NK cells, lack the Fc receptor γ chain (FcRγneg) have enhanced ADCC function. However, it was unclear if the lack of Fc γ chain was the reason for increased functionality or if it only served as a marker for adaptive NK cells. Our goal was to know why adaptive NK cells have enhanced cytotoxic function in malaria. Therefore, we developed a CRISPR/Cas9 protocol to ablate genes associated with ADCC in primary NK cells. We then evaluated the effect of those ablations on NK cell function and found that the absence of FcRγ does not enhance NK cell ADCC. We then searched for other alterations in adaptive NK cells in malaria subjects that correlated with enhanced ADCC function. We found that a decrease in the expression of the inhibitory receptor Siglec-7 (Sialic Acid Binding Ig-like lectin 7) correlated with increased NK ADCC function in individuals with a history of malaria infection. Importantly, Sigelc-7 negative NK cells correlated with FcRγneg NK cells in malaria. Because Siglec-7 is an inhibitory receptor, we hypothesized that when the NK cells lack this receptor, this could be cause for adaptive NK cell increased function. We then ablated Siglec-7 using CRISPR/Cas9 and found enhanced ADCC functionality and enhanced killing of Plasmodium-infected red blood cells. Therefore, we predict Siglec-7 is an important protein of interest to study for the protective effects of NK cells in malaria. This is further supported as unaffected individuals without a history of malaria infection did not have a decrease in Siglec-7 expression. The ultimate goal is to use this data to leverage insights from NK cell protective mechanisms to create better therapeutics and vaccines for malaria.

5702

GUT MICROBIOTA-DERIVED METABOLITES ALTER HUMAN-DERIVED MACROPHAGE STIMULATION AND MAY INCREASE IMMUNE RESPONSES TO ORAL CHOLERA VACCINE

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Immune responses to oral cholera vaccines (OCV) vary among individuals; studies of host factors have only partially explained these differences. We have observed correlations between gut microbes and responses to OCV

in persons receiving two doses of OCV (Shanchol) in Dhaka, Bangladesh, a cholera-endemic area. We previously found that OCV recipients with specific gut microbial profiles were predictive of Vibrio cholerae O-specific polysaccharide memory B cell responses (OSP MBC), a response known to be correlated with protection. Interestingly, the microbes most correlated with OSP MBC produce sphingolipids (SL). To test the association of SL and OCV responses, we isolated microbes from the stool of vaccine recipients that produce SLs including Bacteroides species. Lipids extracted from cultures of Bacteroides xylanisolvens were then applied to human-derived macrophages, a model of mucosal innate immune responses that may contribute to the development of OSP MBC after OCV. We found lower production of interleukin-6 (IL-6) and other inflammatory cytokines after microbe-derived SLs were applied to the model, compared to lipid layers in which SL synthesis was inhibited ($P<0.0001$, t test). This indicates a lower level of baseline innate immune activation in the model when SLs are present. We hypothesize that this low level of baseline stimulation at the mucosal surface (i.e. when microbe-derived SL are present) may increase responsiveness to vaccine antigen. We tested this by preconditioning our model with microbe-derived SLs and then applying lipopolysaccharide (LPS) for 24 hours. Macrophages preconditioned with microbe-derived SL had greater IL-6 production ($P=0.0003$, t test) after stimulation with LPS compared to cell preconditioned with bacterial lipids lacking SL, indicating that the innate immune response to LPS was greater in the presence of microbe-derived SL. Here, we have identified SL-producing microbes isolated from vaccine recipients that correlate with OSP MBC responses in OCV recipients and found that lipids from these microbes impact innate immune responses to vaccine antigens in vitro.

5703

TITLE: ASCERTAINING TRUE CHOLERA BURDEN AND SUBNATIONAL CHOLERA RISK WITH A NOVEL CONTINUOUS DISEASE ENDEMICITY INDEX

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Despite efforts to control and eliminate cholera, it continues to impose large public health impacts in low and middle-income countries. Implementing effective and efficient intervention programs to control cholera in affected regions relies on knowing the actual cholera burden. The current WHO cholera endemicity definition is defined as having reported cholera within three of the past five years, which is subject to bias because of discrepancies in national-level reporting to the WHO. We introduce a novel endemicity index using 20 years of cholera data extracted from publications, WHO, and national ministries of health reports. The index is the sum of the product of weighted reported years and annual incidence rates at national and subnational levels where the years' weights are calculated using a truncated Gaussian distribution. We used Gradient Boosted regression incorporating environmental and socio-economic covariates, potentially associated with cholera occurrence, and a spatial random effect for countries to estimate the endemicity index for subnational regions without adequate cholera data. The endemicity index predictions were largely consistent with previous estimates of endemicity in both endemic and non-endemic areas. Within Africa, Eastern and Central Africa are estimated to have persistent cholera, while western Africa is at a lower risk of cholera transmission except for portions of Liberia and Nigeria. Southern China, the northern provinces of India, Bangladesh, and the Philippines are regions that are at a higher risk of cholera in South East Asia. The endemicity index indicated 29 out of 186 countries are highly endemic (have at least one subnational region with an endemicity index greater than zero), and in 8 of these 29 countries, this held true for 90% or more of their subnational regions. In addition, 11 out of 186 countries showed moderate risk of endemic transmission (an endemicity index between (-5,0)). Our results will help public health agencies to identify cholera-endemic regions, estimate the true cholera burden in these regions, and direct intervention programs to these areas more effectively.

5704

ENHANCED CHOLERA SURVEILLANCE AS A TOOL FOR IMPROVING VACCINATION CAMPAIGN EFFICIENCY

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Oral cholera vaccines (OCVs) are effective in reducing risk of cholera caused by Vibrio cholerae O1 and deployed increasingly for preventive vaccination campaigns, although global demand has exceeded global supply in recent years. Systematic testing for V. cholerae O1 is rare, even in high burden cholera surveillance systems, which means that the limited supply of vaccines may not be delivered to areas with the highest true cholera burden. We explored the effect of increasing V. cholerae testing capacity on OCV campaign impact using a spatial modeling framework that simulates detection, vaccine targeting, susceptibility and burden for projected cholera in 35 African countries from 2022-2035. We compared public health impact, vaccination campaign efficiency (number of true cholera cases averted per 1,000 fully vaccinated persons), and cost-effectiveness across 18 vaccination scenarios with different assumptions about bacteriological confirmation capacity and OCV targeting strategy. When districts with an observed cholera incidence rate exceeding 10 per 10,000 population were targeted with OCV, in scenarios with and without systematic V. cholerae testing, 29 million (95%PI: 21-37 million) and 71 million (95%PI: 65-78 million) individuals were fully vaccinated and 19% (95%PI: 15-22%) and 25% (95%PI: 22-27%) of true cases were averted to yield 10.3 (95%CI: 8.3-13.0) and 5.6 (95%CI: 4.6-6.7) averted cases per 1,000 fully vaccinated persons, respectively; increasing testing cost by $37 (95%PI: 29-52) per averted case reduced OCV campaign costs by $376 (95%PI: 275-556). Compared to status quo, which targets OCV to areas with high clinical cholera incidence rates, expanding V. cholerae testing capacity and targeting OCV campaigns to areas with the highest incidence rate of test-positive V. cholerae has the potential to greatly improve the efficiency and cost-effectiveness of OCV campaigns, while averting nearly as many true cholera cases and using far fewer vaccines. Integration of systematic testing into cholera surveillance, including use of rapid diagnostic tests, could improve efficiency and reach of current global supply of OCV.

5705

RE-EMERGENCE OF CHOLERA IN HAITI LINKED TO ENVIRONMENTAL VIBRIO CHOLERAE O1 OGAWA STRAINS

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Cholera was introduced in Haiti in October 2010. Between February 2019 and August 2022, no further cholera cases were registered. On September 25th, 2022, a new outbreak occurred in the Ouest Department of Haiti, where our group previously demonstrated the establishment of an environmental reservoir of toxigenic V. cholerae O1 in the aquatic ecosystem and its active role in fuelling the epidemic during lull periods. We investigated the origin of the new outbreak by analyzing the full genome sequence of 41 Vibrio cholerae O1 toxigenic Ogawa strains isolated between October 3rd November 21st, 2022 collected by GHEISKIO. We performed maximum likelihood phylogenetic analysis of 2,129 toxigenic V. cholerae O1 sampled worldwide, from 1937 to 2022, and in-depth

Bayesian phylogenetic and molecular clock analysis of 31 new strains obtained from Haiti in 2018, at the nadir of the previous outbreak, as well as 294 Haitian strains sampled between 2010 and 2017, and 16 sequences from the 2022 outbreak publicly available. Our phylogenetic analysis firmly shows the new strains clustering within the Haitian monophyletic clade that emerged at the time of the 2010 outbreak. Our Bayesian phylogenetic also demonstrated that the new strains of V. cholerae cluster shared a most recent common ancestor with a 2018 Haitian Ogawa strain isolated from the aquatic ecosystem and cluster with the previous Ogawa clade that was circulating in 2015-2016. Our case data points out to the original epicenter of the outbreak in Port-Au-Prince and the exponential spread in different directions. Our phylogeography analyses based on the plateau phase of the epidemic, shows further spread within Port-Au-Prince and towards outside. In conclusion, our results show that the new outbreak strains originated from strains that have been circulating undetected at sub-epidemic levels in the aquatic environment. Our data strongly indicates that re-emergence of cholera in Haiti is the likely result of a spill-over event at the aquatic-human interface related to persistence of V. cholerae O1 in the environment.

5706

EFFECTIVENESS OF THE EUVICHOL® ORAL CHOLERA VACCINE AT 2 YEARS: A CASE-CONTROL AND BIAS-INDICATOR STUDY IN HAITI

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The World Health Organization (WHO) recommends use of oral cholera vaccine (OCV) in cholera control efforts. Studies of Shanchol® - a bivalent killed whole-cell OCV - have established its effectiveness in preventing cholera. Euvichol®, a similar product, was pre-qualified by WHO in 2016 and is now the leading component of the Global OCV stockpile, but data on its field effectiveness are limited. Between November - December, 2017, a Euvichol® campaign was implemented in Haiti. We conducted a case-control study to evaluate the effectiveness of this OCV, and a bias-indicator study to evaluate likelihood of study bias. Residents of Mirebalais, Haiti who were eligible for vaccination were enrolled beginning 10 months after the vaccination campaign. Cases were individuals presenting to a cholera treatment unit with acute watery diarrhea (AWD). Stool samples were tested by culture and RT-PCR of the V. cholerae O1 cholera toxin gene. For each case, four control individuals without diarrhea were matched by location of residence, enrolment time, age and sex. Participants were interviewed for sociodemographics, cholera risk factors, and self-reported vaccination. Cholera cases were analyzed in the vaccine effectiveness (VE) study. AWD cases negative for cholera by culture and RT-PCR were analyzed in the bias-indicator study. Data were analyzed by conditional logistic regression, adjusting for matching factors. From 9/12/2018 - 3/12/2020, we enrolled 100 AWD cases. 18 had cholera and were matched to 72 controls. 82 cases without cholera were matched to 325 controls. In the VE case-control, 10 (55.6%) cases reported vaccination compared to 54 (75%) controls. Adjusted VE for 2 doses of OCV was 62% (-67 - 91%). VE for 2 doses of OCV in the bias-indicator study was 40% (-12 - 68%). Between 10 - 27 months after vaccination, Euvichol® was effective at preventing cholera. VE estimates and bias-indicator estimates for Euvichol® in Haiti are comparable to prior estimates of Shanchol® in Haiti, which demonstrated robust evidence of VE up to 2 years post-vaccination. Further research to evaluate the effectiveness of OCV in children and over longer periods are needed.

5707

THE EFFECTIVENESS OF ONE DOSE OF ORAL CHOLERA VACCINE: MATCHED CASE-CONTROL STUDIES FROM UVIRA, DEMOCRATIC REPUBLIC OF CONGO

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Amid a global surge in cholera outbreaks and shortage in oral cholera vaccines (OCV), a single-dose regimen, rather than the standard two-dose regimen, is being used in outbreaks. However, single-dose protection data are limited, especially for children and durations of longer than a few months. We conducted two case-control studies in Uvira, Democratic Republic of Congo, to examine the vaccine effectiveness (VE) of a single-dose of the Euvichol-plus vaccine up to 29 months after vaccination. We recruited matched community controls for confirmed cholera cases admitted at health facilities 12-17 months after vaccination, from October 2021 to March 2022 (Study 1). We then prospectively enrolled community controls for cases admitted 24-29 months after vaccination, from October 2022 to March 2023 (Study 2). Eligible cases included culture and/or PCR-confirmed cholera cases who were eligible for the vaccine during the vaccination campaigns. Four controls with no history of cholera in the past 3 years were matched to each case by age, sex, and neighborhood, as well as by household size and presence of a child under-5 in Study 2. We used conditional logistic regression to estimate VE. We enrolled 1202 participants (268 cases, 934 controls) in Study 1 and 855 participants (167 cases, 688 controls) in study 2 with 18% of the cases being <5 years old in Study 1 and 30% in Study 2. The adjusted single-dose effectiveness for all ages was 50.6% (95% CI 30.1-65.2%) 12-17 months after vaccination and 37.7% (5.5-58.9%) 24-29 months after. VE point estimates were similar across age groups in both studies. Estimates for children under 5 years old were 45.1% (-39-78%) in Study 1 and 43% (66-80%) in Study 2, compared to estimates for older participants of 49% (25-65%) in Study 1 and 41% (3-65%) in Study 2. We demonstrate significant clinical protection from a single dose of Euvichol-plus both one and two years after vaccination. While uncertainty remains around the protection conferred to children under 5, these provide important new data to help with the planning of future vaccination campaigns.

5708

SINGLE DOSE ORAL VAXCHORA VACCINE (CVD103-HGR) FOR THE PREVENTION OF CHOLERA IN TRAVELERS

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Cholera remains an ongoing threat for travelers to areas with endemic/epidemic Vibrio cholerae infections. A single dose vaccine which provides rapid protection, especially for those leaving on short notice, is desirable. To assess the safety, immunogenicity and efficacy of Vaxchora® (Cholera Vaccine, Live, Oral) for protection against cholera diarrhea in travelers, 5 prospective, randomized, double-blind, placebo-controlled trials were performed in 4357 subjects 2-64 years of age in

the US. Endpoints included safety, immunogenicity, shedding, protective efficacy, lot consistency, and immunologic bridging following a single dose. The phase 1 study documented serum vibriocidal antibody (SVA) seroconversion in 88.9% of subjects at day 14, and stool shedding of vaccine organisms in 11% through day 7. In a phase 3 study, protective efficacy against moderate-to-severe diarrhea following challenge with virulent V. cholerae was 90.3% and 79.5% at days 11 and 91, respectively. SVA seroconversion, which occurred in 79.8% and 89.4% of subjects at days 8 and 11, respectively, was a strong correlate of protection. In a phase 3 lot consistency study, SVA seroconversion occurred in 93.5% of adults 18-45 years of age at day 11, while a phase 3 immunogenicity study in older adults 46-64 years demonstrated a non-inferior 90.4% seroconversion rate. A phase 4 study in children 2-17 years of age demonstrated a 98.5% SVA seroconversion rate, which was non-inferior to that seen in the lot consistency study. An adolescent sub-study of the pediatric trial documented persistence of SVA seroconversion at 2 years in 64.5% of vaccine recipients. In a post-hoc analysis of the pediatric trial of those subjects who consumed less than the full dose of vaccine, SVA seroconversion was documented in 100% of those who took 50-80% of the dose and in 69.2% of those who took some but <50%. Vaccine was well tolerated in all studies. A single oral dose of Vaxchora vaccine provides safe and rapid protection in adults and children traveling to areas with cholera. SVA seroconversion, the correlate of protection in the cholera challenge trial, occurs in most individuals in as little as 7 days.

5709

LONG TERM MUSCULOSKELETAL MANIFESTATIONS ARE ASSOCIATED WITH A DYSREGULATED IMMUNE RESPONSE IN POST-EBOLA SYNDROME (PES)

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Long-term post-acute sequelae following viral infections have become recognized as highly prevalent in recent years, including in the contexts of Ebolavirus disease (EVD) and SARS-CoV2. As these diseases continue to emerge—Sudan ebolavirus (SUDV) in Uganda; Marburg virus (MARV) in Equatorial Guinea—the long-term health consequences following acute infection are garnering attention. In the context of EVD, a large proportion of survivors develop a range of long-term sequelae with complaints including ophthalmologic, auditory, musculoskeletal (MSK), neurocognitive, and psychiatric. Our group recently defined these sequelae phenotypically into three groups: symptomatic survivors with or without MSK involvement, and asymptomatic. The mechanisms defining long-term sequelae, including MSK, are currently unknown making targeted treatment challenging. Due to the association of inflammatory biomarkers with MSK sequelae in other viral contexts (ie: HIV/AIDS and Chikungunya virus), we developed a 20-plex Luminex panel to assess the relationship between inflammatory markers and MSK sequelae in an ongoing cohort of EVD survivors from Eastern Sierra Leone. Our custom Luminex panel included pro- and anti-inflammatory cytokines, metalloproteinases, and markers of mucosal integrity associated with inflammation. We found that contrary to our hypothesis of increased inflammation in survivors suffering from long-term MSK, that in fact survivors with MSK had lower concentration of serum biomarkers compared to asymptomatic EVD survivors. In collaboration with colleagues at WSU, we tested antibody driven Fc-mediated innate effector function and observed significantly lower levels of monocyte/macrophage phagocytosis and decreased complement deposition in survivors in the MSK group. We are currently investigating alternative hypotheses including the presence of autoantibodies, a phenomenon that has been observed in the context of SARS-CoV2 following recovery from acute disease. Our preliminary data suggest an immune dysregulation and possible immunosenescence associated with long-term MSK sequelae in EVD survivors.

5710

EXPLORING BAT INNATE IMMUNE CELL RESPONSES TO FILOVIRUSES

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Various species of bats are reservoirs of diverse zoonotic viruses, including multiple filoviruses such as Marburg virus (MARV, naturally transmitted by Egyptian rousette bats; Rousettus aegyptiacus) and Bombali ebolavirus (BOMV, recently isolated from Angolan free-tailed bats; Mops condylurus). The ability of bats to host viruses that are highly-pathogenic to humans likely correlates with co-evolved functional anti-viral immune response mechanisms. How bats achieve efficient anti-viral innate or adaptive immune responses at the molecular or cellular level, without developing overt signs of disease themselves, remains to be addressed. In this study, we profile the phenotypes, functionality and anti-viral immune responses of dendritic cells (DC), key primary host cellular targets of filoviruses. We infected bone marrow-derived DCs (bmDCs) from R. aegyptiacus with recombinant MARV or Sudan ebolavirus (SUDV) expressing fluorescent proteins, allowing us to directly compare how DCs respond to infection by a filovirus that these bats harbour in nature (MARV), to a filovirus efficiently cleared by rousette bats in vivo (SUDV). Despite similar rates of progeny virus production, bmDCs supported increased intracellular MARV-ZsG replication out to 3 days post-infection, while ZsG median fluorescence intensity (MFI) in SUDV-infected bmDCs was decreased, indicating differential control of infection of these two viruses. Conversely, MARV- and SUDV-infected bmDCs both upregulated CD40 and HLA-DR surface expression, indicative of functional cell activation. Similarly, bmDCs from M. condylurus sustained steady rates of replication with fluorescently-tagged Zaire ebolavirus (EBOV-GFP) and displayed a notable upregulation of CD40 at 1 day post-infection. Our findings highlight that despite being susceptible to infection, bat DCs display unimpaired activation and antigen presentation capacities following disparate filovirus infections, in contrast to the described impaired maturation and functionality observed in filovirus-infected human DCs.

5711

COMPUTATIONAL DESIGN OF STABILIZED RBD ANTIGENS ENABLES POTENTLY NEUTRALIZING SARS-COV-2 VACCINES

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Waning immunity and emerging variants necessitate continued vaccination against SARS-CoV-2. Improvements in vaccine efficacy, safety, tolerability, and ease of manufacturing would benefit these efforts. Receptor-binding domain (RBD)-based vaccines are effective vaccines used in several

countries, in part due to their ease of manufacturing. Here, we report a novel computational design strategy (SPEEDesign) that improves RBD vaccines. SPEEDesign was used to create RBD immunogens with amino acid changes that enhance neutralizing antibody titers, focus the immune response to neutralizing epitopes, increase production yields, and improve antigen stability. In one application of SPEEDesign, immunogens with 9 amino acid changes elicited neutralizing antibody titers approximately 10-fold greater than the native RBD, and comparable to a benchmark stabilized spike antigen. Crystal structures of these immunogens revealed the structural basis for these improvements. A second application of SPEEDesign produced a stabilized, non-glycosylated RBD that resolved issues hindering the efficient nanoparticle display of the native RBD. This non-glycosylated RBD can be genetically fused to diverse single-component nanoparticle platforms maximizing manufacturing ease and flexibility. All engineered RBD-nanoparticles elicited potently neutralizing antibodies in mice that far exceeded monomeric RBD. A 60-copy particle (noNAG-RBD-E2p) also elicited potently neutralizing antibodies in non-human primates. The neutralizing antibody titers elicited by noNAG-RBD-E2p were comparable to a benchmark stabilized spike antigen and reached levels against omicron BA.5 that suggest it would provide protection against emerging variants. The stabilizing mutations we have identified in both applications of SPEEDesign are adaptable to all vaccine platforms and they are distinct from the changes in emerging variants, making them compatible with updated vaccines. Finally, the SPEEDesign pipeline is a generalizable method that can be used to improve vaccine antigens from diverse pathogens.

5712

EPSTEIN BARR VIRUS SYNERGIZES WITH PLASMODIUM FALCIPARUM MALARIA TO INDUCE ABERRANT EXPRESSION OF ACTIVATION INDUCED CYTIDINE DEAMINASE

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Early age at EBV infection and repeated episodes of Plasmodium falciparum (Pf) malaria are known risk factors for the development of endemic Burkitt's lymphoma(eBL), the most common pediatric cancer in equatorial Africa. To date, the extent and by what means these two factors interact to drive eBL pathogenesis is yet to be fully understood. Both EBV and P.f have been considered as potential drivers of increased Activation Induced Cytidine Deaminase (AID) activity, the major hallmark of eBL. AID activity is typically restricted to B cells in the germinal center reaction. However, recently low levels of AID expression in immature transitional B cells in peripheral circulation have been reported. Additionally, AID expression has been reported in B cells in peripheral circulation in children and adults from malaria endemic areas. Studies in vitro and in mice have also demonstrated either P.f or EBV can induce expression of AID in peripheral blood. In this study, we hypothesized that EBV and P.f malaria synergistically induce dysregulated expression of AID. We analyzed the expression of AID on B cells from peripheral blood of children experiencing an episode of acute P.f malaria and healthy controls by intracellular flow cytometry. Furthermore, we determined the in vitro induction of AID expression on primary human B cells following infection with EBV with or without CpG (a TLR9 ligand used to mimic P.f DNA). We report a significantly higher frequency and MFI of CD19+ AID+ B cells in children presenting with acute malaria than in healthy controls. In vitro analysis confirmed the synergy between EBV and P.f malaria in the amplification of AID expression since we observed >50% increase in the frequency of CD19+AID+ cells following infection with EBV and CpG. Interestingly, co-stimulation with BAFF, a B-cell cytokine that is elevated during acute malaria infection, further amplified the expression of AID in B cell in vitro. Taken together, our study confirms the synergistic linkage between these two pathogens in the etiology of eBL through the induction of aberrant expression of the highly mutagenic AID that is likely to exacerbates the pathogenesis of eBL.

5713

ANTIBODY FC CORRELATES OF PROTECTION AGAINST SEVERE DENGUE DISEASE

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Four dengue virus serotypes (DENV1-4) are associated with ~50 million cases annually worldwide, with disease presenting as mild (dengue fever, DF) or severe (dengue hemorrhagic fever/shock syndrome, DHF/DSS). Pre-existing cross-reactive antibodies have been associated with both protection and risk for developing severe dengue upon secondary heterotypic infection, but antibody characteristics that provide protection from severe disease remain poorly understood. We performed systems serology on plasma/serum samples collected from 66 individuals (33 DF and 33 DHF/DSS) before secondary DENV2 and DENV3 infections resulting in either DF or DHF/DSS from a longstanding pediatric cohort study in Nicaragua. We measured binding antibodies by Luminex using beads conjugated to recombinant envelope (E), E domain III, and nonstructural protein 1 (NS1) of DENV1-4 and the related Zika virus (ZIKV). For Fc effector function assays, we used beads conjugated to DENV2, DENV3, and ZIKV antigens. Our study revealed that higher levels of total IgG, IgG2, IgG3, IgG4, and both antibody-dependent complement deposition (ADCD) and antibody-dependent cellular phagocytosis (ADCP) were associated with protection against DHF/DSS. In contrast, neutralizing antibodies to mature DENV2 and DENV3 virions, measured by focus reduction neutralization test on Vero cells, were not significantly different. We also observed a stronger association of ADCD activity with protection when assays were conducted with ZIKV antigens. We validated these findings with a complement-mediated virolysis assay using DENV, ZIKV or yellow fever virus virions. We found that virolysis of ZIKV virions mediated by samples from DENV-exposed, ZIKV-naïve individuals was most strongly associated with protection, suggesting that 1) anti-DENV antibodies that cross-react with ZIKV and 2) antibodies that target virion-specific epitopes are correlated with protection from severe dengue disease. In sum, our study provides important insights into the biophysical features and effector functions of cross-reactive antibodies that may inform the development of effective dengue vaccines.

5714

ANTIBODY CORRELATES OF SEVERE DISEASE IN SECONDARY DENGUE VIRUS INFECTION AFTER A PRIMARY ZIKA VIRUS INFECTION: A POSSIBLE ROLE FOR IGA

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Sequential infections of dengue virus serotypes 1-4 (DENV1-4) and Zika (ZIKV) can lead to protection or severe disease. We observed in our

long-standing pediatric cohort in Nicaragua that ZIKV infection increases risk of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) during secondary DENV2 infection, potentially due to antibody-dependent enhancement. However, immune correlates of disease severity are not completely understood. Here, we analyzed antibody characteristics in samples taken after primary ZIKV infection that were associated with DHF/DSS vs. dengue fever (DF) during subsequent secondary DENV2 infection in 24 children (n=12/group) from our Nicaraguan cohort study. We characterized anti-DENV and anti-ZIKV antibodies (IgG1-4, IgA, IgM) in pre-secondary infection samples using a multiplex Luminex assay against recombinant E protein (recE), E domain III, and nonstructural protein 1 (NS1) of DENV1-4 and ZIKV, as well as the Fc effector functions antibody-dependent complement deposition (ADCD) and antibody-dependent cellular phagocytosis. After modelling a dose-response curve, the effective dilution at which mean fluorescence intensity was reduced by 50% (ED50) was significantly associated with DHF/DSS for IgA but not for other isotypes. A bivariate logistic binomial regression showed that a 0.1Log10 increase in the ED50 of anti-NS1 DENV2 IgA and anti-NS1 ZIKV IgA, among others, increased odds of DHF/DSS by 3.07 (95% Confidence Interval [95%CI] 1.62-9.77) and 2.02 (1.31-4.34), respectively. A LASSO multivariate regression selected ED50of anti-NS1 DENV2 IgA as the most relevant feature associated with DHF/DSS. Finally, a Bayesian network analysis revealed that ED50 of anti-NS1 DENV2 IgA and anti-NS1 DENV4 IgA increased the probability of DHF/DSS. We are currently analyzing the amount of IgA1/IgA2 and dimeric vs. monomeric IgA, avidity of IgA against DENV/ZIKV antigens, and markers of neutrophil function in pre-secondary infection and acute-phase samples from these individuals. We hypothesize that IgA may be involved in a pathogenic pathway associated with DHF/DSS that deserves further study.

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IN-DEPTH ANALYSIS OF THE IMMUNOGENICITY OF A SINGLE DOSE OF DENGVAXIA IN BASELINE DENGUE-NAIVE CHILDREN IN CEBU, PHILIPPINES

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The first licensed dengue virus (DENV) vaccine, Dengvaxia® sensitizes dengue seronegative (SN) children to experience more severe breakthrough infections compared to unvaccinated children. In clinical trials of this live attenuated tetravalent chimeric yellow fever/DENV vaccine, neutralizing antibodies (NAbs) to the 4 DENV serotypes were detected in most SN vaccinated individuals demonstrating that not all the antibodies that neutralize in vitro are predictive of durable protection in humans. When Dengvaxia® was introduced as a pediatric vaccine in the Philippines in 2016, investigators at the Univ. of Philippines in Manila established a cohort of 2,960 children (60% vaccinated) to study vaccine immunogenicity, efficacy and safety by baseline (BL) DENV serostatus over a 5-year follow-up period. Here we report the results of a sub-study to investigate vaccine immunogenicity in BL SN children 1 Year after receiving a single dose. We analyzed paired blood samples collected at BL and Yr1 from 136 vaccinated and 87 unvaccinated children using a) a multiplex-Luminex assay designed to measure antibodies to 8 DENV antigens (EDIII and NS1 proteins from the four serotypes), b) an ELISA for detecting Abs to yellow fever virus NS1 antigen expressed by the vaccine only, c) a DENV neutralization assay designed to measure NAb responses to contemporary circulating strains of mature DENV1-4. Among the vaccinated children we did not observe any vaccine-induced antibody responses in 34% (44/136) after one dose. Among the children who responded to the vaccine, the frequency of NAbs to each serotype was 66% (DENV4), 21% (DENV1), 15% (DENV2) and 10% (DENV3) supporting a DENV4 biased vaccine. We relied on the presence of DENV NS1 Abs as surrogate to capture all DENV infections in Yr1 blood samples. We observed a high attack rate of DENV infection (53%) between BL and Y1 in the unvaccinated children. Among the vaccinated children, 22% experienced DENV infections demonstrating modest efficacy against infection. Clinical vaccine efficacy and safety in years 1-5 after vaccination and immune correlates analyses are ongoing.

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ACUTE PUBLIC HEALTH THREATS GLOBALLY: A 10-YEAR WORLD HEALTH ORGANIZATION ANALYSIS

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One of the World Health Organization's (WHO) key activities is the detection and response to acute public health threats to prevent morbidity and save lives. Therefore, WHO adopted a unique all-hazards approach to the global detection and verification of acute public health events of potential international public health concern, under the mandate of the International Health Regulations (2005). Here, we analysed 10-year trends of acute public health events globally. Data on substantiated acute public health events reported between 2013 and 2022 was extracted from an internal WHO platform, the Event Management System (EMS), which is used for tracking health threats globally. Substantiated events are those for which the presence of a hazard was confirmed or the number of human cases exceeded normal thresholds. These events were assessed, by WHO Region and over time, using descriptive statistics in R. Between 2013 and 2022, 3214 acute public health events were recorded globally in EMS, of which six were declared public health emergencies of international concern. For each year of the 10-year period, infectious diseases were the main cause of events, ranging from 68% - 90% per year. Globally the five most common infectious diseases, excluding COVID-19, were cholera, measles, dengue, zika, and avian or human influenza. Natural disasters (9.5%, N=305) were the second most common cause globally. In all WHO Regions infectious diseases were the main cause of public health events, ranging from 47%-84% between Regions. In addition, natural disasters were a common driver of events and the second cause, ranging from 9%-36%, in four of six Regions. Moreover, the proportion of events due to natural disaster has increased in recent years in these Regions. In conclusion, infectious diseases are the main cause of events globally reported to WHO. However, health emergencies by natural disasters are on the rise and marked differences, in health threats, between Regions exist. To prepare for future health threats an understanding of previous acute public health events and changing trends is key.

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DETECTION OF HUMAN CASES OF CRIMEAN-CONGO HEMORRHAGIC FEVER DURING AN ONGOING MULTIDISTRICT OUTBREAK OF EBOLA VIRUS DISEASE IN UGANDA, 2022-23

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In September 2022, Uganda experienced its 5th outbreak of Ebola virus disease (EVD) due to Sudan ebolavirus (SUDV) that spread to multiple districts across the country. During the subsequent national-wide enhanced surveillance activities, several cases suspected of viral hemorrhagic fever (VHF) were found to be caused by other viral etiologies, including yellow fever, Crimean-Congo Hemorrhagic fever (CCHF) and Rift Valley fever. We report the epidemiologic and laboratory findings of human CCHF cases that were concomitantly detected during the EVD response activities. A VHF suspected case was any person presenting with acute onset of fever (≥38.0°C), with no alternative diagnosis, and with other signs and symptoms such as intense fatigue, chills, general body pains, headache, anorexia, vomiting, diarrhea, jaundice, and unexplained bleeding from any site. Between September 2022 and February 2023, a total of 1,107 samples were submitted for VHF testing at Uganda Virus Research Institute, Entebbe, Uganda. Overall, 13 CCHF cases (including 7 deaths; CFR = 54%), aged 4 to 60 years, were identified by PCR from 10 districts, including the same districts as the SUDV outbreak. Of these, most cases were males who also engaged in livestock farming and exposure to wildlife (n = 8; 62%). Four cases were identified in the EVD treatment unit, thus complicating diagnosis and management of CCHF cases during an active SUDV outbreak. Among confirmed cases, the most common clinical symptoms were hemorrhage (n = 12; 92%), followed by fever (n = 11; 85%), anorexia (n = 10; 77%), fatigue (n = 9; 69%), abdominal pain (n = 9; 69%) and vomiting (n = 9; 69%). Further investigations to characterize these viral infections as well as alternate etiologies is ongoing and will be presented. These findings highlight the need for broad diagnostics for VHFs and other viral and high-consequence pathogens, even during confirmed VHF outbreaks, to properly identify all possible causes of acute febrile illnesses detected during periods of heightened surveillance. This approach is especially critical in countries with a broad range of endemic high-consequence zoonotic viral pathogens.

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A COMPREHENSIVE REVIEW OF CLINICAL PRESENTATIONS OF NIPAH VIRUS INFECTION: EVIDENCE GENERATED FROM NIPAH VIRUS OUTBREAKS OF 2023, BANGLADESH

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Nipah virus is endemic to Bangladesh, and human infections have been reported almost every year since 2001. Till March 2023, Bangladesh experienced ten outbreaks of Nipah virus infection. Team of experts led by the Institue of Epidemiology, Disease Control and Research (IEDCR) conducted the outbreak investigations with support from icddr,b, and EcoHealth Alliance to detect more cases linked to the outbreaks and to prevent further spread in the community and healthcare setting. The teams identified the source of infection and obtained comprehensive information of the patients since their exposure to the virus. From January 4 to March 2, 2023, three clusters and seven sporadic Nipah outbreaks were identified from seven districts of Bangladesh. A total of 14 Nipah cases were reported, which included 86% (12/14) laboratory-confirmed and 14% (2/14) probable cases. There were 11 cases of primary infection, all with the history of raw date palm sap consumption prior to symptom onset. During the investigations, 675 contacts were identified; among them, three individuals were infected with the Nipah virus, indicating person-to-person transmission. On average, Nipah infection was confirmed 8 (range, 4 to 14) days after symptom onset and 3 (range, 1 to 9) days after hospitalization. The median incubation period was 11 days, ranging from 1 to 18 days. Most cases were males (57%) with a median age of 20 (15 days to 70 years) years. Ten (71%) cases died during the infection; the rest survived with significant neurological sequelae. In most cases, symptoms started with fever (100%) followed by headache (64%) and vomiting (64%). Subsequently, all patients developed signs of neurological manifestations ranging from incoherent behavior, confusion, increased salivation, neck stiffness, altered level of consciousness to coma. This year's outbreaks exceeded the past eight-year record, and several instances of human-to-human spread indicate the potential to cause larger epidemics in the future. The findings of these outbreak investigations highlight the urgent need for increased efforts in developing vaccines and treatments for Nipah virus infection.

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ENVIRONMENTAL SURVEILLANCE TO DETERMINE COVID-19 PREVALENCE IN DISTRICTS IN NORTHERN GHANA WITH NO REPORTED COVID-19 CASES: EVIDENCE TO INFORM PUBLIC HEALTH INTERVENTIONS

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Environmental surveillance (ES) is a convenient, sensitive, low-cost method to estimate COVID-19 prevalence. Most ES in high-resource countries is implemented in sewered systems. Non-sewered sanitation is common in low-resource settings, and few studies have deployed ES in such environments. We applied ES to detect COVID-19 in two districts with no reported cases of COVID 19 since the beginning of the pandemic to inform public health policy and practice. Mion (pop. 94,930) and Nanumba North (188,680) are rural areas in the Northern region of Ghana. Both localities are sparsely populated. Neither district has a sewerage system, and >70% of the population rely on shared public toilets. Stakeholder analysis was deployed to identify population centers in the community that should be targeted for wastewater or fecal sludge sample collection. Schools (primary, secondary, and college), healthcare facilities, markets, and streams were identified and mapped. From September to November 2022, grab and Moore swab samples were collected daily from septic tanks, pit latrines and surface water. Samples were stored and transported weekly to a central

lab in Accra. Liquid samples were concentrated using Nanotrap particles, RNA extraction, and analyzed by multiplex RT-qPCR. 46 sampling sites were identified, and 194 samples (128 solids samples, 3 Moore swabs, and 63 liquid samples) were collected. 13%, 33.3% and 20% of the liquid, Moore swab, and solids samples tested positive for SARS-COV-2 RNA, respectively. 8.9% of the 78 samples from Mion were positive for SARS-COV-2. Out of the 116 samples from Nanumba North, 24.3% tested positive for SARS-COV-2. Positive samples were from healthcare facilities (6.6%), public latrines (17.7%) and schools (22.5%). No COVID-19 cases were reported from either district during the study period. The Ghana Health Service used the results to develop public health response action plans -including health education and targeted mass vaccination in schools and communities. These findings demonstrate the value of ES to guide the public health response in remote low-resources settings even when clinical cases are not detected.

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MEASLES ANTIBODY RESPONSE AND DURATION IN INFANTS WITH HIGH EARLY-LIFE MALARIA EXPOSURE COMPARED WITH LOW MALARIA EXPOSURE

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Measles continues to cause significant morbidity and mortality globally despite a highly effective vaccine. Immunomodulation caused by high malaria exposure during early-life may impact the response to measles vaccine and the duration of this response. In the present study, we assessed measles antibody levels in a 2-year longitudinal cohort of 166 infants from two sites in Kenya with different levels of malaria transmission. After excluding infants with likely measles exposure prior to vaccination, we categorized measles antibody levels at 10-12 months of age into high/medium/low tertiles and compared the proportion of infants in each tertile between study sites. Using the categories defined by these tertiles at 10-12, 16-18, and 22-24 months of age, we used repeated ordinal logistic regression to compare change between categories over the study duration between study sites. Prior to measles vaccination at nine months of age, 30.6% of infants had measles antibody levels indicative of exposure to the virus. Among infants without pre-vaccine measles exposure, more infants at the low-malaria study site were in the high category of antibody response at 10-12 months compared with infants at the high-malaria study site (42.1% vs. 24.0%, p=0.1). At both sites, more infants moved to the high antibody category throughout the duration of the study, but this change in categories did not differ between study sites. In sum, infants living in the low-malaria community had better vaccine-elicited immunity, on average, than infants in the high-malaria community. The substantial number of infants with likely measles exposure prior to vaccination combined with the increasing antibody levels throughout the duration of the study suggest measles may have been circulating in these populations during the study period. In endemic settings, immunization schedules should take into account gaps in seroprotection prior to vaccination. Further research is needed to understand how to best address potentially lower vaccine response in areas of high malaria transmission.

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MACROLIDE RESISTANCE 36 MONTHS AFTER MASS AZITHROMYCIN ADMINISTRATION IN A CLUSTER-RANDOMIZED TRIAL IN NIGER

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Mass drug administration (MDA) of azithromycin decreases child mortality but has been shown to select for macrolide and nonmacrolide resistance 24 months after initiation. However, resistance prevalence over time is not well studied. Herein, we evaluate resistance 36 months after initial azithromycin treatment and compare mean prevalence between treatment and control arms. In the MORDOR cluster-randomized trial of mass azithromycin distribution, children ages 1-59 months received either azithromycin (15 villages) or placebo (15 villages) every six months. In total, 423 children were randomly selected to provide nasal swab samples after receiving their 36-month administration of treatment or placebo. Streptococcus pneumoniae isolates from cultured swabs were tested for macrolide and nonmacrolide resistance. The primary outcome was prevalence of macrolide and nonmacrolide resistance for treatment versus placebo groups at 36 months. Of the 423 swabs obtained, 322 grew S. pneumoniae (146/202 in the treatment group and 176/221 in the control group). Macrolide resistance prevalence was 14.6% in treatment villages and 8.9% in control villages (OR=2.0, 95% CI: 0.99-3.97) in a mixed effects regression model. Resistance prevalence of several nonmacrolides did not differ between treatment and controls (p>0.18 for all). Our results suggest that increased exposure to resistance determinants or spillover from treatment villages increased prevalence in control villages. Furthermore, although macrolide resistance prevalence increased significantly from MDA initiation to 24 months, overall resistance at 36 months was only marginally greater than at 24 months, indicating that resistance after twice-yearly azithromycin administration to young children flattens before exponential growth occurs. This longitudinal flattening may not hold for MDA regimens that confer high antibiotic pressure by targeting larger proportions of the population with more frequent dosages, like mass azithromycin for endemic trachoma.

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RISK FACTORS FOR COLONIZATION WITH EXTENDED-SPECTRUM CEPHALOSPORIN RESISTANT AND CARBAPENEM RESISTANT ENTEROBACTERALES AMONG HOSPITALIZED PATIENTS IN BANGLADESH: ANTIBIOTIC RESISTANCE IN COMMUNITIES AND HOSPITALS -ARCH-STUDY

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Understanding risk factors for colonization with antimicrobial resistant (AMR) organisms is critical for implementing effective prevention strategies to reduce transmission and risk for developing invasive infections. During Apr-Oct 2019, we conducted a period prevalence study in three hospitals in Dhaka city during which we continuously enrolled patients using simple random sampling. We collected stool samples from hospitalized adult patients to detect extended-spectrum cephalosporin resistant (ESCrE) and carbapenem resistant (CRE) Enterobacterales. We recorded information on patient characteristics, admission wards, antibiotic use, duration of hospitalization at enrollment, and healthcare exposures. Based on a conceptual framework, we used multivariate logistic regression models adjusting for potential confounders to identify the risk factors for colonization. Of 743 enrolled patients, the median age was 40 (IQR:30-55) years, 54% were male, and 44% had underlying chronic illnesses. Median time between hospital admission and patient enrollment was 3 days (IQR:

2 - 6 days) with stool typically collected the following day. Among enrolled patients, 592 (82%) were colonized with ESCrE and 267 (37%) with CRE. Risk factors for ESCrE colonization were stay in a surgical ward compared with a medicine ward (aOR 2.1, CI: 1.3-3.2) and hospitalization for 3-7 days (aOR 1.9, 1.2-3.0). Risk factors for CRE colonization included admission from another healthcare facility (aOR 3.1, 1.5-6.4); stay in a surgical ward (aOR 1.7, 1.1-2.5); hospitalization for 3-7 days (aOR 1.7, 1.2-2.4) and >=7 days (aOR 2.9, 1.8-4.6); invasive procedures (aOR 2.4, 1.3-4.4); urinary catheter use (aOR 2.1, 1.1-4.2); and antibiotic administration in the last 14 days (aOR 2.9, 2.0-4.0). In conclusion, longer hospital stays and more invasive procedures were associated with increased risk for colonization with AMR organisms. These findings emphasize the need for enhanced infection prevention and control efforts to mitigate the transmission of AMR organisms in Bangladeshi hospitals.

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MOLECULAR EPIDEMIOLOGY OF ASYMPTOMATIC CRYPTOSPORIDIUM, GIARDIA, AND ENTAMOEBA INFECTIONS: THREATS TO THE HEALTH OF NIGERIAN CHILDREN?

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Intestinal parasitic infections have significant impacts on the health of children. Apart from causing diarrheal diseases, Cryptosporidium and Giardia infections have negative impacts on children's growth and cognitive development and may result in death in immunocompromised individuals. At the national level, there is a scarcity of information on the molecular epidemiology of Cryptosporidium, Giardia and Entamoeba infections in children in Nigeria. As a result, we present for the first time in Nigeria a nationwide assessment of the prevalence, associated risk factors, and genetic profiles of Cryptosporidium, Giardia and Entamoeba species in children aged 10 and below. In total, 985 stool samples were collected from ten states, along with an epidemiological questionnaire. We used real-time PCR and DNA sequencing to detect and genotype the three enteric parasites in stool samples. A variety of statistical and bioinformatic tools were used to analyze the data. The most common parasite found in this study was Giardia sp. (77.4%), followed by Cryptosporidium (19.5%) and Entamoeba (12.3%). Coinfections with two or all three parasites were found in 10% of the children in this study, with Cryptosporidium + Entamoeba coinfection being the least common. Several socioeconomic factors, including toilet type, drinking water source, livestock rearing, and hygiene habits, were identified as risk factors for infection with one or more of the parasites.The main circulating species were identified through genetic analysis as C. parvum, Giardia Assemblage A2 and B, Entamoeba histolytica and Entamoeba dispar. Regardless of the presence or absence of symptoms, our study found a high burden of intestinal parasitic infection in children in Nigeria which was linked to poor hygiene and poverty-related factors.

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A CONTINENTAL PICTURE OF SLEEPING SICKNESS: USING MODELS FROM THE DRC TO ESTIMATE GLOBAL GAMBIENSE HUMAN AFRICAN TRYPANOSOMIASIS BURDEN AND PROJECTED RESOURCE USE AND COST UNDER VARIOUS CONTROL STRATEGIES

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Gambiense Human African Trypanosomiasis (gHAT, sleeping sickness) affects several countries across central and western Africa, spanning a diverse range of geographies and epidemiology. In 2019-2020, 70% of all reported gHAT cases were recorded in the Democratic Republic of the Congo (DRC). We have previously fitted a dynamic transmission model to historical data in 168 endemic or formerly endemic health zones of the DRC, across a range of geographies and levels of case reporting from no cases in the last decade to thousands. In this study, we produce a picture of the resources required for gHAT control across the whole continent. We classified the health zones of the DRC for which we have enough data to fit the transmission model by their risk level according to the WHO definitions and then combine them to produce aggregated fits for each risk level. We then used these aggregated fits in combination with WHO estimates of the population living at each level of risk to produce projections across the whole continent. A set of possible interventions were then considered based on estimates of local capacity for screening and geographical suitability for vector control. We made projections under multiple strategies and predicted the disease burden and probability of elimination over time as well as estimating resource use and cost. These projections were used to produce a global health economic analysis under a modified, previously published, version of the net monetary benefit framework. Each strategy's cost-effectiveness is considered with respect to disease burden and its effect on probability of elimination. We also forecast the number of drug doses, diagnostic tests, and tiny targets needed under each strategy and in each country to reach elimination. These projections are made available in a graphical user interface to allow them to be explored and visualised easily.

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CHAGATYPER: DEVELOPMENT OF A RAPID RESPONSE, SEMI-AUTOMATED, HIGH-RESOLUTION GENOTYPING PLATFORM FOR CHAGAS DISEASE

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Approximately 30% of Trypanosoma cruzi seropositive individuals develop end-organ cardiovascular and/or gastrointestinal pathology, so-called chronic determinate Chagas disease. The determinants of progression in Chagas disease are not clear. Parasite genetics - at the DTU or sub-DTU level - has long been thought to play a role. However, the difficulty in isolating and genotyping the parasite directly from patients has frustrated efforts to define the link with pathology. Through a collaboration between the University of Glasgow's School of Biodiversity, One Health and Veterinary Medicine (SBOHVM), the Diagnostic Parasitology Laboratory at the London School of Hygiene & Tropical Medicine and the UK Chagas Hub, we aim to establish a prototype clinical genotyping platform for Chagas disease. The UK Chagas Hub has detected and linked into care 100 new cases of Chagas disease in the last year, with screening and active case-finding initiatives ongoing. Over a quarter (27%) of these patients confirmed to be seropositive were also T. cruzi PCR positive. A genome-wide AmpSeq approach to provide high-resolution

genotypes directly from biological samples has been developed. This AmpSeq approach has been successfully piloted with two peripheral blood samples from newly-diagnosed (chronic indeterminate) cases of Chagas disease detected through UK Chagas Hub screening. We are currently generating an AmpSeq reference strain database, with 100 reference strains covering different major genetic lineages (DTUs) and geographic localities. The reference database will support a user-friendly, interactive, online visualisation tool through which PCR amplicons from clinical samples can be compared. The platform will be tested by 100 further UK Chagas Hub clinical samples (data from PCR amplicons sequenced by a third-party added to the online genotyping platform). A semi-automated, high-resolution genotyping platform for Chagas disease will allow the combination of genotype and clinical phenotype information from large cohorts of patients, which can inform our understanding of the determinants of Chagas disease progression.

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MOLECULAR-BASED EVIDENCE OF TRANSMISSION OF ATYPICAL TRYPANOSOMIASIS (A-HAT) IN HUMANS IN SELECTED COMMUNITIES IN THE SUHUM MUNICIPALITY OF GHANA

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Human African Trypanosomiasis is transmitted by only two subspecies of Trypanosoma (Trypanosoma brucei gambiense and T. brucei rhodesiense) in sub-Saharan Africa. However, case reports of some Trypanosomes (T. congolense, T. evansi, T. brucei brucei, and Trypanosoma vivax) thought to be natural parasites only to animals have been reported to cause “atypical Human African Trypanosomiasis” (a-HAT). The study therefore aimed at providing molecular-based evidence of the transmission of atypical trypanosomiasis in humans in selected communities in the Suhum Municipality of Ghana. A cross-sectional community-based study design was employed to sample venous blood from 240 human participants. Demographics and risk assessment data from participants and polymerase chain reaction (PCR) assays were performed, using trypanosome internal transcribed spacer 1 (ITS1) generic primers from extracted DNA. PCR products were purified and subcloned into pJET1.2/blunt plasmid. Single clones were checked by ITS1 inner primers (colony PCR). Positive clones were cultured overnight at 37°C at 220rpm in 5mL LB medium with 100µg/mL Ampicillin. The cultures were purified and sent to MicroSynth Labs. Sequences were analyzed and aligned with Geneious Pro 5.5.9. The overall prevalence of trypanosome infection was 15.8% (39/240). Age categories 11-20yr and 41-50yr recorded high prevalence of 21.6% and 22.2% respectively. Infection distribution among males and females was 18.0% and 13.6% (X2=0.9001 p>0.05). The highest prevalence of 19.2% a-HAT was recorded at Zorrh followed by Nkantekwan (17.9%) while no evidence of infection at Santramor No.1 was observed. Trypanosome parasites found in this study area were T. evansi, T. congolense, T. vivax and T. simiae. No association was established between tsetse fly bite and Trypanosomiasis (X2 =1.344 p> 0.05). There is a high prevalence of atypical human trypanosomiasis(a-HAT) in the study area. This underscores the need to investigate the impact of animal parasites on human health in order to institute measures that can help prevent the spread of these parasites

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LEISHMANIA INFANTUM VERTICAL TRANSMISSION IN NATURALLY INFECTED DOGS FROM AN ENDEMIC REGION OF BRAZIL

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Visceral leishmaniasis (VL) due to Leishmania infantum is a parasitic illness reported in Europe and Latin America. Dogs are considered the main parasitic reservoir in periurban areas of Brazil. Leishmania transmission in these regions has been traditionally considered to be vector-borne. Although vertical transmission of Leishmania has been shown to have a major impact in maintaining a population of infected dogs, it is not considered yet in control strategies for Brazil. The aim for this study was to evaluate whether and how frequently vertical transmission of Leishmania occurs in a highly endemic setting of Natal, Brazil. We hypothesized that transplacental transmission of Leishmania parasites in Natal may occur at a similar frequency to that observed in dogs in non-endemic regions. To address this, a total of 7 naturally Leishmania-infected pregnant females and their resultant pups (n=48) were recruited and divided into two groups. The first was a cross sectional study to assess presence of parasites in tissues of (aborted) puppies (n=30) from euthanized female dogs (n=4) and the second a prospective evaluation of 3 liters (n= 18), born at a sandfly free facility, to evaluate parasitemia and anti-Leishmania serology for 12 months. In the first study, we found disseminated Leishmania infection in feti, by RT-qPCR, from four pregnant dogs via L. infantum kDNA (89.28%) and detected splenic parasite antigen via IHC in 85.7% of feti. All dogs (100%) from the prospective cohort study were Leishmania positive by both soluble parasite antigen ELISA and parasitemia. Positive correlation between parasitism in umbilical cord blood and in the pup over time supported not only mechanistic evidence of transmission of parasites through umbilical vessels, but also suggests the use of this tissue as a clinical tool to predict Leishmania vertical transmission. These findings support the hypothesis that the incidence of vertical transmission of Leishmania infantum parasites in dogs in endemic areas of Brazil is high and demonstrates the need for novel strategies to control canine VL, including regions where human VL is also endemic.

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CLINICAL AND METAGENOMIC CHARACTERIZATION OF CEREBRAL TOXOPLASMOSIS IN THE PERUVIAN AMAZON.

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Neurological opportunistic infections are a significant cause of morbidity and mortality in people living with HIV (PLHIV). We conducted a study of 140 PLHIV with acute neurological symptoms from Iquitos, Peru. Participants were evaluated for cerebral toxoplasmosis. Poisson regression with robust variance was used to assess differences between patient with and without cerebral toxoplasmosis. A subset of samples were evaluated by metagenomic next-generation sequencing (mNGS) of cerebrospinal fluid (CSF) for comparison with standard diagnostic techniques and identification

of additional diagnoses. 27 participants were diagnosed with cerebral toxoplasmosis by CSF qPCR. Compared to participants without cerebral toxoplasmosis, abnormal Glasgow coma score (p=0.05), unilateral focal motor signs (p=0.01), positive Babinski (p=0.01), and multiple intracranial lesions on head computed tomography (CT) (p=0.002) were associated with cerebral toxoplasmosis. mNGS identified 7 cases of cerebral toxoplasmosis, 7 cases of cryptococcal meningitis, and other possible cases of TB(n=5), hepatitis B (n=1), and pegivirus (n=1). CSF mNGS had a positive percent agreement of 71% and a negative percent agreement of 91% with qPCR for T. gondii. An infection was definitively diagnosed by any method for only 35% of participants, demonstrating the challenges of diagnosing neurological opportunistic infections in this population and highlighting the need for broader, more sensitive diagnostic tests for CNS infections.

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RISK FACTORS FOR MOTHER-TO-CHILD TRANSMISSION OF TRYPANOSOMA CRUZI AND HEPATITIS B IN THE CROSS-BORDER AREA OF ARGENTINA AND PARAGUAY

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Mother-to-child transmission (MTCT) of Trypanosoma cruzi and hepatitis B virus (HBV) contribute to increased morbidity and disability in Latin America and the Caribbean region. The framework for eliminating MTCT of HIV, syphilis, hepatitis B, and Chagas (EMTCT Plus) has been implemented in the region since 2018 by Mundo Sano in collaboration with several private-public institutions. This study aims to: (i) identify the risk factors for MTCT of T. cruzi and HBV; and (ii) evaluate the effectiveness of the implementation of the framework in the cross-border area of Argentina and Paraguay. Data on T. cruzi and HBV infection among pregnant women and their infants was collected from the antenatal care registries during June 2018 to December 2022. MTCT rates and access to the screening were examined. Bivariate and multivariate analyses were used to explore associations between the infections and socio-demographic factors. Additionally, we conducted 34 Key Informant Interviews (KIIs) for both implementers and service recipients to identify barriers to and promoters for access to screening and treatment of these infections. Finally, we integrated the quantitative and qualitative data using the Consolidated Framework for Implementation Research (CFIR) to evaluate the effectiveness of the intervention. Our preliminary results show approximately 1,493 mothers accessed antenatal care screening for these two infections. The prevalence of T. cruzi among mothers and newborns was estimated at 6.36% (CI95% 5.12-7.60) and 15.9% (CI95%: 1.90-45.44), respectively. However, the screening coverage for newborns who born to the T. cruzi seropositive mothers was only 57.0%. Treatment coverage for newborns was 100%, but post-partum treatment coverage among mothers was only 35.8%. Potential identified barriers were geographical distance to health care services, cultural beliefs, and lack of knowledge about the diseases in the communities. Our findings will be shared with high-level policymakers in the two countries and may be used to improve the implementation of T.cruzi and HBV programs in the region.

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ETIOLOGY, GAPS, AND CHALLENGES IN THE DIAGNOSIS AND MANAGEMENT OF SEPSIS AMONG UNDER-FIVES ENROLLED IN THE KENYA CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE NETWORK (CHAMPS) PROGRAM

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Sepsis remains the third leading cause of death in children under five years globally, despite reduced mortality through improved treatment. Diagnosis and clinical management continue to pose a challenge in developing countries. Child Health and Mortality Prevention Surveillance (CHAMPS) is a multi-country surveillance program that systematically identifies causes of under-five mortality from defined catchment areas in seven countries in sub-Saharan Africa and South Asia. Here, we describe the etiology, gaps and challenges in diagnosis and treatment of sepsis in children under 5 years of age enrolled in CHAMPS-Kenya. Causes of death (COD) were determined by a panel of experts using data from post-mortem investigations conducted using minimally invasive tissue specimen testing, clinical records, and verbal autopsy. Between May 2017 and Dec 2022, 697 children below 5 years had their COD determined. Of these, (132) had sepsis in the causal chain leading to death. Of those, 53 (40.2%) were community-based deaths and 48(36.4%) were neonates, 50 (37.9%) were infants, 32 (24.2%) were children above one year of age and 2(1.5%) were stillbirths. The main causative agents of sepsis were Klebsiella pneumonae (42, 34.1%), Escherichia coli (22, 17.9%) and Streptococcus pneumonae (17, 13.8%) respectively while 32 (24.2%) cases had multi pathogen sepsis. One third of hospitalized cases died within the first 24 hours admission; admission diagnoses included shock, severe dehydration, and severe gastroenteritis in 40% of cases. Ninety-five percent of hospitalized cases were not diagnosed with sepsis before death. Blood chemistries were performed in 30% of all hospitalized cases, but none of the cases had peripheral blood cultures or blood gases performed. Sepsis is common among CHAMPS cases in Kenya, with significant antemortem disparities in diagnosis and clinical management of identified cases. Given the complexity of sepsis diagnosis, especially in under-five, maternal health education on danger signs, a high index of clinical suspicion, and training on optimal clinical management could reduce sepsis-related deaths.

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GENOMIC CHARACTERIZATION OF EXTRAINTESTINAL PATHOGENIC ESCHERICHIA COLI ISOLATED FROM STILLBIRTHS AND EARLY NEONATAL DEATHS: AN OBSERVATION FROM CHAMPS BANGLADESH

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Extraintestinal pathogenic Escherichia coli (ExPEC) are non-diarrheagenic E. coli (EC) known to cause urinary tract infection, sepsis and neonatal meningitis. Presence of specific virulence genes aids to this characterization. Here we aim to use whole genome sequencing (WGS) to characterize ExPEC isolated from postmortem blood collected from stillbirths and neonates enrolled in the Child Health and Mortality Prevention Surveillance (CHAMPS) project in Bangladesh. CHAMPS uses laboratory diagnosis, clinical, demographic and epidemiological data to determine the causes of stillbirths and under-5 deaths. From Aug 2017 to Dec 2021, blood culture data from 357 post-mortem stillbirths (n = 173) and neonates (n = 184) were analyzed. WGS was performed and analyzed for sequence typing, virulence and antimicrobial resistance genes. EC was detected from

3.9% (14/357) cases including macerated stillbirths (n = 10) and neonates (n = 4). EC was not attributed to be in the causal chain after review by a panel of experts. However, WGS identified ExPEC associated virulence genes from half (7/14) of the EC isolates (5 stillbirths and 2 neonates). All ExPEC isolates belong to different sequence type and serotype. Six (6/7) ExPECs were closely related to uropathogenic EC and harbored virulence genes such as P fimbriae (papA, papC), S fimbriae (sfaD, sfaS), K1 capsule (kpsMII, neuC), cytotoxic necrotizing factor (cnf-1), as well as different siderophore systems (fyuA, iroN) and toxins (clbB, tcpC) which help ExPECs to colonize and infect organs other than the gastrointestinal tract of the fetus. Genomic investigation identified 5 of these ExPECs as multi drug resistant and also extended-spectrum β-lactamase (ESBL)-producers (carrying blaCTX-M-15). However, these were sensitive to carbapenem antibiotics. Presence of virulence features and close relatedness to uropathogenic EC indicated the potential that these organisms were transmitted from mother to the fetus, resulting in negative outcomes. Diagnosis of symptomatic or asymptomatic urinary tract infection in pregnant women may reduce the chance of mother to child transmission of ExPECs.

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URECA-LAMP: RAPID, CHEAP AND EFFECTIVE POINT-OF-CARE SCREENING OF CEPHALOSPORIN AND CARBAPENEM RESISTANCE FOR LOW MIDDLE-INCOME COUNTRIES

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Gram-negative bacteria are common causative agents of urinary tract infections (UTIs) worlwide. These bacteria frequently carry genes encoding extended-spectrum beta-lactamases (ESBL) and/or carbapenemases. UTI-screening for these genes with point-of-care testing (POCT) can aid in guiding empirical treatment and reduce antimicrobial resistance (AMR). The novel Urine ESBL and Carbapenemase (URECA) panel is a 7-tube strip. Each well contains primers to detect ESBLs CTX-M-1-group and CTX-M-9-group and carbapenemases OXA-23, OXA-48-like, OXA-50, NDM and VIM. The White Lotus is a novel LAMP-POCT device manufactured by our group. It is portable, battery-operated, low cost and smart phone operable. The aim of this study was to validate the URECA-LAMP panel for rapid screening of ESBL- and carbapenemase-producing bacteria. To this end, a sample set of 70 bacterial strains (10 positive controls per target) was obtained from the well-defined SMART and INFORM bacterial collections. Previous WGS characterization of the strains was used as gold-standard for comparison against URECA-LAMP results. DNA template was prepared by boiling a single bacterial colony from each sample in 0.5 mL of nuclease-free water for 10 minutes. 20 uL of boiled sample was added to each of the wells in URECA panel. 2.5 uL of hydroxy naphthol blue was added to each well for visual detection. Positive results were defined as fluorescence-emitting tubes under blue-led light. After screening the complete sample set, comparison between URECA-LAMP and previous WGS results showed 100% agreement of positive and negative results for each gene. We conclude URECA-LAMP is suitable for detection of ESBLs/carbapenemases in bacteria from UTIs. Our results indicate its feasibility for POC screening of human urine specimens. The lower production cost of the White Lotus instrument makes URECA-LAMP attractive for implementation in low middle-income countries.

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DEVELOPMENT OF A KLEBSIELLA PNEUMONIAE NEONATAL SEPSIS MOUSE MODEL TO EVALUATE VACCINES

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Klebsiella pneumoniae is a major cause of neonatal sepsis in low-to-middle income countries. With the proportion of multidrug-resistant K. pneumoniae strains increasing globally and the lack of novel antibiotics in the pipeline, vaccination to prevent these infections is an attractive strategy. Several K. pneumoniae vaccines are currently in development, however, there are no animal models of K. pneumoniae-related neonatal sepsis that could be used to evaluate vaccine efficacy. Our goal is to identify a model which produces a 50% lethal dose (LD50) of ~106 CFU of 2- to 3-day-old animals and which shows an age-dependent susceptibility to infection. We have previously evaluated species (mice vs. rats), 3 mouse strains, 3 routes of infection, and 5 K. pneumoniae strains. We found that peroral (PO) infection of 2- to 3-day-old C57BL/6 mice with K. pneumoniae B5055 produced mortality. Here we describe characterization of this model in terms of the LD50 and age-dependent susceptibility to infection. We determined the PO LD50 of K. pneumoniae B5055 to be 8.5 x 106 CFU in 2-day-old C57BL/6 mice. We also tested PO infection with 108 CFU and 109 CFU, demonstrating these inocula could reliably produce 77-100% mortality in 2- to 3-day-old C57BL/6 mice (n = 4 litters of 5-9 mice per litter; 109 CFU: 3.1% ± 6.3% survival, mean ± standard deviation; 108 CFU: 23.5% ± 22.3% survival). Furthermore, C57BL/6 mice demonstrated an age-dependent susceptibility to infection, where 2- and 5-day-old pups exhibited 100% (7/7) and 50% (4/8) mortality following PO exposure to K. pneumoniae B5055, respectively. K. pneumoniae was found in the blood, spleen, liver, and intestines of infected neonates. In contrast, 30- and 60-day-old C57BL/6 mice exhibited low susceptibility to infection with K. pneumoniae B5055 administered PO (1/10 and 1/10, respectively) and low bacterial colonization (1/10 and 0/10, respectively). We are currently evaluating 7-, 10- and 15-day-old mice. In conclusion, we have developed a neonatal sepsis model which consists of PO infection of neonatal C57BL/6 mice with K. pneumoniae B5055. We continue to characterize this model.

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FIRST REPORT OF OXA-181-PRODUCING ENTEROBACTERALES IN LATIN AMERICA

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Carbapenemase-producing Enterobacteriaceae (CPE) infections are a growing threat contributing to the global burden of antimicrobial resistance (AMR). Although carbapenemase enzymes KPC, NDM and IMP are the most common enzymes worldwide, β-lactamase type OXA-48-like(oxacillinases) are on the rise. The blaOXA-181(a variant of OXA-48) enzymes show a high level of hydrolytic activity against penicillins and a low level of hydrolysis of carbapenems, with a strong preference for imipenem, which is challenging for laboratory diagnosis and may misguide treatment strategies. CPE blaOXA-181 has been reported in human, animal and environmental samples, but has not yet been reported in Latin America. We characterized five CPE clinical isolates from two healthcare facilities in Lima, Peru. The isolates were identified as Klebsiella pneumoniae (n=3),

Citrobacter portucalensis, and Escherichia coli, all presenting multidrug-resistant phenotypes. Illumina sequencing revealed the presence of the blaOXA-181 gene as the only carbapenemase in all isolates. Genes associated with resistance to aminoglycosides, quinolones, amphenicols, fosfomycins, macrolides, tetracyclines, sulfonamides, and trimethoprim were also found.The plasmid group IncX3 was identified in all genomes in a truncated Tn6361 transposon flanked by ΔIS26 insertion sequences. The qnrS1 gene was found downstream of blaOXA-181, conferring fluoroquinolone resistance to all isolates. The emergence of blaOXA-181 in association with the qnrS1 gene in IncX3-type plasmids may represent the primary vector for the spread of blaOXA-181 in Latin America. Genomic surveillance of atypical AMR patterns in clinical and non-clinical isolates is needed to elucidate the transmission of this CPE genotype, as routine clinical laboratory diagnoses fail to detect these new OXA variants.

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THE RELATIONSHIP BETWEEN CO-MORBID MALNUTRITION AND DIARRHEAL ILLNESS AMONG HOSPITALIZED TANZANIAN CHILDREN UNDER FIVE YEARS OF AGE

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There is a bidirectional association between malnutrition and diarrheal illness wherein malnutrition increases the risk, frequency, and duration of diarrhea while diarrhea further exacerbates malnutrition through nutrient depletion. We analyzed preliminary data on 120 (females: n=47, 39.1%; mean age: 14 ± 10 months) children enrolled in the Diarrhea Etiology and Malnutrition study who were hospitalized with diarrhea at Haydom Lutheran Hospital in Haydom, Tanzania from July 2022 to February 2023. There were 25 (20.8%) severe/moderate malnourished children based on doctor report. An infectious etiology was identified for 70/94 (74.5%) children infected (Ct < 30) with at least one of the top 10 pathogenic causes of diarrhea found in the MAL-ED study (n=28 bacterial and viral, n=22 bacterial, n=19 viral, n=1 parasitic). Log binomial and linear regression analyses adjusted for sex were used to determine the relationship between malnutrition and diarrhea etiology, length of stay (LOS), and respiratory illnesses. There were no associations between malnutrition and identification of an infectious etiology of diarrhea (RR: 0.87; 95% CI: 0.63, 1.21). Children with malnutrition were not more likely to have a bacterial etiology (RR: 0.97, 95% CI: 0.61, 1.53) or viral etiology (RR: 0.51, 95% CI: 0.25, 1.03). Malnourished children with diarrheal illness had significantly longer hospital stays (LOS difference: 8.23 days; 95% CI: 5.26-11.19 days) than children who were not malnourished. No differences in LOS between bacterial and non-bacterial diarrhea were observed (LOS difference: 0.93 days; 95% CI: -2.33, 4.19). Malnourished children were more likely to have co-morbid respiratory symptoms (RR: 1.47; 95% CI: 0.89, 2.46) compared to children who were not malnourished. In conclusion, although malnourished children were not at greater risk for specific diarrhea etiologies, they were more likely to have longer hospitalizations. These data suggest malnutrition may contribute to poor outcomes of hospitalized diarrhea independent of diarrhea etiology.

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ETIOPATHOLOGY OF STUNTING: INFANT GUT CHARACTERIZATION AND MICROBIAL INFLUX ROUTES IN A MOTHER-INFANT COHORT IN CENTRAL-AFRICA

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Background : Environmental enteric dysfunction (EED) is an enigmatic disease of the small intestine intimately associated with child undernutrition, a pressing global health problem with over 149 million children affected globally. The etiopathology of EDD has remained elusive for decades. Recent evidence showed that stunting was associated with small intestinal bacterial overgrowth dominated by bacteria that normally reside in the oropharyngeal cavity in children 2-5 years. However, evidence is limited on how the oropharyngeal cavity and the gut are colonized in the stages preceding the appearance of stunting in a context of a high burden of stunting and a highly microbial polluted environment. Methods : We followed a cohort of 50 infants from birth until 6 months of life in Bangui (Central-African Republic). We performed metagenomic analyses of oral and stool microbiota at birth, and at 1, 4, 11, 18, and 25 weeks. We also analyzed breastmilk microbiota starting at 1 week. We gathered complete socio-economic and clinical data, anthropometric measures and 24-hour recalls and food-consumption questionnaires for diet assessment at each visit. Results : Stunting was significantly associated with stool microbiota of the infants at 6 months (P value of the Permanova = 0.04). The relative abundance of Rothia SGB16985, Streptococcus parasanguinis, and Veillonella dispar was significantly higher among non-stunted infants in both oral and stool samples. Even if there were no significant differences in the breastmilk microbiota depending on stunting status of the infant, 6/10 of the species with the highest relative abundance in breastmilk (Rothia SGB16985, Streptococcus thermophilus, Streptococcus peroris, Streptococcus pneumoniae, Staphylococcus hominis, and Streptococcus salivarius) were significantly associated with stunting in oral and stool samples. Conclusion : The ectopic colonization of oral bacteria in the gut occured also in the absence of stunting. The role of the breastmilk microbiota should be further investigated in the context of stunting and a highly microbial polluted environment.

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DISCOVERY OF A SMALL MOLECULE THAT MIMICS A UNIQUE ZIKA-NEUTRALIZING EPITOPE FROM A LARGE LIBRARY OF RANDOM MOLECULAR SHAPES

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Antigenic similarities between Zika virus and other flaviviruses pose challenges to the development of virus-specific diagnostic tools and effective vaccines. We screened a DNA-encoded one-bead-one-compound combinatorial library of 508,032 synthetic, non-natural oligomers, for compounds that mimic ZIKV-specific epitopes. High-throughput FACS-based screening was used to select molecules that bound IgG from ZIKV-immune but not from dengue-immune sera. Deep sequencing of the encoding tags on beads that retained high levels of antibodies to ZIKV-immune serum and clustering analysis of structurally homologous

hits identified 40 candidate molecular structures. A lead candidate small molecule "CZV1-1" was selected that correctly identifies serum specimens from Zika-experienced patients with high sensitivity and specificity (78.9% and 98.9%, respectively). Affinity chromatography using immobilized CZV1-1 resulted in a ≈ 600-fold enrichment of the antibodies from the serum that recognizes this synthetic molecule. Binding assays revealed that these enriched anti-CZV1-1 IgGs recognize the domain III (DIII) of the ZIKV envelope protein and show minimal reactivity to DIII of dengue virus envelope proteins. Binding competition studies of purified anti-CZV1-1 IgG against known ZIKV-specific monoclonal antibodies (mAbs) showed that CZV1-1 mimics a nonlinear neutralizing conformational epitope in DIII of the ZIKV envelope. Purified anti-CZV1-1 IgG neutralized infection of distinct strains of ZIKV in cell cultures with potencies comparable to highly specific ZIKV-neutralizing monoclonal antibodies. Molecular dynamics simulations revealed that anti-CZV1-1 IgG binds to ZV48, a highly specific ZIKV mAb that targets the C- C' loop epitope of ZIKV envelope DIII, with high affinity and displays a higher rate of native contacts, hydrogen bonds, and configurational stability within the binding site with ZV48 than other mAbs. Collectively, our findings reveal that systematic mining of 'antigenically agnostic' libraries of small molecules can be used to discover biomarker correlates of virus neutralization.

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PHARMACOKINETICS, TOLERABILITY AND SAFETY OF FAVIPIRAVIR COMPARED TO RIBAVIRIN FOR THE TREATMENT OF LASSA FEVER: A RANDOMIZED CONTROLLED OPEN LABEL PHASE II CLINICAL TRIAL

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Lassa fever (LF) is a severe re-emerging infectious disease and defined as priority disease for urgent research and development by the World Health Organization. It is caused by the Lassa virus (LV) which belongs to the segmented negative strand RNA viruses of the family Arenaviridae. Transmission occurs primarily by spill-over from the animal reservoir but secondary cases with human to human transmission are common. LF affects a large number of countries in West Africa, with Nigeria carrying the highest case burden in the world. So far, treatment options are limited to supportive care and the antiviral ribavirin. Evidence for the efficacy of ribavirin in LF is, however, poor. A recent study conducted in Nigeria showed that in vivo plasma concentrations do not suffice to exert a relevant antiviral effect. New drugs for LF treatment are therefore urgently needed but no therapeutic trials have been conducted for this indication in the past decades. Favipiravir is a broad-spectrum antiviral registered for pandemic influenza that has previously been evaluated for Ebola virus disease and Covid-19. It has potent activity against LV in pre-clinical studies. The aim of this phase II clinical trial was to explore the pharmacokinetics, pharmacodynamics, safety and tolerability of favipiravir as repurposed drug in the treatment of LF. The trial was conducted at the Irrua Specialist Teaching Hospital and the Federal Medical Centre of Owo in Nigeria - the worldwide largest LF treatment centres. Blood samples for pharmacokinetic analyses were collected at 0.5, 1, 3, 5, 8, 12 and 24 hours after the first dose and at 0, 1 and 4 hours after drug administration on day 7. Besides clinical parameters, further sampling for virological, serological and immunological analyses as well as hematology and biochemistry safety was done on days 1, 2, and then every other day until the end of the study. Between 2021 and 2022, 40 LF patients were included in the trial. Trial results on cure rates, pharmacokinetics, safety and tolerability of this first GCP compliant phase II clinical trial will be presented to provide first insights into prospects of this new treatment candidate for LF.

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A BEAD-BASED MULTIPLEX SAMPLE-SPARING ANTIBODY ASSAY FOR DETECTING CURRENT AND PAST DENGUE AND ZIKA VIRUS INFECTIONS

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Serological assays to identify recent or past flavivirus infections are needed for surveillance and predicting the risk of severe disease. The four dengue virus (DENV) serotypes and Zika virus (ZIKV) can co-circulate in the population. Prior immunity to one DENV serotype or ZIKV is a risk factor for severe disease during secondary DENV infection. Detecting viral RNA or non-structural protein during acute infection does not identify all acute infections due to brief viremia. Paired serology using the whole virus antigen is sensitive but lacks specificity to distinguish between DENV and ZIKV infections. To address this, we developed a multiplex immunoassay using beads coupled to DENV1-4 and ZIKV EDIII antigens to detect and distinguish acute and past infections. We tested 204 paired blood samples collected at acute and convalescent stages from febrile patients (2-77 years) during the 2016 Zika (n=30) and the 2018 DENV2 outbreaks (n=174) in León, Nicaragua. We developed an algorithm to detect and distinguish acute infections based on increased of EDIII antibody levels from acute to convalescence. Using EDIII binding pattern to the acute sample and our earlier validated algorithm for detecting past infection, we stratified acute infection by prior exposure. Compared to paired serology using whole viruses, the multiplex assay demonstrated a sensitivity of 90.1% and a specificity of 88.2% for detecting acute infections. Despite DENV and ZIKV background immunity being 85.7%, the multiplex assay correctly classified acute DENV or ZIKV infection for 91.9% and was indiscernible for 8.1% of individuals with >2 past DENV infections. The accuracy among the 14.3% naïve individuals for identifying DENV serotype or ZIKV infection was 100%. By comparison, RT-PCR missed one for every two symptomatic cases tested. Thus, the multiplex EDIII assay is robust, requires a small sample volume, and does not require handling virus to determine acute infection and past exposure to DENV and ZIKV. It offers a significant benefit for surveillance, estimating disease burden, and implementing control measures to reduce DENV and ZIKV transmission.

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DEVELOPMENT AND EVALUATION OF NOVEL NANOBODIES AGAINST ZIKA VIRUS INFECTION

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Zika virus (ZIKV) is a human-pathogenic flavivirus that has raised global concerns in recent years as it caused an unprecedented large-scale epidemic of congenital microcephaly and malformations. While the case number of ZIKV infection has seemingly decreased in the past few years, the actual incidence rate may be largely underestimated and ZIKV remains an important public health threat. Despite the clinical importance of ZIKV, treatment and prophylaxis options remain limited. Over 70 therapeutic anti-ZIKV monoclonal antibodies (mAbs) with moderate to high neutralizing activities have been reported, with some demonstrating antiviral effects in preclinical animal models. However, a major concern of these anti-ZIKV mAbs is the potential to induce antibody-dependent enhancement (ADE) of infection. The possibility of exacerbating disease progression by ADE has limited the clinical application of these anti-ZIKV mAbs. In this study, we constructed a nanobody (single-domain antibody) library by immunizing alpacas (Illama pacos) with recombinant ZIKV proteins and

identified a number of nanobodies with high affinity against ZIKV. Among them, a number of nanobodies targeting the ZIKV envelope (E) protein or nonstructural protein 1 (NS1) demonstrated potent anti-ZIKV activity in vitro in viral load reduction, plaque reduction, and cytopathic effect inhibition assays. Type I interferon receptor-deficient A129 mice treated with a single dose of any one of these nanobodies either as prophylaxis (before virus challenge) or treatment (after virus challenge) demonstrated significantly higher survival rate at 10-14 days post-infection (70-100% vs 0%, P<0.05) and lower viral burden in brain tissues. Importantly, ADE assay showed that these nanobodies did not induce ADE. Mechanistically, these nanobodies significantly downregulated interleukin-1-beta in vitro and in mice. Taken together, these results showed that nanobodies are effective antivirals against ZIKV infection without inducing ADE. Clinical trials should be considered to assess the prophylactic and therapeutic effects of anti-ZIKV nanobodies in endemic regions.

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GENERATION OF THERAPEUTIC HUMAN MONOCLONAL ANTIBODIES AGAINST HANTAVIRUSES FROM HUMAN-IMMUNE-SYSTEM HUMANIZED DRAGA MICE

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Hantaviruses are rodent-transmitted viruses that cause Hantavirus Cardiopulmonary Syndrome (HCPS) and Hemorrhagic Fever with Renal Syndrome (HFRS) around the globe. Most hantavirus infections in Asia are caused by Hantaan (HTNV) and Seoul (SEOV), in America by Andes (ANDV) and Sin Nombre (SNV), and in Europe by Puumala (PUUV) and Dobrava-Belgrade (DOBV) virus strains. Collectively, 150,000-200,000 cases of hantavirus disease are reported annually, with a case fatality rate of 12% for HFRS and up to 40% for HCPS. Recent studies in Argentina and Chile reported that the hantavirus strain ANDV can potentially be spread between human through direct and close contact with an infected person. Moreover, the lack of effective vaccines and therapeutics makes hantavirus infections dangerous and raising concern for potential hantavirus pandemics. Humanized DRAGA mice infused with human hematopoietic stem cells from cord blood reconstitute a long-term functional human immune system and demonstrated as a rapid platform for generation of human monoclonal antibodies (hmAbs) against infectious diseases. Here, we primarily describe to identify, characterize and develop therapeutics antibodies against glycoprotein complex (Gn/Gc, M segment) of ANDV from DRAGA mice immunized with DNA-encoding vaccine. Using hybridoma technology, 1026 human B cell hybridoma clones were obtained from splenic human B cells fused with K6H6 myeloma cells. Among them, 63 (6%) hmAb clones showed significant binding affinities for ANDV Gn/Gc protein as determined by ELISA. Nine (14 %) of the ANDV specific hmAbs also showed bind to HTNV Gn/Gc protein; suggesting small pool of generated ANDV-specific hmAbs able to cross-react against two different strains (ANDV & HTNV). Ongoing studies are aimed at immune-characterization, by assessing cross-reactivity and neutralizing activity of these hmAbs with the goal of testing their protective and therapeutic efficacy against different strains of Hantaviruses in animal models. Highly cross-reactive hmAbs have potential as “universal” immunotherapeutics for the prevention of and treatment of hantavirus infections in humans.

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A NON-WHOLE GENOME SEQUENCING APPROACH FOR MONITORING SARS-COV-2 VARIANTS IN BURKINA FASO & KENYA

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The rapid emergence and global dissemination of SARS-CoV-2 highlighted a need for robust, adaptable surveillance systems. However, financial and infrastructure requirements for whole genome sequencing (WGS) mean most surveillance data has come from higher-resource geographies. Consequently, the molecular epidemiology of SARS-CoV-2 in low- and middle-income countries (LMICs) is limited, and there is a need for more cost-accessible technologies in LMICs to help close data gaps in variant surveillance. To address this, we developed a high-resolution melt curve (HRM) method targeting key variant-defining mutations in the SARS-CoV-2 genome, which give unique signature profiles that define different SARS-CoV-2 variants of concern (VOCs). Nasopharyngeal-oropharyngeal swabs from 178 participants (112 in Burkina Faso, 66 in Kenya) on the day of enrolment in the MALCOV (Malaria as a risk factor for COVID-19 in western Kenya and Burkina Faso) cohort study were used in the evaluation of the HRM assay and compared to WGS. A SARS-CoV-2 variant could be determined by both HRM and WGS for 74.7% of specimens. Overall, eleven distinct genotypes of SARS-CoV-2 were identified among Burkinabè and Kenyan cohorts, with Delta VOC most frequently detected. Additionally, the 19A strain, VOCs Alpha and Omicron, and other non-VOCs, including Eta, and those belonging to 19B, 20A, 20B, and 20E were detected, as was evidence of recombinant genomes. The sensitivity and specificity of the HRM assay compared to WGS were 100% and 94.6-100%, respectively, but varied by VOC. HRM-based assays can provide a lower-cost approach (<$1 per test) to conducting molecular epidemiology as part of wider surveillance strategies, particularly in settings where access to WGS is absent or limited. The HRM assay can be implemented on most modern real-time PCR instruments, which are already be available in most diagnostic facilities. Such assays can often be implemented with little capital investment. Additionally, the assay is readily adaptable and can focus on local epidemiological surveillance needs or be updated quickly to accommodate the emergence of a novel variant.

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DETECTION OF BLOOD BIOMARKERS OF NEUROLOGICAL INJURY IN HUMAN CASES OF VIRAL ENCEPHALITIS AND SEVERE DISEASE

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Neurotropic viral infection and the ensuant immune response are a significant cause of morbidity and mortality worldwide, which can range in severity from mild to permanent central nervous system (CNS) damage and death. Encephalitic alphaviruses of military and public health concern include Venezuelan and eastern equine encephalitis viruses (VEEV and EEEV) and Madariaga virus (MADV; Alphavirus; Togaviridae), which are mosquito-borne viruses in the Americas that cause CNS disease in humans and equids. Injury to the CNS is an important determinant of poor outcome

and tools to predict this outcome are lacking. Glial fibrillary acidic protein (GFAP) and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) are proteins that when detected in the serum, signal astrocyte and neuronal injury, respectively. These biomarkers of CNS tissue injury could serve to better assess injury severity, monitor disease progression, direct treatment, and as reliable endpoints to help develop novel medical countermeasures. Recent advances in the use of blood-based biomarkers for diagnosis of traumatic brain injury (TBI) which have FDA approved assays have provided a scientific foundation for expanding the biomarker technology to brain damage caused by other CNS pathologies like viral encephalitis. Here we evaluated the ability to detect these biomarkers in the serum from multiple human cohorts with evidence of viral encephalitis or severe disease. Samples were collected from: 1) human cases infected with the alphaviruses VEEV subtype ID or MADV in Panama; 2) human cases of suspected sepsis in Cambodia and Ghana that were severely ill or diagnosed with encephalitis of unknown origin; 3) hospitalized patients with severe coronavirus disease (COVID-19). We found higher levels of GFAP and/or UCH-L1 in all cohorts and in some cases detection of these biomarkers could predict later developing cognitive impairment. Collectively, our results suggest that the detection of these blood-based biomarkers with an already FDA approved assay may be a good indicator for brain injury resulting from viral or other infections causing severe disease.

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PATTERNS OF SARS-COV-2 ACTIVE INFECTIONS AMONG HUMANS AND COHABITATING DOMESTIC ANIMALS OF EAST CENTRAL TEXAS DURING THE EARLY OMICRON WAVE

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Given that SARS-CoV-2 is now known to infect a wide range of mammals, sustained animal surveillance is a critical tool to help protect public health and support early detection on emerging mutations and variants. We conducted a longitudinal One Health study in 47 households with active human COVID-19 cases in east central Texas during January-July 2022. We evaluated people (n=104; range 1-7 per house) and animals (n=101; 1-12 per house), by RT-qPCR, for the presence of SARS-CoV-2 at three sequential sampling points, each 1-2 weeks apart, with the first visit occurring 0-5 days from detection of the first person with COVID-19. Our study spanned the peak of the BA.1 Omicron wave to the BA.2/BA.5 wave. Household animals were predominantly dogs (n=57) and cats (n=29) but also included goats, horses, pigs, a donkey, a rabbit, a gecko and a tortoise (n=14). People tested positive (64%) by PCR in all but 4 houses. Positivity was highest (60%) in the first sampling than the second (48.5%) and third (20.4%). Serology from dried blood spots revealed antibodies against the spike glycoprotein in 95.7% of the people, indicating either vaccination or natural exposure. Only 5.3% (3/57) of dogs tested PCR-positive, including one with a PCR-positive food bowl, at days 2-9 after diagnosis of the first person in the household. All other animals were negative. Sequencing revealed the BA.2 Omicron in one dog. Positivity among dogs was similar to our prior, pre-Omicron study (n = 396; 6.3%; $\chi 2$, $P > 0.5$) but was higher among cats pre-Omicron (n = 158; 15.2%; $P < 0.05$) despite efforts toward early and multiple sampling in this study. Our longitudinal study found no evidence of onward transmission from the three infected dogs, as no infections were detected in coinhabiting animals at subsequent sampling points. Our results show that fewer animals became infected with Omicron despite its higher transmissibility among humans, suggesting that each variant may interact differently with animals in terms of susceptibility and transmissibility. These differences among variants emphasize the need for continued active surveillance in animal populations.

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REAL-TIME DATA COLLECTION FOR EFFICIENT MICROPLANNING AND MONITORING OF NATIONAL DOG RABIES VACCINATION IN BANGLADESH

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Rabies, the world's deadliest disease with 100% fatality, creates significant public health difficulties in the world's poorest regions. Bangladesh, has the third highest number of human deaths (2000-2500 annually) among all rabies endemic countries. The country's goal was to reduce the number of rabies cases by 90% by 2015 and to eliminate the disease entirely by 2030. The main approach to achieve this goal was to vaccinate dogs which initiated a mass dog vaccination program aiming to deliver 3 rounds vaccination across the country. To do this, microplanning was applied to reach every community to maximize vaccination coverage. For efficient monitoring and microplanning, KoboToolbox was used to collect real-time data of vaccinated dogs. Aggregated daily dog vaccination data were collected on paper forms since 2012 and from 2018 this was converted to electronic data collection using KoboCollect where at the first part, dog vaccination was reported daily in aggregation and later at individual level in the same year with geolocation and photos. From 2018 to 2022, information on 1.6 million dogs was collected with 58.6% data containing the geo-locational data of dogs and 41.3% had no geo-locational data. Average vaccinated dog coverage was 81.6% covering the whole country. Correlation between reported rabies cases and vaccination coverage from 2012 to 2022 including aggregated and individual level gave a coefficient of -0.769 which demonstrates the effectiveness of the program. The shift from aggregate to individual level helped in improving vaccine delivery in progressive rounds as the increasingly granular data was used to identify locations with lower coverage, thus improving possible planning for future rounds to ensure maximum vaccination coverage. Although the system is easy to run and maintain but still there are data with no geo-location. To address this additional training and improved technical support are needed to maximize data completeness for optimal geo-enabled microplanning.

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GENETIC ADAPTATION OF NONTYPHOIDAL SALMONELLA IN HUMANS, ANIMALS AND IN THE ENVIRONMENT-ANTHROPONOTIC TRANSMISSION?

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Nontyphoidal Salmonella (NTS) causes more than 1.2 million annual deaths worldwide, the majority in resource-limited countries such as sub-Saharan Africa (SSA). NTS have also become increasingly resistant to antibiotics and are the most frequent cause of bacteraemia in SSA. Recent data suggests that this typically livestock- associated pathogen has genetically developed and adapted to different hosts and environments, proposing anthroponotic transmission. Within this study, we collected Salmonella from humans (stool and blood), animals and the environment (dust and soil), in Tanzania and in Ghana. Strains were identified by biochemical methods and confirmed using the VITEK 2 System. Serotyping and antibiotic susceptibility testing was performed. Further, isolates were subjected to sequencing using a

NextSeq 500 Illumina machine.9,099 samples were collected. From these, 222 NTS were identified comprising 58 serovars. The highest level of resistance was in humans with fluroquinolone resistance on the increase and multidrug resistance (MDR) highest in isolates from blood cultures (24%, n/N=11/46). Of the invasive strains, MLST analysis confirmed the serovars and sequence types S. Typhimurium (ST313/ST19) being most common followed by S. Enteritidis (ST11/ST1479) and S. Dublin (ST10). A sequence type overlap amongst humans and livestock or environmental strains was detected for ST19.Our study demonstrates a broad serovar distribution of Salmonella from livestock and the environment not typically associated with human infections. The substantially high level of MDR and emerging fluoroquinolone resistance seen in the invasive NTS poses a challenge to current treatment strategies. Interestingly, we found ST19 more common in invasive human disease but also prevalent in samples from livestock compared to ST313, only seen in human samples. These findings are not in line with previous results, mainly from East Africa where ST313 was identified as the dominant sequence type in disseminated human disease, strongly indicating anthroponotic transmission of ST313 but not of ST19 in SSA.

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MOLECULAR AND SEROLOGICAL EVIDENCE OF CRIMEAN-CONGO HEMORRHAGIC FEVER VIRUS IN LIVESTOCK AND TICKS IN CAMEROON

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Crimean-Congo haemorrhagic fever (CCHF) is a widespread tick-borne zoonotic disease, responsible of haemorrhagic symptoms in humans, with a reported case fatality rate of up to 40%. This disease is caused by Crimean-Congo haemorrhagic fever orthonairovirus (CCHFV). Little is known about the occurrence of CCHFV in ticks and animals in Cameroon. Hence this study aimed to determine the prevalence of CCHFV in domestic ruminants and identify its potential tick vector in Cameroon. A cross-sectional study was carried out in two livestock markets of Yaoundé in 2019, 2020, and 2021. Blood and ticks were collected from cattle, sheep, and goats. Anti-CCHFV specific antibodies were detected in plasma using a commercial double antigen Enzyme-Linked Immunosorbent Assay (DA-ELISA) assay. DA-ELISA- positive and a subset of negative samples were further tested by a seroneutralization assay for confirmation. Ticks were screened for the presence of orthonairoviruses by amplification of a fragment of the L segment and the genetic evolution of the virus was inferred by maximum likelihood. Overall, 756 plasma samples were collected from 441 cattle, 168 goats, and 147 sheep. The seroprevalence of anti-CCHFV antibody was 61.77% for all animals, with the highest rate in cattle (433/441, 98.18%) followed by sheep (23/147, 15.65%), and goats (11/168, 6.55%), (p-value < 0.0001). The highest seroprevalence rate was found in cattle from the Sahelian region of Cameroon (100%). Overall, 1500 ticks of the Rhipicephalus (773/1500, 51.53%), Amblyomma (341/1500, 22.73%), and Hyalomma (386/1500, 25.73%) genera were screened. CCHFV was identified in one Hyalomma truncatum pool collected from cattle. Phylogenetic analysis of the L segment classified this CCHFV strain within the African genotype III. These findings undoubtedly demonstrate for the very first time the circulation of CCHFV in Cameroon with the identification of genotype III. The results also highlight the necessity for more studies on CCHFV using a One Health approach and targeting at-risk human and animal populations, as well as ticks in high-risk areas of the country.

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MOLECULAR CHARACTERIZATION OF EXTENDED - SPECTRUM BETA - LACTAMASE PRODUCING KLEBSIELLA PNEUMONIAE AMONG CHILDREN AND LIVESTOCK IN RURAL KOROGWE, TANZANIA

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Extended-spectrum beta lactamase- (ESBL) producing Klebsiella spp. are a global concern, and are on the increase, worldwide. This is mainly attributed to the overuse of antibiotics not only in human medicine but also in animal farming, also in Tanzania. Studies have been conducted on the prevalence of ESBL in children in Tanzania, but few studies have examined Klebsiella in livestock as a possible transmission reservoir. Using a one-health approach, this study investigated the frequency of ESBL-KP and antibiotic resistance in humans and livestock in rural Tanzania. This cross-sectional study was conducted from February 2019 to July 2020 and enrolled study participants at the outpatient department of Magunga Hospital (Korogwe). Stool samples were collected from children aged five and younger with and without diarrhea. Faecal specimens from livestock were sampled at commercial farms or smallscale farms in communities within the Korogwe District. Strains were identified using a chromogenic agar and confirmed using the VITEK2 Compact System. Antimicrobial susceptibility testing was performed by disc diffusion, and isolates subjected to whole genome sequencing using the NextSeQ500 Illumina machine. Of 258 asymptomatic and 259 children with diarrhoea, 16 (6%) and 32 (12%) tested positive for ESBL-KP, respectively. Furthermore, ESBL-KP was detected in 54 (7%) samples from chicken, one (3%) sample from pigs, and one (4%) sample from goats. All isolates were resistant to beta-lactams and cepholosporins and susceptible to carbapenems and tetracyclines. Whole genome analysis revealed ST17 to be the most common sequence type, and phylogenetic analysis revealed thirteen very closely related human and livestock isolate clusters. The results demonstrate the presence of ESBL-KP in human and chicken populations with ESBL-KP being closely related in the two reservoirs under investigation. Livestock represent a potential reservoir for transmission of ESBL-KP to humans. It is therefore essential to implement measures using a one health approach in order to control the spread and transmission of this pathogen.

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RECONSTRUCTING RODENT CONTACT NETWORKS FROM TRAPPING DATA TO UNDERSTAND LASSA FEVER TRANSMISSION NETWORKS

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Lassa fever (caused by Lassa mammarenavirus) is a zoonotic infectious disease endemic to West Africa. Outbreaks of rodent-to-human infections are regularly reported from Nigeria, Sierra Leone and Liberia with sporadic outbreaks reported from elsewhere in the region. The primary rodent reservoir of this pathogen is Mastomys natalensis although evidence of infection has been identified in eleven other rodent species across

the region. The role of these other rodent species in the maintenance and transmission of viral populations among rodent communities is not understood. It is likely the spatially heterogeneous outbreaks of Lassa fever observed in human populations are indicative of complex viral and host population dynamics among rodent communities. Here we use rodent trapping data and rodent serology from a two year study in a Lassa fever endemic region of Sierra Leone, comprising more than 40,000 trap nights and 650 rodent detections to describe rodent communities across landuse gradients and to reconstruct rodent contact networks that will determine viral transmission. We find that rodent communities are structured along gradients of anthropogenic landuse disturbance moderating the hazard of exposure to reservoir species'. We further find that the primary reservoir of Lassa fever displays differential inter- and intra-specific contact rates across these landuse types which will affect the potential of viral persistance in these communities. These findings are important for understanding the dynamic risk of pathogen spillover in human communities. Findings from this study can guide future One Health focussed interventions and are of particular interest when conducting research attempting to assess the prevalence of Lassa fever and risk of spillover.

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HEALTHY CHILDREN, HEALTHY CHIMPS: A RESEARCH-PRACTICE PARTNERSHIP FOR REDUCING RESPIRATORY DISEASE TRANSMISSION FROM HUMANS TO CHIMPANZEES IN UGANDA

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Respiratory disease is a major cause of morbidity and mortality among people in the developing world and also threatens great apes across Sub-Saharan Africa. Our studies of wild chimpanzees in Kibale National Park, Uganda, have identified the causative agents of respiratory disease outbreaks as "common cold" pediatric human pathogens, but reverse zoonotic transmission pathways have remained unclear. Between May 2019 and July 2022, we collected approximately 2,000 paired respiratory symptoms surveys and nasopharyngeal swabs from 264 people (local children and forest workers) and over 700 fecal samples from 141 chimpanzees as part of a prospective cohort study. We characterized respiratory pathogens using a multiplex PCR panel and metagenomic DNA sequencing and examined the transmission risk of various pathogen types, seasons, social factors, and the individual characteristics of humans and chimpanzees. Children exhibited high incidence rates and symptom severities, whereas adults were largely asymptomatic. COVID-19 lockdown in 2020-2021 significantly decreased respiratory disease incidence. Human symptoms peaked in February. In chimpanzees, the most common month for respiratory disease outbreaks was March. Rhinovirus, which caused a 2013 outbreak that killed 10% of chimpanzees in a Kibale community, was the most prevalent human pathogen throughout the study. Rhinovirus was also most prevalent during February and was the pathogen most likely to be carried asymptomatically by people. Our data suggest that respiratory pathogens circulate in children living near Kibale, and that adults in the same communities become asymptomatically infected and may carry the pathogens into the forest and infect chimpanzees. The "Healthy Children, Healthy Chimps" program reflects our hope that reverse zoonotic disease transmission to chimpanzees can be mitigated through a One Health approach that considers the health of chimpanzees and local people to be linked.

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ASSESSING SHIFTS IN BITING PATTERNS OF ANOPHELES GAMBIAE AND AN. FUNESTUS, THE MAJOR MALARIA VECTORS IN SOUTHEASTERN TANZANIA

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Long-lasting Insecticidal Nets (LLINs) and Indoor Residual Spraying (IRS) are key vector control strategies in malaria control initiatives in Africa, including Tanzania. However, the prolonged use of LLINs and IRS has led to mosquitoes developing physiological and behavioral resilience to insecticides, resulting in increased residual malaria transmission that threatens malaria elimination efforts. To assess how mosquito-biting behavior changes could impact malaria epidemiology in Tanzania's southeastern area, a study was conducted using the mosquito electric trap (MET), collecting Anopheles mosquitoes weekly (18:00 - 06:00) from 22 villages from November 2019 to September 2020 in the Rufiji, Kilwa, and Kibiti districts. For each house, two METs were employed; one trap was set inside the house and the other was positioned 15 meters away outside the house. Each trap included a volunteer. A total of 3,586 An. mosquitoes were collected, 1,912 (53.32%) An. gambiae, 1,666 (46.46%) An. funestus, 7 (0.2%) An. coustan, and 1 (0.03%) An. pharoensis. An. gambiae exhibited a greater preference for outdoor biting, at a rate of 0.32 bites per person per hour during 20:00-21:00hr, increasing progressively through the night to reach a peak of 0.48 bites per person per hour during 00:00-01:00hr, while An. funestus showed a higher preference for indoor biting at a rate of 0.35 bites per person per hour indoors and 0.29 bites per person per hour outdoors. This study revealed, for the first time, that An. gambiae density is higher outdoors than indoors in southeastern Tanzania's Kibiti, Rufiji, and Kilwa districts, indicating a behavioral shift of this crucial malaria vector from primarily indoor biting to outdoor biting. These findings highlight the necessity of promptly implementing supplementary interventions to control outdoor biting malaria vectors with the goal of managing residual malaria transmission and ultimately achieving complete elimination.

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THE ROLE OF SEROTONIN IN MOSQUITO SWARMING AND AUDITORY PERCEPTION OF MATES

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Mating is an important aspect of vector biology and is crucial for current control strategies, such as SIT and Gene Drive. It also represents a target for novel control tools. Anopheles mosquitoes mate in swarms at dusk. Within these noisy swarms, males locate females by listening for their wingbeat frequency. However, the molecular underpinning of this process is poorly understood, and greater insight could benefit vector biology and even identify new targets for vector control. We are investigating the contribution biogenic amines to the regulation of this behaviour. One such amine, serotonin, has many well documented roles, for example in human depression. However, serotonergic neurotransmission isn't unique to humans and is found throughout the animal kingdom, particularly in efferent signalling systems, where signals are carried away from the central nervous system to tune peripheral effectors. Mosquitoes have highly complex hearing and are the only documented insect with an auditory efferent system. Our research suggests that this efferent input modulates both swarming itself, and hearing within the swarm. We have found that levels of serotonin show distinct periodic cycles, peaking around dusk. By chemically altering serotonin levels, we see changes in dusk-associated activity - a central feature of mosquito swarming. Furthermore, 3/6 serotonin receptors identified in A. gambiae are highly expressed in the male ear. All three are

G-protein-coupled receptors - highly “druggable” pharmacological targets. Using CRISPR, we have disrupted these vector control targets, and begun characterising their role in audition, swarming, and ultimately reproduction. Initial results show at least two have male-mating phenotypes. We are currently investigating the basis of these phenotypes by interrogating mutant phonotactic behaviour (male attraction to female tones) as well as their biophysical and electrophysiological responses. Thus, in addition to its broad role in swarming, we are beginning to understand the molecular underpinnings of serotonergic signalling within the context of hearing and partner-detection inside the swarm.

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A SEMI-FIELD SYSTEM TO DEFINE THE CHEMOSENSORY BASIS OF MALARIA TRANSMISSION AT HIGH DEFINITION

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Heterogeneity in mosquito biting risk is a key factor influencing malaria epidemiology. To gain insight into the chemosensory basis of mosquito attraction towards the scent of some humans versus others in a malaria endemic setting, we developed a large-scale, multi-choice system that quantifies mosquito olfactory preferences under naturalistic semi-field conditions in Zambia. Using infrared video tracking in an expansive flight cage arena, we engineered a high-content mosquito behavioral assay that tracks landing preferences of the African malaria mosquito Anopheles gambiae towards heated targets mimicking human skin temperature that are baited with whole body odor from sleeping humans or other host-related olfactory stimuli. Using this multi-choice system, we determined that An. gambiae prefers to land on heated targets baited with CO2 emissions reflective of a large human over environmental air, body odor from one human over CO2, and the scent of one human over another. When simultaneously presented with a choice between the scent of six humans, we identified individuals at both ends of the attractiveness spectrum who are consistently more or less attractive relative to other humans over replicate nightly trials. Applying integrative whole body volatilomics across these humans, we have identified a panel of airborne compounds including specific volatile carboxylic acids putatively associated with modulating human attractiveness to this prolific malaria vector. The comparative power of this multichoice preference assay may now readily be used to define the chemosensory basis of malaria transmission at high definition.

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IS THE INVASION AND SPREAD OF THE URBAN MALARIA VECTOR ANOPHELES STEPHENSI INTO AND ACROSS AFRICA MEDIATED BY WINDBORNE MIGRATION?

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The invasion of the urban malaria vector Anopheles stephensi into Africa is a serious public-health threat and a challenge to malaria elimination. Whereas malaria in Africa has been primarily a rural problem, the recent establishment and expansion of the invasive urban Asian vector Anopheles stephensi will likely drastically increase the risk in Africa, elevating urban malaria. It is widely believed that this incursion and subsequent spread was mediated by transport on ships, airplanes, and cars. Here, we examine the geographic, genetic, and related data and propose that the invasion and spread of An. stephensi in Africa has been mediated primarily by high-altitude windborne migration. The key evidence supporting windborne invasion and spread include i) the gradual range expansion over serval decades exhibits an unmistakable diffusion process, ii) distribution that does not concentrate near major sea ports, airports, or even main highways, but is correlated with predominant winds, iii) genetic evidence of high diversity that is incompatible with a single introduction such as by a ship and similarity between populations from southern Arabia (Yemen) with those in Africa, and iv) low tolerance of An. stephensi eggs to desiccation limiting their capacity for long travel, but strong capacity of gravid Anopheles females to to be carried by wind for tens or hundreds of kilometers. To our knowledge, no An. stephensi mosquitoes were intercepted on ships or other vehicles, nor in high altitude (>100 m above ground); however, sampling should be carried out to evaluate both possible modes of transport. The possibility of windborne migrations of gravid An. stephensi should be incorporated in surveillance efforts while testing this and the transport of these mosquitoes in human vehicles in tandem. Understanding the contributions of the different mechanisms of spread is critical to mitigating the impact of An. stephensi and other invasive vectors in future.

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VECTOR AND HOST DIVERSITY SHAPE WEST NILE VIRUS TRANSMISSION IN URBAN GREEN SPACES ALONG AN URBAN-RURAL TRANSECT

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Urban green space is associated with a wide range of societal benefits, including for conservation, human well-being, and to mitigate effects of climate change. Relatively little however is known regarding the importance of urban green spaces for West Nile virus transmission dynamics and whether this role changes as one moves further away from the urban core. To elucidate this, we set out traps at 10 sites in the Greater Chicago area that spanned a transect from the heart of the city to the rural edge. Specimens were collected weekly between June and October, identified to species, and pools of Culex pipiens, Cx. restuans, and Cx. salinarius tested for the presence of WNV. The host species from which blood meals were obtained in blood-fed females was determined through MiSeq sequencing. We monitored the relative activity of medium- and large mammals with camera traps and estimated avian abundance by performing point counts at three times during the summer at each site. Blood-meal origins for Cx. pipiens and Cx. restuans females were predominantly from avian species such as American robins and Northern cardinals and did not differ strongly between more urban and more rural sites. For Cx. salinarius, a possible bridge vector, white-tailed deer and humans were the most common hosts, but the relative frequency of blood meals taken on humans increased in the more urban locations. West Nile infection rates differed significantly among vector species and sites. To explain variation in prevalence we assessed the impact of land use and environmental parameters. The amount of impervious surface around the collection site itself was only weakly associated with WNV infection rates, but the proportion of land consisting of turf grass had a significant positive relationship. WNV prevalence was also significantly associated with the community competence index, as well as with abundance of species including American robins and house sparrows. Together, this work highlights that urban green space with certain characteristics that provide ample suitable habitat for important avian host species with repercussions for risk of WNV exposure in humans.

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MOSQUITO GENE SURVEILLANCE (MGSURVE): A FRAMEWORK TO OPTIMIZE TRAP PLACEMENT FOR GENETIC SURVEILLANCE OF MOSQUITO POPULATIONS

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Genetic surveillance of mosquito populations is becoming increasingly relevant as genetics-based mosquito control strategies advance from laboratory to field testing. Especially applicable are mosquito gene drive projects, the potential scale of which leads monitoring to be a significant cost driver. For these projects, monitoring will be required to detect unintended spread of gene drive mosquitoes beyond field sites, and the emergence of alternative alleles, such as drive-resistant alleles or non-functional effector genes, within intervention sites. This entails the need to distribute mosquito traps efficiently such that an allele of interest is detected as quickly as possible - ideally when remediation is still possible. Additionally, insecticide-based tools such as bednets are compromised by insecticide-resistance alleles for which there is also a need to detect as quickly as possible. To this end, we present MGSurvE (Mosquito Gene SurveillancE): a computational framework that optimizes trap placement for genetic surveillance of mosquito populations such that the time to detection of an allele of interest is minimized. A key strength of MGSurvE is that it allows important biological features of mosquitoes and the landscapes they inhabit to be accounted for, namely: i) resources required by mosquitoes (e.g., food sources and aquatic breeding sites) can be explicitly distributed through a landscape, ii) movement of mosquitoes may depend on their sex, the current state of their gonotrophic cycle (if female) and resource attractiveness, and iii) traps may differ in their attractiveness profile. Example MGSurvE analyses are presented to demonstrate optimal trap placement for: i) an Aedes aegypti population in a suburban landscape in Queensland, Australia, and ii) an Anopheles gambiae population on the island of São Tomé, São Tomé and Príncipe. Further documentation and use examples are provided in the vignettes at the project's repository. MGSurvE is freely available as an open-source Python package on pypi. It is intended as a resource for both field and computational researchers interested in mosquito gene surveillance.

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DESIGN AND PRELIMINARY FIELD VALIDATION OF A HANDHELD TOOL FOR AUTOMATED MORPHOLOGICAL IDENTIFICATION OF MOSQUITO SPECIES, SEX, AND ABDOMINAL STATUS BY VILLAGE HEALTH TEAMS IN UGANDA, FOR COMMUNITY-BASED VECTOR SURVEILLANCE

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Vector surveillance, a critical pillar of malaria control and elimination strategy, is limited by the global lack of trained medical entomologists and Vector Control Officers (VCOs), especially in low- and middle-income countries. We present the design of VectorCam, a novel Artificial Intelligence-enabled handheld field tool that automatically identifies the species, sex, and abdomen status of wild-caught mosquitos. The system consists of a low-cost smartphone running an Android application attached to low-cost hardware that can uniformly magnify and illuminate at a set distance. The system can effectively task-shift vector surveillance to Village Health Teams (VHTs), allowing them to rapidly image a batch of specimens and pack them into individual Eppendorf tubes with unique identifiers for quality assurance. This tool was designed with the iterative feedback of over 60 VHTs and 10 VCOs in Uganda through multiple formative usability studies that finalized the design and performance parameters. The core algorithm uses a Convolutional Neural Network architecture run on smartphones without internet connectivity. The classification accuracy against molecular identification using wild-caught mosquito specimens was as follows: Anopheles funestus s.l. (96%), An. gambiae s.l. (94%), other Anophelines (91%), Culex sp. (97%), and other genera (97%), with an overall F-1 macro score of 95 ±3%. A recent addition to the algorithm included An. stephensi, an invasive species of concern in Africa. With colony-bred specimens of An. stephensi, we achieved a classification accuracy of 98%. Accuracy for sex and abdominal status against morphological labeling by VCOs presented as 95±1%, and 86±4%, respectively. VHTs were placed in pairs of imaging and loading roles to evaluate their effectiveness in using VectorCam. They were trained by VCOs for an average of four hours, resulting in an average imaging speed of 1:11 ± 0:38 minutes per mosquito. VectorCam is a novel system that could help task-shift a major expertise bottleneck in Africa and Asia, allowing for a community-based approach towards vector surveillance.

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ELUCIDATING THE INTERACTIONS OF PFCRT AND PLASMEPSINS 2/3 IN MODULATING FITNESS AND RESISTANCE IN PLASMODIUM FALCIPARUM TO PIPERAQUINE AND OTHER ARTEMISININ PARTNER DRUGS

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Failure of dihydroartemisinin and piperaquine (DHA+PPQ) combination therapy (ACT) in Southeast Asia has been linked to the Plasmodium falciparum KEL1/PLA1 co-lineage, which harbors the DHA resistant Kelch13 (k13) C580Y mutation and PPQ-resistant marker multicopy plasmepsins 2 and 3 (pm2/3). PPQ resistance-associated novel mutations in the P. falciparum chloroquine resistance transporter (pfcrt) including F145I or M343L, have also emerged on KEL1/PLA1 parasites expressing the Southeast Asian Dd2 pfcrt allele. However, it is unclear whether multicopy pm2/3 or mutant pfcrt is the major determinant of PPQ resistance in clinical isolates, and how they impact the efficacy of other ACT partner drugs. To examine the contributions of these PPQ-resistant markers, we generated an isogenic panel of CRISPR/Cas9 pfcrt-edited parasites harboring 1 to 3 copies of pm2/3 from progeny derived from the genetic cross of NF54 and RF7, a KEL1/PLA1 parasite. PPQ dose assays revealed that pfcrt is epistatic to pm2/3 in conferring high-level PPQ resistance, and both pfcrt M343L and pm2/3 amplification were necessary to produce a biphasic response at >1 μM PPQ. In addition, we identified Dd2 pfcrt and multicopy pm2/3 as key determinants of resistance to MMV675939, a preclinical compound. In contrast, the African 3D7 pfcrt allele led to a ~3-fold increased sensitivity to ACT drugs, lumefantrine and mefloquine, when compared to the Southeast Asian Dd2+M343L isoform. We also performed long-term competitive fitness assays between isogenic RF7 clones harboring 1 or 3 copies of pm2/3 to investigate fitness costs. Our results revealed that multicopy pm2/3 led to a moderate parasite fitness defect in the absence of drug pressure. Overall, our findings suggest that PPQ selects for pm2/3 amplification in mutant pfcrt parasites, and the poor fitness associated with multicopy pm2/3 may explain the loss of pm2/3 amplification in clinical isolates upon the switch from DHA+PPQ to artesunate+mefloquine. Furthermore, we demonstrate higher sensitivity of PPQ-resistant pfcrt alleles to lumefantrine and mefloquine, thus reinforcing their appeal as effective ACT drugs in Southeast Asia.

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UNDERSTANDING LEAD DISCOVERY ANTIMALARIAL DRUGS RESISTANCE TRANSLATION FROM LAB TO FIELD PARASITES TOWARD SUSTAINABLE MALARIA ELIMINATION

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Not anticipated chloroquine resistance has had serious consequences for public health worldwide. It has subsequently led to the use of artemisinin-based combination therapies (ACTs) as first-line treatments for Plasmodium falciparum malaria. The aim of drug combinations was to anticipate appearance and spread of artemisinin resistant parasite on the field by protecting short-life artemisinin with long lasting existing antimalarial drug. Thus,for chloroquine, atovaquone, pyrimethamine and the current frontline artemisinin, major investigations have not been made at early discovery stage to identify which gene, mutations or conditions will cause drug resistance and can translate into field parasites. It has taken years to figure out the molecular determinant driving the resistance until complete loss of the drug.The discovery process of new alternative molecules to anticipate loss of ACTs should subsequently investigative their drug resistance markers that can translate from lab to field parasites and select partner drug accordingly for combination to ensure long lasting use of new antimalarial drug after their approval and field deployment. In a proof of concept study, we demonstrated that some key mutations found in lab parasites translate into field parasite conferring field parasites drug resistance Merck M5717 antimalarial drug candidate. With the great vision to ensure efficient long-term use M5717, we applied mathematical modelling to isobologram data to show that Pyronaridine is a viable partner for M5717. We extended this study to one of the most advanced lead discovery antimalarial, Novartis KAF156 which is currently in phase IIb clinical trial entering to phase III. We report that when exposed to GNF179 (Imidazolopiperazine: IPZ), close analogue of KAF156, recrudescent field parasites were detected which is being investigated for resistance purpose. This approach allows us to study the presence of resistant genes in field strains and predict resistance to antimalarial drugs, in order to anticipate therapeutic combinations before the new molecules are deployed.

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CONFIRMED ARTEMISININ PARTIAL RESISTANCE AND HIGH EFFICACY OF ARTEMETHER - LUMEFANTRINE AND ARTESUNATE - AMODIAQUINE FOR THE TREATMENT OF UNCOMPLICATED PLASMODIUM FALCIPARUM MALARIA IN NORTH-WESTERN TANZANIA

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This study was conducted from April to September 2022 to assess efficacy and safety of artemether-lumefantrine (AL) and artesunate-amodiaquine (ASAQ) for the treatment of uncomplicated falciparum malaria Tanzania due to reports of artemisinin partial resistance in Rwanda and Uganda. It was a single-arm prospective study that recruited 176 patients aged 6 months to 10 years who were treated with AL and ASAQ. Capillary sequencing was used to determine the prevalence of single nucleotide polymorphisms in Pf kelch 13 and multi-drug resistance 1 (mdr1) genes PCR corrected cure rates, safety of the two drugs, parasite clearance time and molecular makers of resistance in k-13 and mdr1 genes were assessed. PCR corrected adequate clinical and parasitological response (ACPR) for AL and ASAQ was 96.6% for AL and 100% for ASAQ. Among patients treated with AL and ASAQ; 11/88 (12.5%) and 17/88(19.3%) had parasitaemia beyond 72 hours, respectively. The slope half-life was <3.9hrs in both groups but it was significantly higher (>6.5hrs) in patients with day 3 parasitaemia and/or k-13 mutations at enrolment. In both groups, ≥23% of the patients had 561H mutations at enrolment. The day 3 patients with parasitaemia, 9.1% in AL and 11.4% in ASAQ had 561H mutations. The Mutations in k-13 gene were significantly associated with day 3 parasitaemia but they were not associated with recrudescent or recurrent infections in AL. Common adverse events reported were cough, runny nose, abdominal pain and fever; and not related to the study drugs. Confirmed artemisinin partial resistance, high cure rates and adequate safety were observed with 96.6% ACPR for AL and 100% for ASAQ. Containment strategies are urgently needed to prevent mutated parasites from spreading to other parts of the region and the entire country. 1

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A RAPID DECLINING OF MULTIDRUG RESISTANT KEL1/PLA1 PLASMODIUM FALCIPARUM PARASITE IN VIETNAM DURING 2020-2022, A RESULT OF DRUG POLICY CHANGE

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Genetic surveillance has been proved as a useful tool to monitor drug resistance and provided support evidences for the National Malaria Control Programs in decision making including drug policy change. In collaboration with the Vietnam NMCPs, genetic surveillance has been conducted in twelve malaria endemic provinces located in Central Highland and Southern of Vietnam since 2017. Our continuous results from six years surveillance have timely informed and alarmed the NMCPs about the efficacy of current first-line treatment and joined supported the change of National Treatment Guideline in 2020 in areas confirmed multi drug-resistant malaria (including Binh Phuoc, Dak Nong, Dak Lak, Gia Lai, Phu Yen provinces). Over 400 Plasmodium falciparum samples have been collected in those provinces during 2020-2022. The parasites have been genotyped follow transfered Amplicon Sequencing procedure from Welcome Sanger Institute and GenRe Mekong project. Our preliminary results show a declining of multidrug resistance KEL1/PLA1 P. falciparum parasites after national drug policy changed. The P. falciparum parasites carried C580Y Kelch13 mutation without associated piperaquine and mefloquine resistance (evidenced by amplification in the plasmepsin2/3 and pfmdr1 genes), has been gradually predominant in those malaria provinces. This indicated that the reversal back to a single plasmepsin2/3 genotype was the result of the change in first line therapy away from dihydroartemisinin-piperaquine in Vietnam.

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ASSOCIATIONS BETWEEN SULFADOXINE-PYRIMETHAMINE+AMODIAQUINE CONCENTRATIONS, MALARIA INCIDENCE, AND RESISTANCE MARKERS IN CHILDREN RECEIVING SEASONAL MALARIA CHEMOPREVENTION IN BURKINA FASO

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Seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine+amodiaquine (SP-AQ) is given monthly during the transmission season to prevent childhood malaria in the sub-Sahel region of Africa. Optimal SP-AQ concentrations to confer protection against malaria and prevent selection of SP-AQ resistance are unknown. We conducted a prospective cohort study of children in Sourkoudougou, Burkina Faso 3-59 months old and eligible to receive SMC. 89% of the children were enrolled prior to the first SMC cycle, and all were followed longitudinally through the malaria transmission season (July to November, 2022). SMC was administered in four cycles: July 9-12, August 7-10, September 5-8, and October 4-7. Plasma levels of sulfadoxine, pyrimethamine, amodiaquine and its metabolite desethylamodiaquine were collected on days 7 and 28 following SMC administration and additionally on days 3 and 14 in a sub-cohort of 57 children for whom all three doses of SMC were directly observed. Incidence of malaria infection was assessed during routine and unscheduled clinic visits by blood smear. Dried blood samples were collected for assessment of genotypes. Among the 178 children enrolled, 103 incident malaria infections were recorded (incidence rate = 1.82 episodes per person-years). Across SMC cycles, malaria infection incidence was highest at four weeks after SMC administration (just before the next SMC cycle). Mean parasite prevalence was 5.9% [range: 4.0%-8.3%] on day 7 and 8.1% [range: 4.8%-10.8%] on day 28 after treatment. Compared to the full cohort, parasite prevalence was significantly lower among participants of the sub-cohort (whose SMC regimens were directly observed) on day 7 (1.9% [range: 0%-3.9%]; p=0.001), but not on day 28 (5.8% [range: 0%-9.1%]; p=0.09). Assessments of SP-AQ drug levels and drug resistance genotypes are ongoing. With these data we will perform population pharmacokinetic/pharmacodynamic modelling to characterize associations between drug exposure, malaria infection incidence, and drug resistance selection.

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POTENTIAL SUITABILITY OF SULFADOXINE-PYRIMETHAMINE PLUS AMODIAQUINE FOR SEASONAL MALARIA CHEMOPREVENTION IN AREAS OF HIGH, PRE-EXISTING DRUG RESISTANCE

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Seasonal malaria chemoprevention (SMC) targets the burden of malaria in children under five in areas of seasonal malaria transmission. Previously, the WHO recommended SMC only in the Sahel region which has low levels of sulfadoxine-pyrimethamine (SP) drug resistance, one of the drugs used for the intervention. However, in 2022 geographic restrictions were removed from WHO guidelines prompting new countries to consider SMC as a possible intervention. There is a need to understand whether SP-AQ would still be effective in areas with high SP resistance to guide the scale-up of SMC to new geographies. Here, we utilize data from the first randomized controlled trials of SMC outside of the Sahel region to estimate the protection provided by SMC which demonstrated a day 28 protective efficacy of 77%, even in areas with established high-level SP resistance. We use Bayesian inference methods to estimate the probability that SMC using SP-AQ would prevent an infection given time since drug administration, seasonality, baseline transmission and existing frequency of SP-resistance conferring mutations. We are currently using these results within an existing, extensively validated individual-based Plasmodium falciparum transmission model to estimate the potential impact of implementing SMC under a variety of scenarios, including exploring the number of cycles, their timing, and the suitable age range. Initial results suggest that in an area with 64.7% of clinical cases in 4 months and established dhfr-dhps quintuple mutation, SMC using four cycles of SP-AQ could prevent 51.1% (95% CI: 37.0 - 65.2%) of annual clinical P. falciparum cases in children under five years. Despite the high drug resistance already present in east and southern Africa, we predict that SMC has the potential to be a highly effective malaria intervention and could help avert some of the substantial malaria burden in young children in these geographies. It will be important to consider the impact of scaling up SMC on driving resistance to SP and AQ in areas where SP resistance is already relatively high.

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WUCHERERIA BANCROFTI MICROFILARIAE POSITIVE INDIVIDUALS SHOW AN INCREASED HUMAN IMMUNODEFICIENCY VIRUS INCIDENCE IN A GENERAL POPULATION STUDY IN SOUTHWEST TANZANIA

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As part of a large prospective general population study, our group had described a 2.3-fold increase in HIV incidence among individuals with Wuchereria bancrofti infection, as measured by the circulating filarial antigen of the adult worm. However, during the first study no night-blood was collected, which is essential for measuring of microfilariae (MF) of W. bancrofti was taken, because the focus of this activity was on soil-transmitted helminths and malaria. A new study presented here aimed to retrospectively determine the microfilariae status of the participants to reveal whether the increased HIV susceptibility previously described was associated with patent (MF-positive) or latent (MF-negative) filarial infection. Circulating filarial antigen(CFA)-positive biobanked human blood samples (n = 350) were analysed for W. bancrofti MF chitinase by real time PCR. The PCR provided a positive signal in 12/350 (3.4%) samples. During the four-years of follow-up period (1109 person years (PY)), 22 study participants acquired HIV infection. Three new HIV infections occurred in 39 PY of W. bancrofti MF chitinase positive individuals (7.8 cases per 100 PY), in contrast to 19 seroconversions in 1070 PY of W. bancrofti MF chitinase negative individuals (1.8 cases per 100 PY, p = 0.014). Immunomodulation induced by W. bancrofti appears to be more pronounced in microfilariae-positive individuals, as the HIV incidence observed in this subgroup

exceeded the moderately increased HIV risk previously described in all individuals with W. bancrofti (regardless of MF status) compared with uninfected persons from the same area.

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DEVELOPING THE NATURAL PRODUCT CORALLOPYRONIN A TO TREAT FILARIASIS, STIS AND STAPHYLOCOCCI

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Corallopyronin A (CorA) inhibits bacterial DNA-dependent RNA polymerase at a different binding site to rifampicin. Thus, it kills rifampicin-resistant Staphylococcus aureus. CorA also kills Gram-negative Wolbachia endobacteria of filarial nematodes that cause onchocerciasis (river blindness) and lymphatic filariasis (elephantiasis). Depleting the essential endosymbionts causes worm sterility and slow adult worm killing. We demonstrated CorA activity against Neisseria gonorrhoeae and multi-resistant S. aureus. At 4x MIC no CorA resistant N. gonorrhoeae could be selected (predicted frequency of mutation of ≤10-10). CorA also has activity against established S. aureus biofilms and prevent their formation. With its excellent biodistribution into bone, we have received funding to investigate CorA as a new antibiotic class to treat osteomyelitis and S. aureus biofilms. To develop CorA as a novel solution to several targets of the WHO Priority Pathogen List for which new antibiotics are needed, we conducted standard non-GLP ADMET studies. In-vitro toxicity tests (off-target, AMES, micronucleus, hERG, phototoxicity) demonstrated that it is non-toxic and pharmacologically safe; in vivo toxicity studies in rats and dogs measured a maximal tolerated dose (MTD) in both species of 1000 mg/kg. Seven-day repeated dose studies in rats and dogs demonstrated no prohibitive safety issues: predicted NOAEL=150 mg/kg/d; predicted HED=4 mg/kg. CorA drug substance is heterologously produced in genetically modified Myxococcus xanthus. Up-scale to industrial scale (15m3) was achieved in 2022 at Bio Base Europe Pilot Plant (Belgium). The Helmholtz Centre for Infection Research purified this large amount of material, achieving 90-95% pure HQ-RGM material. With amorphous solid dispersion formulation principles, two solid oral formulations were developed that increased stability (>3 months at 30 °C, >6 months at 5 °C) and oral bioavailability (mouse >59%, dog>53%) compared to neat CorA. We are establishing drug product production at GMP facilities. After finalization of the pre-clinical work, we plan to enter the clinical phase I in 2025/2026.

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ANIMALS AS RESERVOIR OF BRUGIA MALAYI IN BELITUNG DISTRICT, INDONESIA, AS A POTENTIAL THREAD FOR THE ELIMINATION OF LYMPHATIC FILARIASIS IN HUMANS

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In Indonesia, Brugia malayi is the most common filarial parasite in Sumatra, Kalimantan, Sulawesi, and adjacent islands. B. malayi occurs in two ecotypes; the zoophilic type that infects both humans and animals, and the anthropophilic type that is only found in humans. Belitung district was known to be endemic for zoophilic B. malayi but received 5 rounds of mass drug administration (MDA) with DEC and albendazole between 2006 and 2010 at high coverage, passed 3 transmission assessment surveys (TAS) and was assumed to be free of infection in 2017. In 2021 a surveillance survey in 7 villages found that 5 villages were endemic for B. malayi with an average microfilaria (Mf) rate of 2.1% (40/1910 adults). Mf positive subjects were treated using ivermectin, DEC and albendazole, and a more extensive survey in the entire district was performed in 2022 that found an average Mf rate of 1.3% (87/6898 participants). There are several reasons that could explain the presence of B. malayi despite of MDA and passed TAS. For example, TAS is based on schoolchildren, and may not detect ongoing transmission in adults or an animal reservoir could be responsible for reintroduction of parasites into the human population. To test the later hypothesis, we collected blood from 291 cats and 41 dogs in villages where Mf positive humans were found. Microscopic examination found B. malayi Mf in 3 dogs and 4 cats, most of them from a single village. Dirofilaria immitis was found in 13 dogs while Brugia pahangi was found in 11 cats and 3 dogs. Screening of monkeys is still ongoing, but Mf have been found in 6 of 28 macaques. Molecular species confirmation by qPCR and whole genome sequencing of B. malayi Mf for population genomics is currently underway. Results showed that in Belitung B. malayi is present in animals and could be the source for its reintroduction into the human population. Further studies have to demonstrate gene flow between the B. malayi populations in animals and humans to confirm the role of an animal reservoir. For the elimination of lymphatic filariasis, B. malayi areas with an animal reservoir may need to be declared as special zones with intensified intervention and surveillance.

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SPATIAL ANALYSIS OF THE RELATIONSHIP OF ONCHOCERCA VOLVULUS EXPOSURE BETWEEN HUMANS AND BLACK FLIES IN ETHIOPIA

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Onchocerciasis is a parasitic disease caused by Onchocerca volvulus that spreads through the bite of infectious Simulium flies, which breed in rapidly flowing rivers. Ethiopia has one of the highest burdens of onchocerciasis worldwide. Two key indicators of impact are Ov16 antibody prevalence in children, detected in dried blood spots (DBS) by ELISA, and the presence of infectious O. volvulus larvae in flies, detected through O-150 PCR. However, the quantitative relationship between the measures and their degree of spatial dependence is unclear. We explored associations between O-150-positive pools of flies and the prevalence of human antibodies to Ov16 in temporally and spatially proximal samples. The relationship was explored among villages in 8 zones in southern Ethiopia where S. damnosum sl is the principal vector. Data include DBS from 907 villages with data from 2022, and flies from 22 sites collected from 2021-2022. The study areas had received 4-20 years of ivermectin treatment by then. Clustering of residuals from an intercept-only log-binomial model of DBS locations was assessed using Moran's I and global colocation quotient, and the impact on spatial autocorrelation was measured after adding a covariate for O-150 fly pool positivity at the nearest breeding site within a threshold distance. Threshold distances were tested at 64km, 33km, 20km, and 10km according to the literature and common practice in the program. Results suggested that the relationship between nearby fly site positivity and village parasite exposure may be significant if the fly site is within 33km, with the association growing stronger as the threshold distance decreases. However, estimate precision became weaker as the threshold lowered due to data sparsity. Similarly, examination of residual spatial autocorrelation showed that incorporating fly site positivity to the model began to lower residual clustering at the 33km threshold. These findings will direct the collection and testing of flies to better elucidate the relationship between parasite prevalence in flies and humans across diverse geographies, informing cost-effective surveillance.

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CHALLENGES OF APPLICATION OF THE WHO ONCHOCERCIASIS TECHNICAL ADVISORY SUBGROUP-PROPOSED THRESHOLD FOR INITIATING MASS DRUG ADMINISTRATION AGAINST ONCHOCERCIASIS IN ETHIOPIA

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Mapping is a prerequisite for determining onchocerciasis endemicity and the need for interventions to eliminate transmission. Ethiopia has made nationwide mapping part of its elimination strategy. National guidelines were developed in 2015, in which a woreda (district), the implementation unit in Ethiopia, was considered endemic if the mean Ov16 antibody prevalence in 300 adults (100 from each of three villages) was ≥2%. In 2017, the Onchocerciasis Technical Advisory Subgroup (OTS) of the World Health Organization proposed sampling 500 adults in 5 communities and commencing mass drug administration (MDA) in an implementation unit if Ov16 prevalence in at least one community was ≥2%. Ethiopia embarked on mapping the 671 previously untreated districts between 2015 and 2019 using a combination of entomological and Ov16-serology studies, prioritizing areas adjacent to those already under treatment. Desk review was used first to exclude areas ecologically unsuitable for supporting vector flies and thus O. volvulus transmission. Next, entomologists prospected river systems during the rainy season to confirm these exclusions and to identify a minimum of three first-line communities near suitable vector breeding sites. Investigators excluded 181 districts based on unsuitable ecological conditions for vector breeding; dried blood spot (DBS) sampling was performed in the remaining 490 districts. To date, ELISA analysis for Ov16 has been analyzed for 122,405 DBS from 427 districts. Of these, 53 districts (12.4%) are considered endemic and in need of MDA by Ethiopia's guidelines. An additional 102 districts (23.9%), encompassing 15 million people, would be considered endemic by OTS guidelines. This discrepancy has dramatic resource (cost and labor) implications. We recommend further investigation to determine if OTS thresholds reliably identify district-wide transmission.

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MONITORING IMPACT OF THREE ROUNDS OF MASS DRUG ADMINISTRATION IN EIGHT HIGH-RISK VILLAGES USING A THREE-DRUG REGIMEN ON LYMPHATIC FILARIASIS IN AMERICAN SAMOA

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In 2018, 2019 and 2021, the American Samoa Department of Health (DOH) conducted mass drug administration (MDA) for lymphatic filariasis (LF) with ivermectin, diethylcarbamazine and albendazole (IDA) and conducted impact surveys after each MDA. COVID-19 prevented MDA in 2020. Post-MDA 1, circulating filarial antigen (CFA) and microfilariae (Mf) prevalence in 8 high-risk villages (defined as having ≥3 CFA positive and/or ≥1 Mf positive people in 2019) were 4.3% (95% confidence interval (CI) 2.8-6.4) and 1.3% (95% CI 0.6-2.6), respectively. In 2020, CFA prevalence was 2.0% (95% CI 1.2-3.0) and Mf was 1.1% (95% CI 0.5-2.1). MDA coverage was 78.3% (MDA 1) and 90.1% (MDA 2). In Sep-Oct 2022, DOH sampled 550 people (≥5 years) in the 8 high-risk villages using a sampling strategy based on history of LF and village size. We asked about participation in all 3 MDAs and fingerstick blood samples were screened for CFA; CFA positive persons were tested for Mf and offered IDA. Mf positive persons were examined 7 days after treatment for Mf clearance. We weighted analyses based on the proportion of sampled data over village population. Mean CFA and Mf prevalence in 2022 were 2.2% (95% CI 0.7-3.6) and 0.1% (95% CI 0.0-0.1), respectively. Of participants, 83.4% (95% CI 69.2-97.5) reported taking the medicines in MDA 3, and 76.2% (95% CI 61.6-90.7) participated in all 3 MDAs. Of the 48 CFA positive persons, 64.0% (95% CI 0.1-1.9) were male and most were aged 20-39 years (49.4%; 95% CI 0.1-3.8); 90.1% (95% CI 0.1-1.3) reported swallowing pills in MDA 3. Eight (9.9%) reported never participating in MDA; 7/8 were male (mean age 52.9 years). The 2 Mf positive persons were both males aged 59 years, neither reporting ever taking the medicines. DOH followed up and treated 46/48 CFA positive persons, including the 8 never treated. High MDA coverage (≥65%) and a low proportion of never treated led to a decline in Mf prevalence in the defined villages. Despite Mf prevalence meeting the stop MDA target (<0.5%), high CFA prevalence, vector efficiency and frequent movement between American Samoa and LF-endemic Samoa, supports the need for another MDA, including social mobilization targeting men.

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RATE OF ONCHOCERCA VOLVULUS MICROFILARIAE IN NODULE CARRIERS IN VILLAGES UNDER MASS DRUG ADMINISTRATION IN FUAMAH DISTRICT, LIBERIA

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Onchocerciasis or riverblindness is endemic in most parts of Liberia. In 2021 it was estimated that 3.24 million people required mass drug administration (MDA) with ivermectin to control and eliminate onchocerciasis, and it was reported that 2.3 million (71%) received treatment. Although the entire country is covered by MDA, the coverage rates vary considerably by area/clan. Fuamah district (Bong County) has a population of 56,000 belonging to 5 clans living along the St. Paul river. Before the civil war, the district was a successful mining community, but now the infrastructure has degraded, the population consists mostly of retired mining workers, and subsidence farmers and their families and villages are difficult to reach. Although the district receives annual MDA through the Neglected Tropical Disease Department of the Ministry of Health, onchocerciasis is still highly endemic with Onchocerca volvulus nodule carrier rates in adults of up to 40%. Simulium vector densities are high, but the prevalence of microfilariae (Mf) in the human reservoir is unknown. In order to estimate the prevalence of O. volvulus Mf in the human population and to determine whether the area is suitable for clinical trials to improve the treatment for onchocerciasis, we performed a survey in the entire district. We examined 888 adults (25% women) with palpable nodules by skin snip (2 snips from the iliac crest and 2 snips from the calf) 12 months after the last MDA. The prevalence of Mf in nodule carriers varied between clans from 4.9% to 49.4%. The sensitivity to detect Mf in snips taken from the iliac crest and the calf was similar (94.5%, mean 10 Mf/mg vs 94.3%, 9 Mf/mg, respectively). A total of 353 subjects with palpable nodules and a Mf density ≥3 Mf/mg suitable for a clinical trial were identified. Subjects were pretreated with ivermectin to clear Mf from the eye and to enable future trials with regimens that contain the drug DEC. These results show that despite widespread MDA, subjects with O. volvulus nodules and microfiladermia are still prevalent in Fuamah and clinical trials can be performed in the same communities that will later benefit from new treatment strategies.

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WHOLE-GENOME SCAN OF AFRICAN SNAIL VECTORS IDENTIFIES GENES ASSOCIATED WITH RESISTANCE TO INFECTION BY SCHISTOSOMES

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Schistosomiasis is a chronic inflammatory disease afflicting hundreds of millions of people worldwide. Schistosomes are helminths transmitted by aquatic snails, and the disease can potentially be controlled by blocking transmission at the snail stage. Most cases of intestinal schistosomiasis occur in sub-Saharan Africa, where they are caused by Schistosoma mansoni, transmitted by the snail Biomphalaria sudanica and related species. In contrast to the better-studied neotropical vector B. glabrata, there has been little genomic work on these African snails and the genetic basis of snail-parasite interaction is completely unknown. Identifying snail genes that convey resistance to infection may facilitate ways to leverage these immune mechanisms and disrupt the parasite's life cycle. To uncover such immunogenetic pathways, we have generated an annotated genome assembly of B. sudanica and used it to support a genome-wide association study. We exposed F1 offspring of wild-caught Kenyan B. sudanica, originating from Lake Victoria, to S. mansoni and recorded infection status through cercarial shedding. Pools of infected (N = 493) and uninfected (N = 295) snails were then sequenced across the whole genome at a mean per-individual coverage of over 1x. We have identified several loci associated with infection status, including genomic regions known to influence parasite resistance in B. glabrata as well as previously uncharacterized genes. These results provide a first glimpse into genes of the innate immune system of the major vector B. sudanica and will help inform schistosomiasis control strategies aimed at predicting or manipulating the vector competence of the snail host, particularly in the African communities most severely affected by this disease.

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GENOMIC EPIDEMIOLOGY OF THE CARCINOGENIC LIVER FLUKE OPISTHORCHIS VIVERRINI

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Transmission of the carcinogenic trematode Opisthorchis viverrini is ongoing in Southeast Asia despite decades of control efforts. The resulting bile duct cancer (cholangiocarcinoma) is one of the leading causes of death in regions of Thailand, Lao PDR and Cambodia. Developing evidence-based programs for control require a mechanistic understanding of parasite transmission, however there are several unresolved epidemiological questions including the extent of parasite migration between neighboring countries and whether animals, primarily domestic cats, act as reservoir hosts. To address these knowledge gaps and to stimulate further research into the molecular epidemiology of O. viverrini, we present an improved reference genome which incorporates long read sequencing to give chromosome-level resolution. We then developed methodologies to whole-genome sequence adult worm and egg stages of flukes isolated from infected individuals to understand the pattern of genetic variation in natural parasite populations. Finally we sequenced O. viverrini from Thailand and Lao PDR and compared sequence data between human and animal infective parasites to determine the relatedness between populations and the extent of zoonotic transmission. Our study provides an unprecedented understanding of the molecular epidemiology underlying the transmission of a medically significant, yet highly neglected, human parasite.

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TEST-TREAT-TRACK-TEST-TREAT (5T) APPROACH FOR BREAKING SCHISTOSOMIASIS TRANSMISSION

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The World Health Organization has set the goal to eliminate schistosomiasis as a public health problem worldwide by 2030. Pemba Island, Tanzania, achieved this goal in 2017 and is now aiming for interruption of transmission. In most parts of Pemba, the Schistosoma haematobium prevalence is below 3% and mass drug administration of praziquantel no longer seems justified. As an alternative, we investigate a test-treat-track-test-treat (5T) approach to prevent recrudescence and accelerate elimination. In the 4-year SchistoBreak project implemented in two districts in the North of Pemba, schoolchildren are screened for microhematuria as a proxy for S. haematobium infection at the point-of-care. Positive children are treated with praziquantel and tracked to their homes and the waterbodies they use. Test-and-treat is offered to household members and people present at waterbodies. Additionally, urine samples are examined for S. haematobium eggs by urine filtration. Annual cross-sectional school- and household-surveys are conducted to monitor the prevalence and impact of the intervention. In 2021, 5.5% (239/4347) of the children screened in schools were microhematuria-positive and tracked to 199 households. Among their household members, 21.3% (60/282) were microhematuria-positive and 11.0% (31/282) egg-positive. At 77 waterbodies, 22.4% (30/134) of individuals tested microhematuria-positive and 4.5% (6/134) were egg-positive. The cross-sectional surveys in schools revealed a microhematuria prevalence of 2.4% (47/1933) in 2021 and of 6.3% (111/1767) in 2022. In households, the microhematuria prevalence was 5.6% (162/2972) in 2021 and 13.2% (387/2921) in 2022; the S. haematobium prevalence was 0.5% (14/2971) in 2021 and 0.6% (19/2929) in 2022. Our results show that 5T is an excellent approach to identify and treat individuals with urogenital schistosomiasis in low-prevalence areas. While microhematuria levels increased from 2021 to 2022, the S. haematobium prevalence remained stable. Future study years will confirm if 5T is indeed a suitable intervention to maintain current gains or to accelerate interruption of transmission.

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CHARACTERIZATION AND PROCESS DEVELOPMENT OF SERINE PROTEASE INHIBITOR: A NEXT GENERATION TRANSMISSION-BLOCKING VETERINARY MRNA VACCINE FOR ASIATIC SCHISTOSOMIASIS

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Asiatic schistosomiasis caused by Schistosoma japonicum is a neglected tropical disease resulting in significant morbidity to both humans and animals - particularly bovines - in endemic areas. Infection with this parasite leads to less healthy herds, causing problems in communities which rely on bovines for farming, milk and meat production. Additionally, excretion of parasite eggs in feces perpetuates the life cycle and can

lead to human infection. We endeavored to develop an inexpensive and effective mRNA vaccine based on secretory serine protease inhibitor (serpin) from S. japonicum (Sj-B6). In pathogens, serpins are believed to have evolved specifically to limit host immune responses by interfering with the host immune-stimulatory signals. Transcriptional profiling and proteomics demonstrated that Sj-B6 is expressed in the intra-mammalian life cycle stages but particularly in the eggs, suggesting a possible role in disease transmission. Recombinant Sj-B6 inhibited host pancreatic elastase in a dose-dependent manner and was strongly recognized by experimentally infected rat (naturally-resistant hosts) sera when compared to chronically-infected mouse counterparts, indicating that rSj-B6 is not only highly immunogenic, but critically involved in disease resistance. This study presents a comprehensive functional characterization of Sj-B6 supporting its further development as a vaccine candidate against Asiatic schistosomiasis. A pilot study evaluating the efficacy of a novel Sj-B6 mRNA vaccine using a proprietary technology (HDT-301) invented by our partners at HDT Bio is now underway. The HDT-301 platform consists of a self-replicating RNA (repRNA) adsorbed and stabilized on a Lipid InOrganic Nanoparticle (LION™) carrier. The repRNA/ LION™ vaccine stabilizes the RNA in vivo allowing it to persist longer. A successful veterinary vaccine would play a major role in reducing pathogen transmission to humans by interrupting the parasite life cycle and improving quality of life for people living in endemic countries.

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SCHISTOSOMA JAPONICUM CHALLENGE INFECTION MODEL IN CARABAOS (PHILIPPINE WATER BUFFALO) FOR THE PLACEBO-CONTROLLED TRIAL OF THE SJ97 AND SJ68 VACCINE CANDIDATES

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Schistosomiasis japonica is a zoonosis that persists as a public health problem in Asia particularly the Philippines, where hotspots remain despite decades of mass drug administration. Novel interventions such as vaccines are warranted to control the infection sustainably. Schistosoma japonicum infects over 40 mammals, with water buffalos as major animal reservoirs. We reported the development of an S. japonicum challenge model in carabao (native Philippine water buffalo) to evaluate vaccine candidates. Locally collected snails from endemic areas in Leyte were initially used as the source of cercaria. However, the perfused worm count is much lower than in our previous vaccine-challenge experiments in China, with a mean patency of 2.6%. The carabaos require a four-fold higher infectious dose, necessitating laboratory-reared snails. Weekly trickle infections in juvenile carabaos produced the highest yields upon sacrifice and worm enumeration by perfusion. To demonstrate the utility of the carabao challenge model, we conducted a placebo-controlled trial of the Sj97 and Sj97+Sj68 vaccine adjuvanted in ISA206. Carabaos (N=8 per group) were vaccinated with 3 doses of 500 ug Sj97, Sj97+Sj68, or saline placebo, adjuvanted with ISA206, and administered subcutaneously every 4 weeks. A half-dose booster was given 3 months after the last dose due to pandemic-associated delays. Vaccination induced robust antigen-specific IgG1, IgG2, total IgG responses, and Sj97-specific IFN gamma. Trickle infection with 2,000 S. japonicum cercaria yielded a mean of 251.8 in the adjuvant ISA206-only group upon perfusion 8 weeks post-infection. Carabaos in the Sj97+Sj68 vaccinated group had lower worm burdens than the placebo. Due to the significant variance in worm counts, the 40-70% protection by vaccination didn't reach statistical significance (Mann-Whitney test, p=0.6 for rSj97-rSj68 vs. ISA206; p= 0.5 for rSj97 vs. ISA206). We expect to report on the larger placebo-controlled Sj97+Sj68 vaccine trial with N=20 carabaos per group in the near future.

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TWO KEY ACTINOBACTERIA GENERA BIFIDOBACTERIUM AND COLLINSELLA IN THE HUMAN GUT MICROBIOTA ARE DIFFERENTIALLY ASSOCIATED WITH SCHISTOSOMA MANSONI INFECTION BURDEN

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Among the soil-transmitted helminths schistosomiasis is the least amenable to control due to the ease of reinfection and the difficulty of administration of praziquantel en masse, due to its side effects. The overall goal of the study was to identify the key microbial taxa associated with human gut dysbiosis during Schistosoma mansoni infection and to obtain orthologs information that could form the basis for an alternate schistosomiasis control development. Twenty schistosomiasis positives stool samples and an equal number of age-sex matched negatives from a -endemic rural community, Nyive, in Ghana were studied. The Kato-Katz method was used and the infection intensity scored as egg count per gram (e.p.g.) and positive stool samples further stratified as surrogates of chronic (<400 e.p.g., n=15) and acute (>400 e.p.g., n=5) infections. The composition and biodiversity of the gut microbiota and potential biomarkers associated with S. mansoni infection intensity were determined from 16S rRNA amplicon sequencing method and QIIME2 analytical software. A significant increase in Beta diversity (a measure of similarity) seen in the positives compared to the negatives (ANOSIM R = 0.06, p = 0.0386). There was a significant increased abundance of Bifidobacterium among chronic cases (p = 0.0025), whilst Collinsella was significantly elevated in acute infection samples (p = 0.039). The pathobionts Escherichia-Shigella was significantly reduced in the acute cases (p = 0.027). The KEGG pathway analysis revealed significant enrichment of 31 significant orthologs (p < 0.001, False Discovery Rate (FDR) < 10%) in positive samples. Bifidobacterium is a known probiotic shown to reduce malaria intensity in mice and the identified orthologs would enable exploitation for drug discovery.

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PREVALENCE AND DISTRIBUTION OF FEMALE GENITAL SCHISTOSOMIASIS ACROSS THREE ENDEMIC COUNTRIES, TIMELINE, AND AGE GROUPS

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Schistosomiasis is the world's second-deadliest parasitic disease, affecting 220 million people and causing approximately 200,000 deaths. It is caused by a trematode parasite of the genus Schistosoma, three species of which frequently infect humans: Schistosoma japonicum, S. haematobium, and S. mansoni. Female Genital Schistosomiasis (FGS) is caused by S. haematobium and is predominant in young girls between 12-15 years old. In Lower Middle-Income Countries (LMIC), like Zambia, Ghana, and Tanzania where schistosomiasis is endemic, knowledge regarding FGS is incomplete and often confused with other sexually transmitted diseases. FGS remains largely overlooked within the national health systems and Neglected Tropical Diseases (NTDs) programs, which causes a chronic gynecological condition that leads to substantial morbidity, infertility, cervical cancer, and syphilis disease. It modifies the immunological response to increasing the risk of contracting human papillomavirus (HPV), and human immunodeficiency virus (HIV). The objective of the study is to determine the prevalence of FGS based on the presence of parasite DNA and diagnostic tests in females across age groups from a database of field-acquired human samples from Zambia, Tanzania, and Ghana over multiple years. During the analysis for Ghana, 39 out of 90 samples were females of which 31 (79.5%) were positives and 8 (20.5%) were negatives. In Zambia (2016), 80 out of 133 samples were females of which 46 (57.5%) tested positive and 34 (42.5%) were negative. For Zambia 2017, 60 out of 110 samples were females of which 45 (75%) tested positive and 15 (25%) tested negative. In Tanzania, 70 out of 104 samples were females of which

43 (61.4%) tested positive and 27 (38.6%) tested negative. The outcome highlights that FGS is predominant among females in different endemic countries. This study will help determine and explore the burden of FGS to develop strategies to control FGS and improve current intervention measurements for Schistosomiasis.

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EFFICACY AND SAFETY OF BUTANTAN-DV LIVE-ATTENUATED TETRAVALENT DENGUE VACCINE FROM A PHASE 3 CLINICAL TRIAL IN CHILDREN, ADOLESCENTS, AND ADULTS

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Butantan-DV is a live-attenuated tetravalent dengue vaccine produced by Instituto Butantan. We assessed the efficacy and safety of Butantan-DV. Participants were stratified by age (2-6, 7-17, and 18-59 years old) and randomized 2:1 to receive a single dose of Butantan-DV or placebo in an ongoing, phase III, double-blind trial conducted in 16 sites across Brazil, with projected five years follow-up (NCT02406729). 16,235 participants were enrolled and received Butantan-DV (10,259) or placebo (5,976) between 2016 and 2019; 46.5% of participants were dengue-naïve. Safety was evaluated as the frequency of participants with solicited (local and systemic) vaccine-related adverse events (AEs). Vaccine efficacy (VE) to prevent symptomatic virologically confirmed dengue (VCD) by RT-PCR after Day 28 postvaccination to any dengue virus (DENV) serotype was determined. Secondary objectives, VE by baseline serostatus, serotype, age, and against severe disease/dengue with warning signs, regardless of hospitalization, were also evaluated. Non-serious, solicited systemic vaccine-related AEs were observed in a slightly higher proportion of overall participants receiving Butantan-DV (58.3%) compared to placebo (45.6%) within 21 days postvaccination. The proportion of participants with AEs within each age group was generally comparable to what was observed in the overall population. After two years of follow-up, the overall VE was 79.6% (95% CI:70.0%-86.3%) and was 80.1% (95% CI:66.0%-88.4%) in ages 2-6, 77.8% (95% CI:55.6.0%-89.6%) in ages 7-17, and 90.0% (95% CI 68.2%-97.5%) in ages 18-59. Serotype-specific VE was 89.5% (95% CI:78.7%-95.0%) against DENV1 and 69.6% (95% CI:50.8%-81.5%) against DENV2 in the overall population. Through the extended follow-up period, which included between 2-5 years of follow-up for all participants, there were no cases of DENV3 or DENV4 and VE against dengue with warning signs/severe dengue was 88.2% (95% CI: 50.8-98.2%). In summary, Butantan-DV was generally well tolerated and efficacious against DENV1 and DENV2 symptomatic VCD, regardless of dengue baseline serostatus or age, through the follow-up.

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A PHASE 1 OPEN LABEL TRIAL ASSESSMENT OF A DENGUE HUMAN INFECTION MODEL USING A DENGUE VIRUS SEROTYPE 4 LIVE VIRUS CHALLENGE

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Dengue Human Infection Models (DHIM) are critically needed in dengue vaccine and pharmacologic development and can provide a tool for understanding viral-host immunology in a controlled setting. We conducted a phase 1 open labeled, dose-escalation study evaluating the safety and dose of an attenuated Dengue-4-Virus-Live Virus Human Challenge (DENV-4-LVHC) strain intended for DHIM studies. Ten healthy adult volunteers were challenged with a single subcutaneous dose (95 PFU) of DENV-4-LVHC strain H-241 and followed daily from Days 4-16 (or until RNAemia resolved) with quantitative PCR used for detection and solicited adverse events assessed. All ten volunteers developed detectable RNAemia with mean onset at 4.2 days (range of 4-6 days) and a mean duration of 8.7 days (range of 7-11 days). RNAemia peaked between Days 5-11 (mean 7.3 days) and ranged from 5.28 x 105 to 7.60 x 106 copies/µL. All ten volunteers developed symptoms consistent with self-limited, mild dengue infection. The most common symptoms were fatigue, rash, and headache. All developed a nonpruritic, nontender, morbilliform rash, of which 8/10 involved >50% of their body surface area. The majority of other dengue symptoms were mild to moderate, with one volunteer reporting transient grade 3 (severe) headache and fatigue/malaise. Three of 10 developed mild to moderate fevers (38.1-38.8 oC). Laboratory abnormalities were seen in 8 of 10 volunteers, most common being elevated AST and leukopenia - all spontaneously resolved by Day 28. None developed thrombocytopenia. No serious adverse events were observed, and dose escalation was not required. Compared to a previously optimized DENV-1-LVHC, DHIM-4 resulted in an earlier onset (mean 4.2 vs. 8.3 days, $p < 0.0001$), earlier peak (mean Day 7.3 vs. 13.0, $p < 0.0001$), and shorter duration (mean 8.7 vs. 13.0 days, $p = 0.0002$) of RNAemia. In addition, rashes were more prominent in DHIM-4 than in the previous DHIM-1. Our findings support the safety of low-dose DENV-4-LVHC, resulting in uncomplicated mild dengue infection, and is suitable for use in future DHIM evaluation for vaccine and therapeutic development.

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SAFETY AND IMMUNOGENICITY OF A SYNTHETIC NANOPARTICLE-BASED, T CELL PRIMING PEPTIDE VACCINE AGAINST DENGUE IN HEALTHY ADULTS IN SWITZERLAND: A DOUBLE-BLIND, RANDOMIZED, VEHICLE-CONTROLLED, PHASE 1 STUDY

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Vaccine types other than current antibody-inducing ones are needed to address the global health threat posed by dengue. This study, the first of its kind, assessed the safety and immunogenicity of a CD8+ T cell priming, gold nanoparticle (GNP)-based, multi-valent, synthetic peptide dengue vaccine, designed to provide protective cellular immunity without inducing antibodies. In this randomized, double-blind, vehicle-controlled, phase 1 trial (NCT04935801), healthy individuals aged 18-45 years recruited at the Centre for primary care and public health, Lausanne, Switzerland, were randomly assigned to receive the vaccine candidate (PepGNP-Dengue) or a comparator (GNP without peptides [vehicle-GNP]). Randomization was stratified into four groups based on a risk-minimising dose-escalation strategy (low dose [LD] and high dose [HD], pioneers and followers), allocation was double-blind for participants and investigators. Two doses

were administered by intradermal microneedle injection 21 days apart. Primary outcome was safety, secondary outcome immunogenicity. 26 participants were enrolled (Aug–Sep 2021) to receive PepGNP-Dengue (LD or HD, n=10 each) or vehicle-GNP (LD or HD, n=3 each). No vaccine-related serious adverse events occurred. Most (90%) related adverse events were mild; injection site pain and transient discoloration were most frequently reported. Injection site erythema occurred in 58% of participants. As expected, PepGNP-Dengue did not elicit anti-DENV antibodies of significance. Significant increases were observed in specific CD8+ T cells and dengue dextramer+ memory cell subsets in the LD PepGNP-Dengue but not in the HD PepGNP-Dengue or Vehicle-GNP groups, specifically PepGNP-activated CD137+CD69+CD8+ T cells (day 90, p= 0·046), differentiated effector memory (TemRA) and central memory (Tcm) CD8+ T cells (day 35, p=0·014 and p=0·024, respectively). Results provide proof of concept that a synthetic nanoparticle-based peptide vaccine can successfully induce virus-specific CD8+ T cells. The favourable safety profile and cellular responses observed support further development of PepGNP-Dengue.

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CHIKUNGUNYA VACCINE VLA1553 INDUCES CROSS-NEUTRALIZATION AGAINST DIFFERENT CHIKV GENOTYPES

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Chikungunya virus (CHIKV) is a small spherical RNA virus and a member of the Alphavirus genus in the family Togaviridae. The virus is vectored by the daytime-biting Aedes aegypti and Ae. albopictus mosquitoes and spread in over 100 countries with more than 2.6 million suspected cases alone in the Americas since 2013. CHIKV is classified into three genotypes including the West African, the East-Central and South African (ESCA) and the Asian lineage. Currently, neither specific antiviral treatment nor a vaccine is available to prevent CHIKV infection. Valneva´s attenuated CHIKV single-dose vaccine candidate, VLA1553, comprises a large deletion in the non-structural replicase complex protein nsP3, which leads to attenuation of the virus in vivo. The vaccine is based on the La Reunion (LR) strain belonging to the Indian Ocean sublineage of the ECSA genotype. Cross-neutralization testing with other lineages is of importance to provide information on a broad neutralization activity by the vaccine. For this purpose, a panel of human sera (n=72) collected at day 1, 29, 85 or 180 from a phase 3 clinical study has been tested by a classical PRNT against wt CHIKV strains from different lineages. The tested strains include the La Reunion strain (LR2006_OPY-1) of the Indian Ocean/ECSA lineage, strain 37997 from the West African lineage and the Caribbean M109 strain from the Asian lineage. Neutralizing antibodies were detected against all three CHIKV strains in sera 28 days after a single dose of VLA1553. The PRNT50 titers of CHIKV baseline-negative participants increased on day 29, and sustained neutralization was measured on days 85, and 180 post-vaccination. The high titer vaccine sera reached neutralization titers comparable to convalescent sera (collected during outbreaks in Latin America 2015-2016) tested in the same PRNT against the various wt CHIKV strains. In summary, analysis of human serum from the phase 3 clinical trial of Valneva´s live-attenuated vaccine demonstrated a broad spectrum of neutralizing antibody activity against all major CHIKV genotypes.

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IMMUNOGENICITY OF AN EXTENDED DOSE INTERVAL FOR THE AD26.ZEBOV, MVA-BN-FILO PROPHYLACTIC EBOLA VIRUS VACCINE REGIMEN IN ADULTS AND CHILDREN IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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During the 2018-2020 Ebola virus disease (EVD) epidemic in north-eastern Democratic Republic of the Congo, we undertook a large, population-based Phase 3 trial of the two-dose Ad26.ZEBOV, MVA-BN-Filo vaccine regimen in healthy participants aged ≥1 year in Goma (Protocol DRC-EB-001; NCT04152486). However, all face-to-face activities were suspended five months into the study due to the COVID-19 pandemic, resuming five months later. As a result, 6,043 out of 20,408 participants received dose 2 outside the recommended 56-day (-14/+28 days) window. We reconsented adults (≥18 years), adolescents (12-17 years), and children (4-11 years) who received dose 1 but not dose 2 and returned after the study suspension and enrolled them into an immunogenicity subset to assess the impact of receiving dose 2 outside the recommended window. We collected blood samples before dose 2 and 21 days later and tested them for IgG binding antibodies against Ebola virus glycoprotein by the Filovirus Animal Non-Clinical Group (FANG) ELISA. No sample was taken from participants who received two doses with a 56-day interval in this trial. Results were available for 49 adults, 32 adolescents and 52 children. The median interval between dose 1 and dose 2 was 9.3 months. The pre-dose 2 antibody geometric mean concentration (GMC) in ELISA Units (EU)/mL was 217 (95% CI 157-301) in adults, 378 (95% CI 281-510) in adolescents and 558 EU/mL (95% CI 471-661) in children. At 21 days post-dose 2, the GMC increased to 22,194 (95% CI 16,726-29,449) in adults, 37,896 (95% 29,985-47,893) in adolescents and 34,652 (95% CI 27,906-43,028) in children. The post-dose 2 GMCs were higher than those noted in previous African trials using a 56-day regimen (VAC52150EBL2002 and VAC52150EBL3001), but similar to GMCs in participants who received a delayed dose 2 in these trials. We conclude that extending the two-dose interval from two to nine months may increase vaccine immunogenicity. These results support the practical deployment of the Ad26.ZEBOV, MVA-BN-Filo EVD vaccine, which might require vaccination campaigns in remote areas with logistical challenges that could delay dose 2 delivery.

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DETERMINANTS AND DURABILITY OF ANTIBODY RESPONSE TO RVSVΔG-ZEBOV-GP AND AD26.ZEBOV,MVA-BN-FILO EBOLA VIRUS DISEASE VACCINES: A MODELLING STUDY FROM THE PREVAC RANDOMIZED TRIAL

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Both rVSVΔG-ZEBOV-GP and Ad26.ZEBOV,MVA-BN-Filo vaccines against Ebola virus disease (EVD) have been approved by regulatory agencies and prequalified by the WHO. In the absence of the ability to measure long-term clinical protection, the evaluation of kinetics of the humoral immune response after vaccination is crucial. We used data from PREVAC's large phase 2 randomized double-blind clinical trial, which assessed three vaccination regimens against placebo in four Western African countries in children older than 1 year and adults. Linear mixed-effect regression models were used to evaluate the waning of anti-Ebola virus glycoprotein (GP1,2) binding antibody concentrations after rVSVΔG-ZEBOV-GP or Ad26.ZEBOV,MVA-BN-Filo vaccination protocols, and their potential determinants. The models included data from 1572 (781 vaccine, 791 placebo) and 1565 (779 vaccine, 786 placebo) participants, respectively. After a post-vaccination peak, each vaccination regimen was associated with a decrease of antibody concentrations with distinct kinetics. One year after dose one, the EBOV GP binding antibody concentrations were higher in children compared to adults for both vaccines. However, different effect sizes were identified, with the following ratios of mean antibody concentrations [95% confidence intervals] for rVSVΔG-ZEBOV-GP at 1 yr compared to adults: from 1.4 [1.1; 1.6] for the 1–4 yr group to 1.4 [1.2; 1.6] for the 12–17 yr group. For Ad26.ZEBOV,MVA-BN-Filo, the ratios were from 3.1 [2.6; 3.7] for the 1–4 yr group and 1.7 [1.5; 2.0] for the 12–17 yr group. Antibody concentrations also differed according to geographical location, pre-vaccination antibody concentration, and sex. Our findings show distinct dynamics of the antibody responses after either of the two vaccines, with age and several other determinants having an effect, especially for Ad26.ZEBOV,MVA-BN-Filo. In combination with information on memory response to the EBOV GP antigen, characterization of the major determinants of the immune response durability of the two licensed vaccination protocols may guide future EVD control strategies.

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HIGH DIMENSIONAL IMMUNOPHENOTYPING OF ACUTE EBOLA VIRUS INFECTED NONHUMAN PRIMATES

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Ebola Virus Disease (EVD), caused by the filoviruses of the genus Ebolavirus, is a hemorrhagic fever with a high mortality rate. Research on the immune response during acute EVD has been limited by limited samples and the necessity of high biosafety level practices. Here we report the use of high dimensional spectral cytometry to broadly phenotype the immune response during acute EVD in rhesus macaques. Rhesus macaques (n=2) were infected with 1300 PFU of the Makona strain of Zaire Ebolavirus and supported in an ICU model of care under BSL-4 conditions. Daily blood samples were drawn and peripheral blood mononuclear cells (PBMCs) isolated and cryopreserved, then analyzed with a 29-color immunophenotyping panel using a spectral cytometer. We identified key transitional steps in the immune response including loss of CD14 and HLA-DR from monocytes starting at day 4 post infection, progressive upregulation of the hemoglobin scavenger CD163 through day 5, and collapse of the monocyte lineage at day 6. Among lymphocytes we observed selective loss of CXCR3 positive B and T cells starting on day 4, expansion of naïve B cells, and activation of NK cells starting on day 5. Changes particularly in monocytes correlated with progression of sepsis physiology. We demonstrate here that significant changes in immune phenotype occur as early as day 4 post infection and continue through disease progression, as well the demonstrate the feasibility of performing broad immunophenotyping on Zaire Ebolavirus positive specimens with spectral cytometry. This detailed timeline of acute EVD will assist in future work to treat this highly fatal disease.

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CHARACTERIZING THE ROLE OF TICK SPECIES IN POWASSAN VIRUS FITNESS AND EVOLUTION

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Powassan virus (POWV, Flaviviridae) is a reemerging tickborne virus endemic in North America and Russia. POWV was first isolated in 1958 from a fatal encephalitic case in Canada. In 1997, a POWV-like agent was isolated from Ixodes scapularis in New England and determined to be genetically distinct from the original POWV isolate. This revealed the existence of two lineages: lineage 1, prototype Powassan (POWV-1) and lineage 2, deer tick virus (DTV). Each lineage is maintained in separate enzootic cycles with POWV-1 thought to be primarily maintained between I. cookei and woodchucks and I. marxi and squirrels, while DTV is primarily maintained between I. scapularis and small mammal hosts. POWV-1/DTV, however, have been detected in a range of tick genera. In New York State (NYS) between 2018-2022, POWV-1 was isolated for the first time from I. scapularis and detected in Dermancentor variabilis and DTV was isolated from Ambylomma americanum. These novel findings suggest POWV-1/DTV circulation in a broader range of tick hosts which is further supported by the overlapping and expanding geographic and mammalian host ranges of these genera. The propensity for POWV-1/DTV to further adapt to new tick hosts and transmission cycles following these rare spillover events is unknown but could facilitate the emergence of increasingly transmissable strains. To understand the potential for adaptation of POWV-1 and DTV to distinct tick genera, we conducted experimental evolution of recently isolated POWV-1 and DTV strains from NYS in I. scapularis, D. variablis, A. ambylomma, and Haemaephysalis longicornus. Experimentally infected ticks were collected at 20-day intervals for 100 days. Infection rates, viral kinetics, and full genome sequences of viral outputs were conducted to assess changes in the viral population. Early timepoints suggest introduction of POWV-1 and DTV into noncanonical tick vectors results in viral diversification and emergence of mutations potentially involved in invertebrate host immune evasion. These data suggest the capacity for POWV vector expansion and demonstrate the need for expanded viral surveillance of non- Ixodes ticks.

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ARE THE BITES OF NON-INFECTED SAND FLIES IMPORTANT FOR THE MAINTENANCE OF CUTANEOUS LEISHMANIASIS ANIMAL RESERVOIRS?

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Sand flies transmit several pathogens, of which, Leishmania parasites are the most prominent. More than 20 Leishmania species cause disease in humans worldwide. Strikingly, all but one are zoonotic agents; animal reservoirs play an essential epidemiological role in leishmaniasis. However, our understanding of such animal reservoirs, and particularly, their interactions with sand flies is still limited. Since in the wild, rodents were incriminated as reservoirs of L. major parasites, here, we took advantage of two rodent models of cutaneous leishmaniasis (CL) to try to understand

whether the bites of non-infected Phlebotomus duboscqi sand flies impact disease progression. In the susceptible model, a single exposure event in the context of CL active lesions - three weeks after the infection of BALB/c mice with 1000 L. major metacyclics - did not impact disease progression, as per the similar ear thickness measurements recorded in exposed versus non-exposed animals. This translated into similar ear parasite burdens throughout the follow-up period in exposed BALB/c versus non-exposed control animals. Similar results were obtained in the context of a single exposure of CL active lesions to the bites of P. duboscqi sand flies in the self-healing mouse model (C57BL/6 mice). However, when we performed a single exposure to non-infected sandfly bites in the context of healed CL lesions (C57BL/6 self-healing model; 9 weeks post-infection), a transient pathological response was observed, as per the increase in the ear thickness of exposed versus control animals. Importantly, this phenotype was accompanied by a significant increase in the ear parasite burden of exposed versus control animals. Of note, pathological changes of greater magnitude were observed in the context of multiple exposures of healed CL lesions to the bites of non-infected P. duboscqi sand flies. These preliminary results may suggest a role of sand flies in the maintenance of competent Leishmania reservoirs, in line with a previous study reporting that sand fly bites favor the transmissibility of the anthroponotic L. donovani parasites by infected hosts.

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THE HUMAN SKIN MICROBIOTA CHANGES IN RESPONSE TO SCABIES INFESTATION, WITH AN INCREASE IN OPPORTUNISTIC PATHOGENS

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Scabies is amongst the most common dermatological diseases worldwide with an estimated prevalence of 300 million cases and is recognised as a neglected tropical disease. Prevalence is high in tropical regions where a link with secondary bacterial infections has been established through clinical epidemiological studies. This research has demonstrated that scabies mites promote opportunistic bacterial infections with Staphylococcus aureus and S. pyogenes. Recent molecular data has also linked Acinetobacter baumannii, another extensively drug resistant nosocomial pathogen, to scabies infections. Our aim is to provide the fundamental molecular evidence of how scabies interferes with the host microbiome, to better understand the role scabies mites play in severe secondary bacterial infections and to improve treatment outcomes. We present here a first dataset from a collaborative multi-national study that collected skin scrapings from scabies infected patients from three countries (India, France and Australia), representing a diverse climate and socio-economic range. Microbial DNA was extracted from 751 samples, and 16s full-length rRNA and ITS long-read amplicon PacBio sequencing was performed. Using an established bioinformatics pipeline in R, we have analysed the data to determine the microbial profiles present during scabies infection. We have assessed samples from 134 patients from 3 different countries, and preliminary data demonstrates that there is an increase in opportunistic pathogenic bacteria in scabies lesions. This study is the first to quantify the scabies associated microbiome at the molecular level, and address how it might differ globally.

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EVALUATION OF THE EFFECT OF LONG-LASTING INSECTICIDE IMPREGNATED BED NETS ON PHLEBOTOMUS ARGENTIPES EXPOSURE USING SALIVARY BIOMARKERS: AN EARLY ANALYSIS AFTER SIX MONTHS

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Salivary proteins are useful serological markers of sand fly exposure. Long-lasting insecticidal-impregnated bed nets (LLINs) have been used for vector control interventions. However, their effectiveness against exposure to sand fly bites in Sri Lanka is unknown. The study aimed to evaluate the effectiveness of LLINs on exposure to Phlebotomus argentipes, a vector of CL in Sri Lanka using salivary biomarkers. A cluster randomized controlled trial was carried out in an endemic region of CL with a total of 600 (300 per group) individuals in intervention & control groups LLINs were given to the intervention group (at least 3 nets per house) & normal bed nets for the control group. 3cc blood was collected in the baseline survey from 310 individuals in the intervention group & 235 individuals in the control group prior to the intervention. In the post-intervention survey after 6 months, blood samples were collected from 259 & 208 individuals in the intervention & control groups respectively. A previously validated indirect ELISA assay against composite rPagSP02+rPagSP06 antigen of Ph. argentipes was used to measure the anti-saliva antibody levels of two groups & compared with the baseline sera. The geometric mean ELISA optical density (OD) of an intervention group in the baseline was 0.124 ± 0.083 whereas that was 0.138 ± 0.100 in the control group. The mean OD of an intervention group (post-intervention OD: 0.069 ± 0.062) declined significantly ($p < 0.05$) after 6 months in comparison to the baseline where that remained more or less constant in the control group (post-intervention OD: 0.139 ± 0.070). The difference in difference (DID) standard model showed that LLINs reduced exposure to Ph. argentipes by 43.54% at 6 months where the effect of the intervention was -0.054 at 95% CI. We observed a significant difference in serological markers of sand fly exposure in the intervention group in a tested cohort & need to combine the results with entomological data to validate the effect of LLINs mediated intervention.

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EXPANDING TOOLBOX FOR ODOR-BASED TSETSE FLY CONTROL IN EAST AFRICA

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Tsetse fly - transmitted Human African Trypanosomiasis (HAT) and Animal African Trypanosomiasis (AAT) are among most neglected tropical diseases in sub-Sahara Africa. Tsetse fly control strategies constitute cornerstones efforts in suppression and eradication of HAT and AAT. Tsetse fly lures that attract the flies to traps/insecticide-treated targets and repellents that minimize contact between infective flies and their vertebrate hosts can augment the strategies. We formulated a Novel Attractant Blend (NAB) comprised of ε-nonalactone, nonanoic acid, 2-nonanone and acetone) and Novel Repellent Blend (NRB) (δ-nonalactone, heptanoic acid, 4-methylguaiacol and geranyl acetone) based on tsetse-refractory waterbuck odor constituents, their structural analogues and attractant buffalo odor. Using two-choice wind tunnel in the laboratory

and Latin square experimental design in the field, we establish that 1) NAB is 2.4 times as attractive to Glossina pallidipes tsetse flies as POCA (3-n-Propylphenol, 1-Octen-3-ol, 4-Cresol, and Acetone) blend routinely used in tsetse control and 2) NRB is two-folds more efficacious than current commercial repellent blend against most savannah species. We microencapsulated the optimized NRB into β-cyclodextrin nano particles by kneading technique, evaluated responses of G. pallidipes tsetse to the microencapsulated blend and established kinetic release rates from the microcapsules under field conditions. We established significantly ($p<0.05$) lower release rate (5.35mg/h) in microencapsulated blend than the un-encapsulated control (11.82 mg/h) and that the micro-capsulation did not significantly affect responses of the tsetse flies to traps. We assessed efficacy of NRB in livestock protection using randomized block experimental design and established at least 95% repellence of G. pallidipes from oxen by NRB. We successfully masked the NRB in fragrance for odor appeal (for potential use in security and hospitality industries) and are developing NAB and NRB into semiochemical prototypes for integrated push-pull deployment in areawide control of tsetse flies in Eastern Africa.

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ONCHOCERCIASIS TRANSMISSION IN BENIN: BITING AND PAROUS RATE OF SIMULIUM DAMNOSUM COMPLEX ALONG THE OUEME, SOTA AND ZOU RIVERS

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Having up to date knowledge of the entomological indices of onchocerciasis vectors is critical for countries targeting the elimination of the disease as recommended by the WHO roadmap. This entomological study targeted breeding sites located in the former Special Intervention Zones (ZIS) as previously described by the Onchocercias Control Programme (OCP) where mass drug administration with ivermectin has being implemented for several decades in Benin. Females of Simulium damnosum complex were collected using human land catch method from August to the mid-November 2022 on 13 breeding sites: Agonlin Pahou, Sokpounta, Bethel, Bouri, Fonkpodji, Samiondji, Ayissakpo, Bétérou, Kika Barrage, Oubérou, Térou, Bétécoucou, and Atchérigbé in the districts of Kétou, Ouèssè, Glazoué, Gogounou, Djidja, Zangnanado, Tchaourou, and Dassa. These sites are in savannah areas distributed along the Ouémé, Sota, Okpara and Zou rivers. The blackflies were collected at fixed points located within 100 to 200 metres of the riverbanks from 7am to 6pm by two collectors who alternate every hour. The vectors were identified morphologically using characters based on the Meredith and Townson key. While the collection expanded over four months, the dissection was only conducted during two months, when the flies density was high, in the middle of the rain season. The average biting rate in the study areas was 119 bites/man/day (bp/day), significantly higher than the tolerable threshold of 30 bites/man/day ($p<0.001$). The monthly parous rate at the evaluated sites is an average 79.23% ±1.94% (95%CI). The parous rate varies from 46% [32.19 - 59.81] to 98% [94.12 - 100.00] during the second month, to 48% [34.15 - 61.85] to 98.75% [96.32 - 100.00] in the third month. Pending confirmation of the infectivity rate at these sites, these entomological data indicate ongoing intense transmission in the study area. Molecular identification of the different species collected and cytotaxonomy on larvae from these sites to further clarify vector competence among the Simulium sibling specie would help NTD programme to refine their strategy toward elimination.

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VERTICALLY INFECTED DOGS AS A RESERVOIR FOR LEISHMANIA INFANTUM IN AN ENDEMIC AREA FOR VISCERAL LEISHMANIASIS

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Leishmania infantum (Li) transmission to mammals occurs mainly via sand flies. However, vertical Li transmission has been demonstrated in locations with no apparent competent vectors, as well as in humans. The aims of this study were (1) to evaluate the Li infection rate in sand flies from an area endemic for human and canine visceral leishmaniasis (VL), and (2) to determine whether oligosymptomatic dogs vertically infected with Li are a reservoir of infection in Brazil. Weekly sand fly capture was performed for 2 years using CDC light traps in the peridomestic areas of 18 houses around Natal, Brazil. Eight puppies born to naturally Li-infected dogs were maintained in a kennel protected by insecticide-impregnated screens. These pups were followed for clinical progression. A Lutzomyia longipalpis colony was established and female sand flies at 5th and 6th generation were used for the xenodiagnoses. After ~18 months, xenodiagnosis was used to determine whether these pups could transmit Li to sand flies. Li infection of sand flies was measured by qPCR with a kDNA target. A total of 215 female sand flies were captured near the 18 houses and the Li infection rate in the endemic areas was 9.3%. Xenodiagnoseis using sand flies raised in the insectary showed that 6 out of 8 (75%) of offspring born from infected dams transmitted Li to sand flies. At the time of xenodiagnosis these dogs were subclinical with negative Leishmania serology and negative blood qPCR. 21.7% of sand flies fed on those dogs were Li positive by kDNA. vertical transmission in dogs may be important for maintaining Li in this region. Furthermore, although xenodiagnosis is not easy to implement, it may be the best way to identify Li reservoirs.

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ASSOCIATION OF HIV/AIDS WITH PSYCHIATRIC ILLNESS AMONG TRANSGENDER POPULATION IN A LOW HIV PREVALENCE COUNTRY

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In Bangladesh transgenders are high-risk group for HIV infection. Gender identity crisis and psychosocial stressors contribute developing psychiatric illness. We aimed to identify association of psychiatric disorders in transgenders by comparing the HIV status in Dhaka city. A cross-sectional study of transgenders aged >18 years was interviewed after taking written informed consent between July 21-June 2022. Sociodemographic, personal, co-morbid condition and psychosocial stressor variables were collected. Self-Reporting Questionnaire 20 was applied for psychiatric evaluation. Psychiatric illness was diagnosed using Mini International Neuropsychiatric Interview 7.0.0. The primary outcome of the study was to detect psychiatric illness among transgender adults irrespective of HIV status. Ethical clearance was taken. Of 157 transgender adults, 34 (22%) were HIV positive. Fifty-nine percent participants were between the 18-30 years of age group. Male biological sex was predominant (97%). Gay or lesbian sexual orientation was predominant (50% vs. 17%; $p<0.001$) and statistically significant and HIV positive transgender people. Fifty-

six percent belong to rural birthplace. Failed suicidal attempts (12% vs. 2%; p<0.001), chronic medical conditions (91% vs. 15%; p<0.001), any romantic relationship (67%vs 36%; p<0.001)) and satisfaction in the quality of life (64% vs. 45%; p=0.04) were significantly associated with HIV positive transgender than HIV negative peers. Among 34 HIV-positive transgender 22 (65%) were diagnosed as having psychiatric illnesses. Generalized anxiety disorder (41%) was the predominant psychiatric illness next to Minor depressive disorder (32%) and obsessive-compulsive disorder (9%). After adjusting the confounding variables, chronic medical condition [OR 98 (9.93-98.18; p<0.001] and life satisfaction [OR 8.7 (1.02-74.3); p=0.048] were significantly associated with psychiatric illness. Psychosocial stressor-based national screening program for early identification of psychiatric disease need to be developed for transgenders with HIV.

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SYNTHESIS OF FINDINGS FROM THE LITERATURE AND A QUALITATIVE RESEARCH STUDY ON THE IMPACTS OF GENDER, DISABILITY, AND ETHNICITY IN NEGLECTED TROPICAL DISEASES PROGRAMMING

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Act to End Neglected Tropical Diseases (NTDs) West, a USAID-funded program that seeks to eliminate or control five NTDs in West Africa, conducted a gender and social inclusion analysis to determine how NTDs differentially impact different population groups and how gender and social norms impact NTD programs. The study used a mixed methods approach, including a literature review; qualitative data collection in Côte d'Ivoire, Sierra Leone, and Ghana with a total of 477 participants; and quantitative analysis of programmatic data. Women and girls face additional health risks as well as social and economic impacts as a result of NTD infection compared to men and boys. Men are somewhat less likely to participate in mass drug administrations (MDAs) due to lack of information about campaigns, lack of access due to being out of the community when MDAs are conducted, and concerns and misconceptions about side effects. Pregnant and breastfeeding women are sometimes excluded from certain types of MDAs for which they are eligible or choose not to participate due to misinformation. MDA training rates for community drug distributors (CDDs) and supervisors are almost universally higher for men than women, even though feedback on the effectiveness of female CDDs is overwhelmingly positive, and female CDDs often have more access to women in conservative households. The role of CDDs can lead to career and social opportunities for both men and women. However, challenges faced by CDDs are seen as a greater barrier for women, including transportation, safety, household responsibilities, and low or lack of wages. Finally, people with disabilities and marginalized ethnic groups may sometimes be excluded from or exclude themselves from MDA. NTD programs can promote gender equity by increasing women's participation in MDA activities and providing financial compensation to CDDs. Additionally, programs should prioritize inclusive training for CDDs, and inclusive messaging about NTDs and MDA for communities. For example, in Sierra Leone, Act | West is now conducting rumor tracking to address misconceptions and collecting data on CDD sex for advocacy purposes.

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NEEDS AND PREFERENCE FOR COMMUNITY HEALTH WORKER SERVICES IN CAMBODIA: A COMMUNITY SURVEY

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Despite ongoing efforts towards universal health coverage, many LMICs still suffer from shortages in health professionals, lack of infrastructure, and inequities in health protection, particularly in remote rural areas, where access to health care and health information are inadequate and where poor communities bear the greatest health and economic burden of disease. In Cambodia, CHWs are identified as key to local health promotion and as a critical link between health centres and the community. However, research on the needs and preferences of communities regarding CHW services is limited.As part of a wider RAI3E operational research project on expanding the role of and integrating village malaria workers we conducted a questionnaire-based community survey in 6 endemic communes of Kravanh District, Pursat province, Cambodia during March and April 2022 with 174 community members (72 males and 102 females; aged 22-71). Community members were familiar with the local community health workers; almost half of respondents had visited a CHW in their community for health services in the past 12 months. Community members and their family's most common health problems included common cold (81%), malaria (72%), unspecified fever (43%), non-communicable diseases (NCDs i.e. diabetes, hypertension, hyperlipidemia, 32%), and dengue (30%). NCDs (35%), influenza (20%), pneumonia (25%), dengue (12%), and malaria (11%) were reported as their greatest health concerns. Over half (54.5%) of respondents preferred home visits from a CHW. Almost two-thirds described a willingness to pay for additional CHW services and, of those, 59% preferred paying 10 USD or less. Nonetheless, a similar proportion of all respondents reported difficulties paying for their healthcare.In summary, there was a varied demand for primary healthcare at the community level in Cambodia, covering infectious and non-infectious diseases. Well-known and accessible, CHWs are well-positioned to meet some of these needs. Ensuring basic equipment for CHWs is key, as are providing adequate capacity building and supervision, particularly if their role is to be expanded.

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ARMED CONFLICT REFUGEES' RESILIENCE: TRANSDISCIPLINARY STUDY ON A DIALOG FOR HEALTH PREVENTION IN THE EASTERN DEMOCRATIC REPUBLIC OF CONGO

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In DR Congo, the resurgence of violence by armed groups in 2023 caused the displacement of more than 5.8 million people. Parasitic infections, malaria, mental health, sexual and gender-based violence are considered more prevalent among refugees. This work argues the ability of refugees to persist, adapt and transform face to sanitary challenges might be limited given that it their context involves the loss of all their basic resources, the effectiveness or not of subsidies and the transitional state of displacement. This work aimed to set a dialog with key actors as to contribute to the characterization of infectious diseases (epidemiological investigation and microorganism identification), of psychosocial risks and to explore the ability of resilience in the context of refugee's camps in the region of Nyiragongo in Eastern DR Congo. Data were collected in a period of January and

February 2023 with socio-anthropological and microbial methods integrating "transdisciplinary approaches" that consisted in co-producing the objectives with stakeholders. The local knowledge was integrated through exploratory survey with key actors. Forty-six (46) sites sample where collected for microbiological analysis. In total, 104 persons were interviewed and 11 FG each consisting of 6 to 9 actors were organized. The "inductive thematic data analysis" was applied. Key findings are attitudes and behavior risks related to infectious diseases, sanitation and the psychosocial burden. Total coliforms, Vibrio ssp., Salmonella ssp., Shigella ssp., and Enterobacteria were identified from camps sites samples. The ability of refuges to persist, adapt and transform are analyzed into dynamic of the actors, resources, interactions context. In perceptive of actions, the results are translated into a grid of powers and interests in relation to the mobilization of resources for the prevention infectious and psychosocial burden. In addition, an analysis of the ability of refugees to persist, adapt and transform as to prevent health risks.

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LIVING WITH HANSEN'S DISEASE IN MALAYSIA: A TRANSDISCIPLINARY RESEARCH APPROACH

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Hansen's Disease (HD) is a chronic bacterial infection that primarily affects the skin, nerves, and other parts of the body. The disease can cause physical deformities if left untreated, which can make daily activities more difficult. While multi-drug therapy is effective at curing HD, allowing many to lead fulfilling lives, stigma still surrounds it. The application of a transdisciplinary research approach can facilitate a mutual understanding of the challenges faced by HD-affected people to identify their needs and concerns and develop solutions that address their unique challenges to reintegrate them into society and become contributing members. Stakeholder identification and mapping were conducted to identify twenty HD-affected individuals and twenty key people and decision-makers from governmental agencies, non-governmental organizations, and community and family members involved in their care (n=40). Participants were purposively sampled. Semi-structured interviews were conducted with each participant, and their responses were transcribed and analyzed with NVIVO software. A stakeholder engagement workshop was held where the problems were discussed and ranked, and solutions were co-created for the problems identified. An interagency meeting followed to discuss the implementation of the agreed interventions. The four main themes that emerged regarding the impact of HD on the affected individuals were biophysical, psychological, social, and economic. The stakeholders' analysis showed that the main challenges were a lack of public and health workers' awareness and knowledge of HD, insufficient resources for prevention and control, and a lack of interagency engagement and communication. Another issue was access to employment and skills training for self-sufficiency. Details of the analysis will be presented. The transdisciplinary approach can facilitate the integration of traditional knowledge and expertise, promoting a more inclusive and participatory approach to research. This collaboration ensures that solutions are empowering and sustainable to enhance the standard of living of the affected people.

5797

CHARACTERISTICS ASSOCIATED WITH SARS-COV-2 SEROPOSITIVITY IN CAMEROON

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It is important to study both symptomatic and asymptomatic infected persons to get a complete picture of SARS-CoV-2 in a population. The aim of this study was to identify characteristics (travel and testing history, exposure to crowded areas, contact with infected persons, household number) associated with SARS-COV-2 seropositivity in adults and in children in Cameroon. We used data from a SARS-CoV-2 country-wide seroprevalence survey conducted in Cameroon from November 2020 to February 2021 among males and females aged 5 to 100 years. A whole blood specimen was collected for SARS-COV-2 serology testing using ABBOTT Architect immunoglobulin G (IgG) and WANTAI total antibodies (Ab). A test was considered positive only if both tests were positive. Descriptive statistics, crude association between each covariate of interest and SARS-COV-2 seropositivity, and multivariable association (logistic regression) were used. Weighted counts (estimates) are presented. Data were available for 9836 participants. Less than 20% (17.53%) of the participants had symptoms of COVID-19 (1423/8116). The seroprevalence of SARS-COV-2 was 10.45% (8347/9321) and the seroprevalence was higher in those with symptoms 12.93 % than those without symptoms 9.97%. In univariate analyses, seropositivity was similar with increasing number of people in household (OR=0.98, 95%CI 0.76-1.28, p=0.90). Those who had travelled abroad had a higher risk of seropositivity than those who did not (OR=1.63, 95%CI 1.08-2.47, p=0.02). In the final multivariate model, seropositivity increased with age, after adjusting for sex, contact history, and testing history (AOR=1.61, 95%CI 1.29-2.01, p<0.001). The risk of seropositivity was higher in those with prior testing compared to those without prior testing (AOR=1.34 95%CI 1.04-1.72, p=0.02). Males had a higher seropositivity rate in both children and adolescents, (AOR=1.79 95% CI 1.24-2.58 p=0.003) and in adults (AOR=1.66, 95%CI 1.35-2.05, p<0.001). In conclusion, these data suggest an association between increasing age, male gender, previous SARS-COV-2 testing and seropositivity for SARS-COV-2.

5798

CONCEPTUALIZING AND UNDERSTANDING STIGMA ASSOCIATED WITH CUTANEOUS LEISHMANIASIS IN A RURAL COMMUNITY OF SRI LANKA

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Stigma is a barrier to health-seeking and treatment adherence, affecting disease mortality, morbidity, a person's quality of life and social inclusion. Cutaneous Leishmaniasis (CL) is widely accepted as a stigmatising skin disease. This disease has been endemic in Sri Lanka for centuries. The drivers and facilitators of the stigma associated with CL are not understood properly compared to those of other stigmatising diseases, preventing the development of holistic interventions, research, and policy. This study aims to identify the drivers and manifestations of the stigma associated with CL in rural Sri Lanka. This study was conducted in 2021 in the Anuradhapura district, a district with one of the highest incidence of CL in Sri Lanka. A multimethod qualitative approach was used with two main components, 1) An ethnographic study; participant observation and an auto-ethnographic diary study, 2) A qualitative study on people with CL

using a Participant Experience Reflection Journal (PERJ) and Post-PERJ interviews. We observed indirect, hidden and unexpressed stigma. Most of the negative reactions were confined to people with notable wounds. Disgust, fear, myths and misconceptions of the disease and the notion that it is a dangerous/deadly disease are identified as potential drivers of stigma. Marginalisation, internalised, anticipated and social stigma were identified as stigma experiences. People with internalised stigma felt sad/disappointed/uneasy; they accepted the disease as bad Karma. People with big/visible wounds also anticipated stigma from others and took measures to cover up/hide the wounds. They had reduced engagement with society as they feared dismissal by others. Social stigma manifested as calling people with a wound 'a distortion' and 'ugly'. The wound was described as disgusting by community members. Ideally, stigma interventions should interrupt the process before the stigma is established. It is important that the drivers we have identified through this study are addressed through public health interventions and policy before the stigma is widely established.

5799

INTEGRATING AND ACCESSING EQUITY IN GLOBAL HEALTH PROGRAM DESIGN

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PATH set out a five-year strategy focused on advancing health equity through innovation & partnerships. The strategy includes four change strategies for becoming a more equitable organization: equity in health, community-focused priorities, respectful partnerships, & inclusive innovation. PATH translated its change strategies into tactical benchmarks. The working group conducted a literature review, 17+ qualitative interviews with staff & partners, & held workshops with 60+ people. 11 project teams piloted & provided feedback on the first version of the Equity in Programming Benchmarks (EBP). The tool is a self-assessment measuring 12 indicators on a continuum from low to transformative & helps identify how each project can progress along the continuum. Project assessments are reviewed by PATH leaders. 35 proposals & projects have used the benchmarks to assess their work. The New Nets Project-a malaria vector control evaluation-used the benchmarks at the end of the project with partners to review results & consider ways to modify mosquito net distribution in the future. Highlights from this discussion include: Identifying structural changes to address barriers for institutions in malaria-endemic countries to access resources from large donors & build capacity; More consideration of systemic inequities within routine processes such as how to conduct & measure mass distribution campaigns of nets. The Technical Assistance Platform Project-a global health informatics technical assistance mechanism-used the EPB tool in annual work planning & made several adjustments including: Evolving the model so partners strengthen their organizational & leadership capacity & take on increasing project leadership, responsibilities, & autonomy over time; Ceding control over certain aspects of project management to colleagues & partners based in Africa & Asia. With the EPB, teams have better tools for understanding equity in their projects & can communicate the rationale for changes to donors & partners. We continue to gather feedback & iterate on the EPB so it meets the evolving needs of teams & the communities where the projects take place.

5800

INCREASING ADOPTION OF MALARIA PREVENTION AND CONTROL USING MULTIPRONGED SOCIAL BEHAVIOR CHANGE APPROACHES

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Social behavior change interventions, in the USAID PMI Uganda Malaria Reduction Activity, implemented by JSI, are data-driven, gender sensitive and targets malaria high burden districts. Aided by behavioral science and human centered design approaches to understand why people make decisions the way they do to tailor interventions that trigger behavioral change. District led programming and working with already existing structures like community health workers or village health teams is the main strategy. Focus is on increasing demand for health services, improving mosquito net use, improving health care provider and client interactions, and influencing social norms for sustainability. A multi-sectoral approach was used to engage district leaders and other stakeholders to inspire change at community level. We engaged district health teams, opinion leaders, epidemic task forces for malaria and other implementing partners. The number of children between 2 months and 5 years old with fever that received malaria rapid diagnostic tests seen by village health teams reduced from 1,194,184 in April to June 2022 to 960,454 in October to December 2022. The number of sick children of the same age range with confirmed malaria decreased from 1,057,854 to 860,548.The number with fever and danger signs seen in the community reduced by 12% from 65,570 to 57,754 and the number seen by village health teams and treated within 24 hours for fever reduced by 51% from 881,890 to 428,374 between April to December 2022. Supporting the districts to identify their own strategies for mobilization empowers district leaders and creates ownership. Each district has its own dynamics and have their own strategies for community engagement that works for them like engaging elders in community mobilization, engaging positive deviants in giving testimonies during community mobilization events, using data to map hotspots, and door-to-door mobilization. The role of community engagement in the planning and execution of community led activities directly leads to better health outcomes and sustainability of the adopted positive behaviors.

5801

EQUALITY IN AJTMH PUBLICATIONS FROM 1952 TO 2022: WHAT CAN WE LEARN TO MAKE GLOBAL HEALTH RESEARCH PUBLISHING MORE EQUITABLE? A BIBLIOMETRIC ANALYSIS

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The long overdue focus on decolonising global health has prompted various institutions to assess existing inequities in global health research partnership and resulting publications. Recent reviews have demonstrated inequities in published global health research between researchers from high-income countries and low- and middle-income countries in terms of authorship, gender and academic affiliations, among others. Reflecting the American Society of Tropical Medicine and Hygiene's aim to advance health equity globally, we propose to conduct a bibliometric analysis of the American Journal of Tropical Medicine and Hygiene (AJTMH) publications between 1952 and 2022. Specifically, we propose to assess the following: - Author order- Author affiliation(s), classified using World Bank country income classifications- Author gender, when available- Funding source- Study type- Study topic- Region of publication- Year of publication.Funding sources will be recorded primarily to identify main stakeholders for further dissemination of our findings. Data will be analysed using Student's t-tests and Chi-square, followed by logistic regression. Results from this review will 1) inform a widening participation strategy launched by the ASTMH in 2022, to reflect the current make-up of global health researchers worldwide and

2) strengthen the record of AJTMH as an innovative publication with not only its finger on the pulse of change, but also actively seeking to equalise the field of global health reporting. Finally, the authors will propose further direct collaboration with the AJTMH and its affiliates to update guidelines and prepare authorship guidelines describing the Journal's commitment to inclusivity, equality and fairness.

5802

ESTABLISHING A RELATIONSHIP WITH THE SURVIVORS OF TORTURE CLINIC AND THE UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE; AN INNOVATIVE ALLIANCE TO MENTOR AND ASSIST REFUGEES

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Kentucky ranks 5th in the nation for the number of refugees. A Physicians for Human Rights chapter was created in response to an unmet need in refugee support services. Students were recruited through an application process and were selected as vice president, secretary, treasurer, and community outreach chair. Our mission is to partner with the Survivors of Torture Clinic at the Univerisity of Louisville. The Survivors of Torture Resource Center offers comprehensive services to refugees and immigrants who have experienced torture in their home countries. They include direct mental health services, social and medical care coordination, and legal service referrals. Through our cooperative relationship, medical students can volunteer and serve as mentors to asylum seekers. Cultural differences often make it difficult for young refugees to adjust to a new country. Besides offering friendship, mentors can also assist them in navigating a foreign country. In addition to exposing them to different events in the city, they can provide them with a wide variety of restaurants to eat at or offer ways to foster their passions. Students will also help them navigate healthcare appointments and schedules. The US healthcare system is extremely daunting, and patients can feel intimidated when seeking to see a provider. A third-party mediator can help the patient explain their feelings to the doctor when there are cultural and linguistic barriers between the provider and patient. Additionally, students can assist refugees in finding transportation and organizing their medications. Through this program, students will gain exposure to working with marginalized populations and increase their cultural competence. Furthermore, refugees will receive much-needed peer support and have an easier time adjusting to life in the U.S.

5803

GROW502: A POP-UP CLINIC TO TACKLE HEALTH DISPARITIES WITHIN THE HOUSELESS POPULATION

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At the height of the Covid-19 pandemic and racial justice movement, students created, Grow502. The goal was to pursue a healthier community by raising awareness which led to the co-creation of a curriculum focused on education, advocacy, community engagement, and creative media. In 2022, we focused on the Houseless community, Refugees, and folks living in the West End. Houseless communities experience disparities in chronic diseases, premature death, poverty, and unemployment; systemic injustice in housing, healthcare, nutrition, and the environment are significant contributors. To raise awareness in our community and provide resources, we launched a pop-up clinic for the Houseless on May 21st. Some of the service offerings at this pop-up clinic included Dental Assessments, Wound Care, Showers, Vaccination, Food, and a Donation Drive. Other services include infectious disease testing and enrollment into Medicare. We kickstarted this event by having an event where we had a case-based discussion breaking down health disparities among the unhoused and barriers to proper health care. Homeless folks were transported to the clinic by Feed Louisville. Flyers were given to shelters in the area. Grow502 acted as a connection between the houseless and organizations in the community. Recognition of the unique healthcare needs of homeless people has encouraged the developing of special services for them. Homeless individuals are unique in the multiplicity of needs they experience, the lack of support networks they face, and the difficulty of their daily activities. Our hope as an organization is that these pop-up clinics will continue to be a vital asset in our community through the coordination of multiple services. Participants saw the pop-up clinic as a means of building awareness, inspiring others to reduce health disparities, and strengthening the partnership between harm reduction, the homeless, and the medical field. Due to volume, we are planning another pop-up clinic.

5804

NUTRITIONAL STATUS, DIETARY DIVERSITY AND FOOD INSECURITY AMONG WOMEN AND CHILDREN IN PERI-URBAN COMMUNITIES OF KARACHI, PAKISTAN

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Malnutrition is a serious public health problem in Pakistan. One of the causes is inadequate consumption of nutrients to support the requirements at various life stages. Undernutrition among women in the reproductive age leads to maternal morbidity and mortality, fetal growth restriction and childhood malnourishment. We conducted a survey in 7 peri-urban areas of Karachi, Pakistan to assess the nutritional status and dietary diversity among married women of reproductive age and their children under 2 years of age. We also assessed household food security. We used a two-stage systematic random technique to select households and enrolled 1470 mother-child dyads (210 at each site). To assess the nutritional status, we followed the 2018 FANTA guide for anthropometric measurements of participants and used the 10-item minimum dietary diversity scale for women and the 9-item minimum dietary diversity scale for children through 24-hour dietary recall. Household coping strategy and hunger tool were used to measure food insecurity. We found that slightly more than 45% women had normal BMI, while 16% were underweight. Among children, 24% were found to be 'wasted', 39% were underweight and 39% were stunted. We found that 22.5% (n=332) of women and 8% (n=188) of children met the standards for consuming 5 food groups. All households reported food insecurity. To cope, 20% (n=290) borrowed food; 30 % (n-438) limited their portion sizes; 31% (n=452) reduced the number of meals consumed, while 24% adults restricted their food consumption. We also found poor food access; 37% (n=549) of women reported not having food at home, 33% (n= 503) slept hungry, and 31% (n=463) reported atleast one day in the previous month in which they did not eat. These findings suggest that even in large cities like Karachi, the peri-urban population suffers from food insecurity and women and children are malnourished. Along with poverty alleviation at the macro level, there is a need for contextually designed interventions to improve the nutrition and health of women and growth trajectories of children.

5805

A SYSTEMATIC REVIEW AND META-ANALYSIS: IMPACT OF THE COVID-19 PANDEMIC ONVIOLENCE AGAINST CHILDREN

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COVID-19 lockdowns caused interruption of child protection services and economic/psychological burdens on parents. It has become challenging for teachers or school counselors to detect and report signs of abuse. Therefore, in this systematic review and meta-analysis (SRMA), we aimed to identify the impact of the worldwide COVID-19 pandemic on violence against children by investigating the change in the prevalence of violence against children before and during COVID-19 lockdowns. The protocol of this study was registered in PROSPERO with the registration number CRD42022377660. We included any studies eligible for meta-analysis comparing violence against children before and during COVID-19. Eleven

electronic databases were systematically searched in March 2022. The meta-analysis was conducted using STATA, pooled odds ratios were calculated, and subgroups by countries and sex of children (when possible) were analyzed. A total of eleven publications were included in the meta-analysis. Overall, we found insufficient evidence to support that the COVID-19 pandemic impacted the prevalence or proportion of any type of violence against children, even after segregating the data to the country or sex levels. Furthermore, one article showed a significant decrease in reporters from school staff, which might be explained by an under-report of child violence. In conclusion, although our results suggest that the COVID-19 pandemic did not result in increased prevalence of child abuse, we should be cautious when interpreting these results because the number of violence incidents could have been under-reported as a result of the lockdown and school closure. Therefore, we believe that the concerns about an increase in child abuse cases during the pandemic –although not statistically evidenced– still hold.

5806

A QUALITATIVE ASSESSMENT OF THE LANDSCAPE AND DYNAMICS OF CAPACITY STRENGTHENING INITIATIVES FOR MALARIA MODELING IN AFRICA

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Modelers in malaria-endemic countries face unique challenges in their pursuit of funding, research collaborations, and modeling training. Through in-depth interviews, this study aims to gathered malaria modeler perspectives on capacity strengthening and training initiatives, delved into the dynamics of implementing partner and modeler relationships with NMCPs and generated recommendations for equitable research collaborations and training initiatives. Preliminary fFindings revealed several opportunities for improving intercountry research collaborations, training, and communication with NMCPs. While there are were mixed perceptions about the role modelers should play in their collaborations with NMCPs, respondents largely agreed that modelers should be exploring questions that are relevant to NMCPs and technical support approaches should be more aligned with the needs of each NMCP. Respondents also highlighted that while communication with NMCPs can be challenging, maintaining flexibility, being highly responsive, and identifying multiple points of contact within NMCPs can help mitigate these challenges. As the study progresses, we will dive more deeply into the role of funders in creating better alignment among technical support and training activities. We will also dive more deeply into how technical support for NMCPs can be improved to generate better buy-in and greater sustainability.

5807

EPIDEMIOLOGICAL PROFILE OF ASYLUM SEEKERS AT THE US-MEXICO BORDER: ASSESSMENT OF DISEASE BURDEN IN A MATAMOROS MIGRANT SETTLEMENT CAMP FROM NOVEMBER 2019 TO MARCH 2021

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Asylum seekers at the US-Mexico border face significant health challenges. While select humanitarian groups deliver primary care at the border, there is a paucity of population-level data on disease incidence among this vulnerable population. Understanding asylum seekers' epidemiological profile is important for migrant health delivery and anticipating health needs upon entry to the US. The aim of this retrospective study was to characterize disease incidence among asylum seekers in the Matamoros, Mexico, encampment. De-identified health records from Nov 2019 to Mar 2021 were obtained from the NGO-run camp clinic. Logistic regression models estimated associations between health outcomes and demographic factors, including age, sex, country of origin, and migration time (time since departing the country of origin). From Nov 2019 to Mar 2021, 11,307 unique patient encounters were recorded. Patients were mostly female (59.9%) and from Central America (67.6%), with a median age of 27.0 (IQR: 9.4-36.8) years and median migration time of 4 months (IQR: 0.1-0.7 years). Acute respiratory diseases were of highest incidence (10.1%; 95% CI: 9.6-10.7), with the highest risk among children (aOR = 1.87, 95% CI: 1.65-2.13) and patients with migration time under 0.5 years (aOR = 1.68, 95% CI: 1.46-1.93). Infectious and parasitic diseases, including mycoses, helminthiases, pediculosis, and protozoal diseases, were more likely to occur among patients with longer migration times (aOR = 1.59 (95% CI: 1.14-2.19) for migration time of 0.5-1 year; aOR = 2.00 (95% CI: 1.23-3.14) for migration time of 1-2 years). Among these, mycoses resulted in the highest incidence (0.7%, 95% CI: 0.6-0.9). Logistic regression analyses found that infection with mycoses was significantly associated with older age, while parasitic diseases, pediculosis, and acariasis were more significantly associated with children and younger adults. These findings have important implications for clinicians, NGOs, and policy makers working to provide healthcare to asylum seekers at the US-Mexico border, including targeted infectious disease reduction and treatment strategies.

5808

EXPLORING THE POTENTIAL OF POLICY IMPLEMENTATION STRATEGIES AS HEALTH JUSTICE-MAKING TOOLS: AN ILLUSTRATIVE CASE OF NEGLECTED TROPICAL DISEASES MASTERPLAN IN ZAMBIA.

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Neglected tropical diseases (NTDs) pose a considerable challenge in Zambia, with more than 12 million people at risk of at least one NTD. Social factors play a critical role in disease transmission and effectiveness of control and elimination measures. National NTD Masterplans are the main policies used in endemic countries, outlining strategies that improve access to key interventions like mass drug administration that facilitate progress towards disease elimination. Implementation processes of Masterplans may result in relational inequities as policy strategies are translated across administrative levels and among different actors. Consequently, populations such as migrants and mobile populations are hardly reached by evidence informed interventions. Policy processes have had limited impact in reducing inequities as proposed options such as collaborative governance are simple yet inequities are a wicked, ambiguous and contested problems. The problematization of NTDs in policy has resulted in a biomedical focus that limits social and policy research, which address key issues like health inequities arising during implementation. Further, few policy studies have systematically evaluated implementation processes and strategies translating NTD Masterplans into accessible services within communities. We use a case study of the process of developing policy implementation strategies for Zambia's National NTD Masterplans to understand if these findings help in shifting our understanding of transformative implementation bringing us closer to realizing the goal of health equity and justice. We evaluate the potential of equity focused implementation strategies to promote transformative implementation of health policies in Zambia. We make a theoretical proposition that implementation strategies developed using Africana critical theories combined with implementation science frameworks can modify policy implementation processes to transform the social, economic and political contexts into which health policies are implemented, reducing health inequities and improving the fit of these policies in their contexts.

5809

NATIONAL GUIDELINES AND LEGISLATION CONCERNING THE MANAGEMENT OF ZIKA VIRUS INFECTION IN PREGNANT WOMEN DURING THE 2015-2018 EPIDEMIC IN LATIN AMERICA

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During the 2015-18 Zika Virus (ZIKV) epidemic in Latin America, microcephaly and congenital abnormalities were shown to be associated with ZIKV infection in pregnancy. Given the multitude of malformations beyond microcephaly experienced with maternal ZIKV infection and the uncertainties associated with diagnosis, the challenges regarding policies for response to an infection in pregnancy including termination options became evident. We examined fourteen documents from eight selected Latin American countries containing the management and guidance for ZIKV infection during pregnancy. Per country, we concentrated on the availability of guidelines, laboratory diagnosis practices, ultrasound screening schedules for standard and at-risk pregnancies, communication of laboratory results of infection, antenatal checkup visits modifications, the legal framework around abortion and their approaches of adaptations as a reaction to the epidemic. All guidelines considered pregnant women with ZIKV infections as high-risk pregnancies that needed to follow stricter protocols and agreed to use molecular RT-PCR test as the diagnostic method of choice. There were discrepancies between country protocols of reporting PCR results to the pregnant women. All guidelines, except for Brazil and Bolivia, have specified their ultrasound scans (US) follow-up schedule in case of ZIKV infection during pregnancy. There was notable increased demand for access to legal abortions during the ZIKV epidemic in included countries, clandestine abortions potentially have substantially surpassed these numbers. The included examined guidelines, apart from Ecuador, have not included early termination issues in its explicitly stated ZIKV-related guidelines. The fear of ZIKV-related congenital abnormalities puts abortion at the center of moral concerns. Our study suggests that the impact of guideline and policy response is an important public health intervention, and early investigation of protocols and policy impacts in real-time during emerging disease events is recommended.

5810

IMPACT EVALUATION OF SOCIAL MEDIA CAMPAIGN TO IMPROVE ATTITUDES AND BEHAVIORS ON COVID-19 VACCINE IN AFRICA: DIFFERENCE-IN-DIFFERENCE ANALYSIS USING TANZANIA AS A CASE STUDY

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In Tanzania, the One by One: Target COVID-19 campaign was launched nationally in July 2022 to address the prevalent vaccine hesitancy and lack of confidence in COVID-19 vaccines. The campaign mobilized influencers to use social media and viral content to increase COVID-19 vaccine confidence and reduce hesitancy, with the ultimate goal of increasing COVID-19 vaccine uptake in the country.We used programmatic data collected through an online survey before and after the campaign to empirically assess the impact of the campaign on three outcomes: vaccine confidence, vaccine hesitancy, and vaccination status. We conducted a difference-in-difference (DiD) analysis and performed a crude, adjusted, and propensity score-matched analysis for each study outcome. Lastly, to observe whether there was any differential impact of the campaign across age groups, we repeated the analyses on age-stratified subgroups. Data included 5,804 survey responses, with 3,443 and 2,362 responses collected before and after the campaign, respectively. Although there was only weak evidence of increased COVID-19 vaccine confidence in the campaign-exposed group compared to the control group across all age groups, we observed a differential impact among different age groups. While no significant change was observed among young adults aged 18-24 years, the campaign exposure led to a statistically significant increase in vaccine confidence (weighted/adjusted DiD coefficient=0.76; 95% CI: 0.06, 1.5; p-value=0.034) and vaccination uptake (weighted/adjusted DiD coefficient=1.69.; 95% CI: 1.02, 2.81; p-value=0.040) among young adults aged 25-34 years. Among adults aged 35 years and above, the campaign exposure led to a significant decrease in vaccine hesitancy (weighted/adjusted DiD coefficient=-15; 95% CI: -21, -8.3; p-value<0.001).The social media campaign successfully improved vaccine hesitancy, confidence, and uptake in the Tanzanian population, albeit to varying degrees across age groups. Our study provides valuable insights for the planning and evaluation of similar social media communication campaigns aiming to bolster vaccination efforts.

5811

USING MALARIA SURVEILLANCE AT ANTENATAL CARE TO DECODE LOCAL PATTERNS IN SEASONAL TRANSMISSION TREND IN TANZANIA, 2014-2022

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Optimal deployment of many malaria control interventions relies upon accurately characterising seasonal peaks in transmission. In West Africa, there exist largely validated rubrics defining seasonality based on rainfall patterns. In East and Southern Africa, rainfall also often exhibits strong seasonality, but other factors, including temperature, land use and bodies of water, are substantially different to the Sahel. Meanwhile, interpreting seasonal transmission patterns in case-reporting systems remains challenging, especially in the context of chemoprevention efforts for children. Malaria screening at antenatal care (ANC) enrolment has been offered routinely to pregnant women throughout Tanzania since 2014. Here, we use monthly summary reports of these tests from 2,437 health facilities across all 184 districts in Tanzania from 1 January 2014 to 31 December 2022 to characterise seasonality patterns across the country. We fit an existing malaria model using particle Markov chain Monte Carlo to account for the lagged nature of prevalence and infer seasonal patterns in incidence across the country. Pearson correlation coefficients measured synchronization

between this estimated incidence and rainfall. Our results suggest the extent to which rainfall explains malaria seasonality varies across the country. Central regions of Dodoma and Iringa had high correlation (r = 0.77 and 0.62, respectively). In contrast, correlation in regions close to major lake or irrigation systems varied from positively (Rukwa, r = 0.76) and negatively (Geita, r = 0.41) correlated to no correlation (Mwanza, r = -0.005). Another motivation for incorporating an existing malaria model within our framework is to provide near-real-time sub-nationally-targeted estimates of the likely impact of current and future interventions – a use case we will demonstrate by projecting Seasonal Malaria Chemoprevention impact. These results highlight the wider value of ANC-based malaria screening data as a tool to inform responsive and locally tailored control strategies.

5812

INTEGRATION, EXPLORATION AND REUSE OF CLINICAL AND EPIDEMIOLOGICAL DATASETS: A CASE STUDY USING MALARIA DATA ON THE CLINEPIDB PLATFORM

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Open access to data from epidemiological studies has tremendous potential to preserve research outputs, increase secondary data use, and accelerate discovery and translational impact. Data sharing is increasingly a requirement for funding and publication of epidemiological research, but it comes with technical and ethical challenges. We present a case study of successful data sharing from the clinical epidemiological database, ClinEpiDB.org, built in 2018 to facilitate access to de-identified data from large, high-quality global health studies. ClinEpiDB currently hosts data from over 1.2 million participants representing 37 global studies in three major domains - malaria, maternal, newborn & child health, and neglected tropical diseases. The PRISM2 team, an International Center of Excellence for Malaria Research (ICEMR), conducted a cohort study of malaria in Uganda and collected socioeconomic, demographic, clinical, entomological, and other data, and was interested in data sharing to maximize use and impact of their research and to meet funder and journal requirements. De-identified data was securely transferred to ClinEpiDB along with codebooks and other contextual metadata. PRISM2 variables were ontologically harmonized for increased interoperability, and after extensive quality checks, data was released on the free, open-access, online data platform ClinEpiDB.org. In their publication, the PRISM2 team included a link to recreate key findings of PRISM2 analyses on ClinEpiDB. Readers can follow the link to learn about PRISM2 cohort study methodologies, discover additional variables collected but not included in the published analysis, download data with no restrictions, and modify their copy of the published analysis to explore their own hypotheses in a point and click interface. Metrics reveal that PRISM2 data is being accessed regularly even three years after publication. The PRISM2 team gained visibility while retaining ownership of data and making all data access decisions. ClinEpiDB will expand in 2023 with integration of new datasets as well as enhanced visualization tools and the ability to derive variables.

5813

IMPROVING EFFICIENCY IN DETECTING ANOMALIES IN HEALTH SUPPLY CHAIN DATA USING AN AUTOMATED CONSUMPTION ANOMALY DETECTION TOOL IN ZAMBIA

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Identifying data anomalies help correct data errors and improve accuracy in supply forecasting and planning for medicines. However, it is challenging to detect anomalies from over 3000 facilities and over 5000 health products through eLMIS, because of the lengthy and less accurate manual process given that the system is not designed to automatically generate such reports. In 2019, the USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) project developed an automated data analysis tool for detecting consumption anomalies and establishing the causes of the data errors using Python and Applied Statistical Process Control (SPC). This tool uses eLMIS data over a period of 24 months to determine the moving average of consumption over a set threshold and then uses the result to detect anomalies monthly. The automated system streamlined the process and improved the accuracy of anomaly detection from less than 100 a month with a manual process to over 200 detections monthly, using about 25 minutes to produce a list of all anomalies for over 3000 facilities and over 5000 health commodities, thereby improving accuracy and speeding up decision-making for all health products, including malaria, commodities. The anomaly report is shared monthly with the Central Pharmacy Unit of the Ministry of Health and the Chief Provincial Pharmacists to investigate and address data quality issues. The National Drug Theft Task Force (NDTTF) and provincial task forces also use the report to investigate anomalies that are not linked to incorrect data entry through on-the-spot checks at health facilities. Since October 2019, GHSC-PSM has supported the MOH by using this tool to identify and correct several data quality issues such as incorrect use of units of measure and transpositions errors. The anomaly detection tool replaced a time-consuming and less accurate manual process, allowing supply chain actors to correct data quality issues quickly and adjust supply plans accordingly. The tool is open-source and can be easily adopted by other countries to detect anomalies or other quality issues.

5814

COMBINING ORTHOGONAL ANALYTICAL TECHNIQUES TO IDENTIFY SUBSTANDARD OR FALSIFIED FORMULATIONS OF PHARMACEUTICALS

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Near infra-red (NIR) technology is a powerful tool to assess the quality of pharmaceutical dosage forms. The NIR spectrum is sensitive to multiple factors: the identity and concentration of analyte, but also the excipient materials, capsule opacity and color, and pill coatings. Most NIR instruments use libraries of authentic products to discriminate between good quality and bad quality products, but assembling and maintaining those libraries is difficult in many low- and middle-income countries because markets are not stable and there are unreported changes to product formulations. Therefore, we have been developing methods to identify substandard or falsified pharmaceuticals that do not rely on libraries of authentic products. In this poster, we will report on several aspects of this work. Machine learning models were trained on lab-formulated mixtures of a target API with different excipients. Although the ML models all have “blind spots”, a simple voting algorithm compensates for the blind spots. The algorithm was applied to 40 samples of good and bad quality acetaminophen dosage forms and was able to classify them with accuracy of 94%. Capsule opacity and color is known to interfere with in-situ NIR analysis of dosage forms. We probed twenty different empty gelatin capsules with scanning electron microscopy and X-ray fluorescence, finding different amounts of opaquing agents and dyes that could be distinguished by clustering analysis of the NIR spectra of materials inside these capsules. NIR methods can be complemented by other field analysis methods, such as chemical color tests applied using paper analytical devices (PADs). PADs are engineered micro-fluidic systems that analyze capsules or

tablets for chemical constituents by using stored reagents and water flow, generating unique color patterns. These color patterns were used to train a convolutional neural network and other machine learning tools, giving accurate classification of 20 types of APIs. Hybrid classification algorithms were developed to combine the data from both PADs and NIR, which significantly improved the results better than either method if used alone.

5815

USING THE DISTRIBUTION OF CLINICAL DATA FROM ROUTINE USE OF AN ELECTRONIC CLINICAL DECISION SUPPORT ALGORITHM TO IDENTIFY CLINICAL SKILL GAPS IN PRIMARY CARE IN RWANDA: A RETROSPECTIVE ANALYSIS

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Clinical Decision Support Algorithms (CDSAs) that guide clinicians throughout the consultation have the potential to enhance quality of care in resource-limited outpatient settings. However, the extent of the improvement depends on the accuracy of the inputs entered, which depends on the clinical skills (ability to identify specific signs or symptoms). In this retrospective analysis, we used data from an electronic CDSA deployed in 16 health centers in Rwanda for one year to evaluate the clinical skills of primary care clinicians, identify and understand the gaps, with the goal of designing an eLearning platform to address them. We analyzed data from 20,204 consultations with children aged 1 day to 14 years, conducted between November 2021 and October 2022, focusing on a set of numerical variables: temperature, MUAC, weight, height, z-scores (MUAC for age, weight for age, and weight for height), respiratory rate, blood oxygen saturation, and heart rate. Based on statistical summary measures (median, IQR, distribution, % of missing values) and their variation in individual health centers as compared to the average, we identified 11 health centers with potential important clinical skill gaps, signaled by high frequency of skipping measurements, entering the same plausible value repeatedly, and entering implausible/likely incorrect values. We then observed 209 consultations in the problematic health facilities to understand the potential causes of errors. These field observations showed that 19% of measurements were skipped -respiratory rate behind the most problematic one (43%) - due to misplaced equipment, not considering it necessary, or the child being agitated. More frequently (57%), measurements were done incorrectly -the worst ones being weight (82%), MUAC (77%), temperature (75%), and height (69%). As a next step in the project, we are creating eLearning content that is tailored to the clinical skill gaps we observed. The eLearning modules will be introduced to the health workers in June 2023, and their impact evaluated through re-analysis of the CDSA data around August or September 2023.

5816

ELECTRONIC DATA CAPTURE IMPLEMENTATION DOCUMENTING MASS DEWORMING CAMPAIGNS:

PILOT ANALYSIS IN THE DOMINICAN REPUBLIC

2019-2021

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High-quality data is critical to evaluating outcomes and interventions in low- and middle-income countries (LMICs). Health information and communication tools (ICTs) are increasingly being used to improve data documentation. However, ICT evaluation remains limited. Without proper study, several pilots fail to scale due to lack of funding and stakeholder engagement. In partnership with the Children's Hospital of Philadelphia, the Niños Primeros en Salud (NPS) clinic in Consuelo, Dominican Republic implemented electronic data capture (EDC) to document and evaluate biannual deworming campaigns. This study evaluates the data quality, efficiency, and efficacy of this pilot, adding to the literature on ICT utilization in LMICs. EDC was implemented via tablet-based software CommCare. All children registered at NPS ages 2-5 years with no deworming in the prior 4 months were eligible. Providers visited nine neighborhoods and documented deworming during the visit. This is a retrospective post-implementation analysis of five distinct campaigns between 2019-2021. Descriptive statistics examining demographics and EDC data quality, efficiency, and efficacy were conducted. Analysis of 503 subjects showed 78.7% were dewormed at least once in similar proportions across target neighborhoods. 52.7% of subjects were dewormed 2-4 times, and 57.6% in half or more of campaigns during which they were eligible. Deworming rates per campaign ranged from 26.1% to 66.8%. Post-EDC implementation, 78.7% of subjects were dewormed compared to 64.4% pre-implementation, with more serial dewormings. Only two data fields were missing data. Median task completion time was 5.0 seconds. Median cloud upload time was 16.5 hours. EDC was an efficient, efficacious tool in community deworming campaigns in this rural setting. EDC ensured better data quality, surveillance, and outreach, with improved deworming rates compared to pre-implementation. While EDC holds promise for low-resource settings reliant on community campaigns, funding remains limited due to lack of study. Evaluation is critical to scaling promising pilots and bridging the digital divide.

5817

UNDERSTANDING THE 'CONTEXT' IN TROPICAL DISEASE CONTROL COMMUNICATION: A SRI LANKAN EXPERIENCE

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Preventing NTDs in LMICs requires a collaborative, cross-disciplinary, culturally appropriate approach that goes beyond biomedical interventions. Effective communication is key to controlling tropical diseases, however in LMICs, communication strategies are scarcely informed by scientific evidence. Media ethnography may capture the context-specific communication channels used in everyday community life, including modern and traditional media. We conducted an ethnographic study by using multiple techniques, including participant observation, in-depth interviews, key informant interviews, and auto-ethnographic diaries, to explore community-specific communication pathways and techniques for preventing cutaneous leishmaniasis in rural Sri Lanka. We engaged with local communities to Explore their communication practices and networks and identified various communication types and forms. The modes of communication identified and discussed by the community for disease prevention activities included interpersonal, group, public, mass, and virtual methods of communication, as well as verbal, non-verbal, performing, written, audio, visual, formal, and informal forms of communication. We identified that rural communities prefer and perceive more effective traditional communication methods, such as Loudspeaker, Group communication, schools, door-to-door campaigns, posters, notice boards, leaflets, and street dramas, to mass media in disseminating health information. We also observed the critical role of community networks in gathering and sharing health information. Our study highlights the need for evidence-based communication strategies that are context-specific and tailored to local communities. Using ethnographic research methods, we can better understand rural communication practices and networks and develop context-specific health communication models to prevent NTDs.

5818

MATCHING DATA FOR THE STATE PARTIES SELF-ASSESSMENT ANNUAL REPORTING (SPAR) TOOL FROM 2010 TO 2021

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Since 2010, States Parties have been required under the International Health Regulations (IHR) to submit self-assessment annual reporting tool (SPAR) to monitor, track and evaluate compliance on IHR's core capacities, as a key component to World Health Organization (WHO) monitoring and evaluation frameworks (MEFs). Each year data is collected, stored and made accessible in the Electronic State Parties Self-Assessment Annual Reporting Tool (e-SPAR), a web-based platform hosted by the WHO. These data can be accessed by both States Parties and the public to track progress and to identify priority areas for national action. Since its inception, the SPAR has undergone three revisions, most recently in 2021. With each revision, capacities and indicators to assess country health security capacity have changed to improve measurement towards compliance. The revisions, despite their value-added to governments and global health researchers, prevent comparative analysis between tools, hampering country ability to understand systemic challenges to sustained capacity building. This study aimed to develop a method to match data across the three revisions of the IHR self-assessment tool, and to provide a single source to access and compare national, regional and global annual self-assessment scores for IHR compliance. Annual reporting data from 2010 to 2021, for 196 States Parties, was collected and analyzed. From these analyses, we developed a matching framework and aligned MEF data, providing a robust assessment at the capacity level. Ultimately, these analyses have resulted in the creation of a publicly available tool which visualizes IHR MEF self-assessment scores from the period of 2010 to 2021 for all reporting countries with the ability to compare scores over the three MEF revisions for the first time, providing insights on health systems strengthening at the national, regional, and global levels.

5819

RECONSIDERING THE INFECTION RISK OF JAPANESE ENCEPHALITIS VIRUS IN AUSTRALIA

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Japanese encephalitis virus is a leading cause of viral encephalitis worldwide, causing life-changing disability and death in humans. Historically, the disease has only been recognised in Australia in small outbreaks in far northern sub-tropical regions, fuelled by independent introductions. However, since early 2022, the disease has been identified in 35 people and at least 85 piggeries across the central and eastern Australian mainland, including the temperate far south. The transmission cycle of the mosquito-borne virus is complex, with many reservoir species. In this work, we model the geographic distributions of suspected wildlife host and vector species using environmental data. We use the predictions of these environmental niche models to visualise the potential spatial extent of disease transmission during the recent outbreak. By incorporating heterogeneous surveillance effort and detection data we also map the intensity of detected disease transmission. We consider how the outputs of our models and their associated uncertainties might quantitatively inform the spatial allocation of surveillance resources within a structured decision-making framework. This framework will support decision-makers to best respond to future outbreaks of Japanese encephalitis virus in Australia.

5820

USING MACHINE LEARNING TO PREDICT SURGICAL OUTCOMES OF PATIENTS WITH HYDROCEPHALUS POST INTERVENTION AT CURE CHILDREN'S HOSPITAL OF UGANDA

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The major objective of this research is to predict an outcome after surgical intervention of an individual using a machine learning approach. This study was carried out at Cure Children's Hospital of Uganda which is found in the Eastern part of the country about 240 km from Kampala, the country's capital city. This hospital also serves as the country's referral hospital for patients suffering from pediatric hydrocephalus and spina bifida. The data was collected retrospectively from the medical records kept at the hospital premises. A well-trained clinician assisted in data extraction using a questionnaire that was well designed in Redcap, a web-based software used to create and manage research databases and the data extracted covered a period between 2015 and 2019. The variables extracted include; age at presentation to the hospital, surgical procedures carried out, age at the time of head increase, head circumference, place of birth, the season of birth, gestational age at birth, hydrocephalus etiology, child's weight, WBC, CSF volume and brain volume before surgery after carefully doing a literature search. The outcome variable is a binary outcome, a surgical failure or success after surgical intervention. Exploratory data analysis and feature selection were done. A predictive model was developed using a machine learning algorithm of random forests. This model uses mean square error for regression and mean Gini for classification. Model performance was evaluated on a successful surgical outcome by Area Under the ROC curve (AUC), accuracy (AC), specificity (SP), sensitivity (SN), negative predicted (NPV) and positive predicted value (PPV). The model showed a good performance (AUC = 0.773, AC = 0.72, SP = 0.659, SN = 0.751, NPV = 0.586, PPV = 0.772). The prediction outcome can be used by the surgeons to make informed decisions pertaining to patient monitoring and the need for surgery revision before discharging them from the hospital.

5821

A SYSTEMATIC REVIEW OF THE DATA, METHODS AND ENVIRONMENTAL COVARIATES USED TO MAP AEDES-BORNE ARBOVIRUS RISK

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Aedes (Stegomyia)-borne arboviruses pose a global threat, but gaps in surveillance hinder comprehensive assessments of risk. Geostatistical models combine data from multiple locations and use links with

environmental and socioeconomic factors to make predictive risk maps, allowing for targeted interventions. We systematically reviewed past risk mapping approaches for these arboviruses from local to global scales to identify similarities and differences in data types, covariates, and models. We searched online databases for predictive risk mapping studies for dengue, Zika, chikungunya and yellow fever with no geographical or date restrictions. We included studies that needed to parameterize or fit their model to real-world data and make predictions to new spatial locations of some measure of the population-level risk of viral transmission. Study quality was assessed with a modified scoring criteria based on the EPIFORGE checklist. We found a methodological shift in risk mapping through time based on 183 papers. We found that earlier approaches to map risk pooled occurrence data and used high dimensional machine learning models to map suitability for transmission at global or continental scales. Following major epidemics of Zika and chikungunya in the Americas, mechanistic models fit to national-resolution incidence data have been increasingly used to track the dynamic spread of epidemics among countries. With improved dengue case-based surveillance systems now present in many countries, statistical mixed effects models applied at the subnational scale have become increasingly common. Half of the studies reviewed utilized temperature and rainfall as covariates, with human mobility increasingly considered. A robust variable selection procedure was performed in 33 out of 148 studies that did not use mechanistic models or only random effects. Our review shows that approaches to map risk for different arboviruses have diversified based on changing use cases, epidemiology, and data availability. Future studies should consider the purpose of the map; to maximize improvements in data quality and statistical methodologies.

5822

ALTERNATIVE EPIDEMIC INDICATORS FOR COVID-19: A MODEL-BASED ASSESSMENT OF COVID-19 MORTALITY ASCERTAINMENT IN THREE CITIES IN LOW-INCOME COUNTRIES

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Not all COVID-19 deaths are officially reported and, particularly in low-income and humanitarian settings the magnitude of such reporting gaps remain sparsely characterised. Alternative data sources, including burial site worker reports, satellite imagery of cemeteries and social-media-conducted surveys of infection, may offer solutions. By merging these data with independently conducted, representative serological studies within a mathematical modelling framework, we aim to better understand the range of under-reporting using the example of three major cities: Addis Ababa (Ethiopia), Aden (Yemen) and Khartoum (Sudan) during 2020. We estimate 69% - 100%, 0.8% - 8.0% and 3.0% - 6.0% of COVID-19 deaths were reported in these three settings, respectively. In future epidemics, and in settings where vital registrations systems are absent or limited, using multiple alternative data sources could provide critically-needed, improved estimates of epidemic impact. However, ultimately, functioning vital registration systems are needed to ensure that, in contrast to COVID-19, the impact of future pandemics or other drivers of mortality are reported and understood worldwide.

5823

GLOBAL HEALTH INFRASTRUCTURE DEVELOPMENT IN LOW AND MIDDLE INCOME COUNTRIES, THROUGH MEDICAL EQUIPMENT REMANUFACTURE: POTENTIALS, PROSPECTS AND CHALLENGES IN NIGERIA

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Sustainable healthcare delivery through provision of adequate medical equipment is a very critical component of global health. Remanufacture of medical equipment (ME) in low and middle-income countries (LMICs) can be a cost-effective and sustainable way to improve access to healthcare services. Remanufacturing and reverse logistics of remanufactured products are increasingly becoming popular in many developed countries due to several reported benefits, however, most developing countries are yet to fully adopt and integrate ME remanufacturing into their healthcare systems. The objective of the study was to identify the potentials, prospects and challenges impeding the adoption and implementation of ME remanufacture, including reverse logistics in a resource limited country such as Nigeria. The study identified and contacted various stakeholders from relevant professional backgrounds, such as clinicians, engineers, technicians, and policy makers, who are currently working in public and private sectors, academia, biomedical industries, and in healthcare facilities. Information was obtained using semi-structured interviews and focused group discussions allowing participants to give feedbacks which was analysed and ranked in order of significance The following were highlighted as key factors affecting the implementation of remanufacture in Nigeria; lack of adequate power supply, resource constraint, inadequate facilities and infrastructural deficit to support remanufacture, lack of database to keep track of medical equipment lifecycle, shortage of skills and expertise in remanufacture, lack of spare parts and poor coordination of raw materials extraction from equipment core. Overall, remanufacturing medical equipment in LMICs has the potential to improve access to healthcare services and reduce healthcare costs, while also promoting sustainability and reducing waste. However, it requires policies supporting significant investment in skills development and infrastructure, as well as ongoing monitoring and evaluation to ensure that the remanufactured equipment meets the necessary standards.

5824

PLOTTING A PATH THROUGH THE PLASMODIUM VIVAX TREATMENT DILEMMA: A MODELLING STUDY INTEGRATING INDIVIDUAL-LEVEL OBSERVATIONS FROM PRIMAQUINE TRIALS AND POPULATION-LEVEL TREATMENT EFFECTS

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Upon primary infection, some Plasmodium vivax (Pv) parasites develop into hypnozoites that lie dormant in the liver for weeks to months before reactivating to cause relapses. Treatment of Pv thus calls for radical cure, a type of therapy that clears parasites in both blood flow and the liver. Several randomised control trials (RCTs) have compared drug regimens with the liver stage drugs primaquine (PQ) and tafenoquine (TQ). While it is possible to estimate the individual-level efficacy of these drug regimes, their population-level impact still must be evaluated in cluster randomised trials. Such trials are necessary to measure the non-linear effects on transmission due to lower, heterogeneous Pv circulation and decreased population immunity. We developed an infection risk model and fit it to IMPROV trial data (two PQ regimens and a control arm trialled in multiple locations) assuming relapse and biting rates to be location-specific, but

drug efficacy to remain constant across locations. Next, we estimated the population-level impact of introducing radical cure in case management using an existing Pv transmission model covering multiple scenarios that vary by transmission intensity, seasonality, Pv relapse rates and care-seeking behaviour. Combining our efficacy estimates with hazard ratios and adherence data from RTCs, we tested several radical cure regimens varying dosage and duration of administration. The efficacies estimated for the 7- and 14-day IMPROV PQ regimens (7 mg/kg total dose) were of 81% (95% CI: 66%-96%) and 86% (95% CI: 72%-99%), respectively. Introducing radical cure may make elimination feasible where transmission is already low (<2% PCR-prevalence). As transmission intensity increases, the efficacy of radical cure is vastly reduced and differences between regimens even out. To date PQ and TQ have been tested under trial conditions, while real-world implementations introduce many constraints that hamper their population-level impact. Rather than focusing on optimal dose and duration of administration, it might thus be more effective to increase adherence and care-seeking rates, and to widen eligibility criteria.

5825

AN EXPLAINABLE MACHINE LEARNING APPROACH IN THE PREDICTION OF MORTALITY AMONG PEDIATRIC PATIENTS HOSPITALIZED WITH ACUTE GASTROENTERITIS IN WESTERN KENYA

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Diarrhea is the second leading cause of death in children <5 years globally. Mortality prediction scores for diarrhea are currently unavailable but could provide opportunity for early detection of patients at-risk of death following an episode of acute gastroenteritis (AGE). We built and evaluated machine learning (ML) models to predict mortality among pediatric patients admitted with AGE (≥3 loose stools and/or ≥ 1 episode of unexplained vomiting followed by loose stool within a 24-h period) at Siaya County Referral Hospital between 2010-2020. We employed 6 ML algorithms to predict mortality using de-identified data collected from the AGE cases. We evaluated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the area under the curve (AUC) for each of the models. We conducted explanatory model analysis (EMA) and business value evaluation (BVE) of the best model. During the study period, 12, 546 children aged <5 years from the Health and Demographic Surveillance System were admitted, of whom 2,271 (18.1%) had AGE and 164 (7.2%) subsequently died. The sensitivity ranged from 61.0%-78.0% across models, while the specificity and AUC ranged from 71.7%-78.7% and 74.3%-82.6%, respectively. The Random Forest (RF) was the best model achieving 78.0%, 76.6%, 20.6%, 97.8% % and 82.6% for sensitivity, specificity, PPV, NPV and AUC, respectively. The SHAP attributions for the top 5 most important features from the EMA for the RF model were chest indrawing (-0.09), nasal flaring (-0.07), wasting (0.03), stunting (-0.03) and malaria (-0.02). From the BVE, the RF model was able to identify 3 times higher number of deaths compared to a random selection if we picked the top-20% cases based on model probability, and it was able to select 60% of overall deaths from the same selection. We did not observe broad variations in the performance of the models. These findings demonstrate alternative algorithms for prediction of patients at risk of death for targeted interventions to increase chance for survival following an episode of AGE.

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TROPICAL TROUBLES: NEURASTHENIA AMONG MISSIONARY EX-PATS IN AFRICA, 1900-1945

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Discussions of "tropical neurasthenia" (TN) abounded in early 20th century medical journals. TN provided specialists in the emerging field of tropical medicine with a diagnostic classification to explain the vague symptoms that North American and European ex-pats often complained of in tropical climates. The condition was also used to account for high rates of invaliding among colonial staff and missionaries. One 1913 report in the British Medical Journal estimated that NT invalided 20% of all missionaries at tropical posts. Climate-based theories concerning the aetiology of NT were common. Some experts blamed not simply "tropical light" itself but exposure to its different spectra. Others blamed climate, heat, humidity, and altitude, while others cited ex-pats' contacts with "diseased or depraved indigenous peoples or simply the sense of loneliness and despair." Symptoms included irregular heartbeat, irritability, loss of appetite, sexual dysfunction, depression, and even suicide. Relying primarily on archival and published primary sources, this presentation will examine the rise and fall of TN as a clinical entity during the first quarter of the 20th century.

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LOCAL PERCEPTIONS OF YELLOW FEVER OUTBREAKS IN UGANDA: A QUALITATIVE STUDY

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Yellow fever (YF), a mosquito-borne viral hemorrhagic fever, is endemic in Uganda and causes frequent outbreaks. We investigated the largest YF outbreak to date in Uganda and three subsequent smaller outbreaks. The aim of this study was to explore local perceptions of YF outbreaks to inform future public health campaigns. In this qualitative study we conducted 43 semi-structured interviews, 4 focus group discussions and 10 expert interviews - in total 76 participants. Data were collected in six affected districts with yellow fever outbreaks in 2010 and 2016. We included vulnerable groups such as elderly people ≥ 65 years and pregnant women. Participants perceived YF as a deadly disease. Although signs and symptoms of YF were broadly known the disease was frequently confused with newborn icterus, severe malaria, and hepatitis. Despite excessive awareness campaigns participants believed YF could be contracted by multiple pathways such as mosquito bites, airborne, close contact, sexual intercourse, vertical transmission, lack of hygiene, and through excessive consumption of yellow foods. Furthermore, people in remote areas affected by YF outbreaks were frequently unaware of the cause of outbreak. If a disease and its transmission pathway is not understood preventive measures cannot be successfully implemented. Moreover, timely diagnosis and reactive outbreak measures may be delayed. Thus, we recommend improving health education in communities at risk through village health teams, education at health centers, schools, and trusted community members. Awareness campaigns should be in conformity with local language habits. Additionally, public participation could be an important strategy to improve awareness among communities at risk.

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PREVALENCE AND PREDICTORS OF INTENTION TO USE TOBACCO AMONG ADOLESCENTS IN OYO STATE, NIGERIA

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Tobacco use is a major public health problem globally, especially in developing countries like Nigeria. Despite the well-known risks associated with tobacco use, many individuals still initiate and continue to use tobacco. The intention of tobacco use is an important predictor of the actual use of tobacco, so therefore, understanding the associated factors is critical to developing effective tobacco prevention interventions. The goal is to assess

the predictors of intention to use tobacco among school-going adolescents in Oyo State, Nigeria. This was a cross-sectional survey among randomly selected adolescents (2,590) attending 28 secondary schools across six Local Government Areas (LGAs) in Oyo State, Nigeria. The participants' sociodemographics, knowledge, attitude, harm perception, tobacco use, SHS exposure, and intention of tobacco use were assessed using the modified GYTS questionnaire. Data were analyzed with SPSS version 25 and P-value was <0.05. Participants' mean(±SD) age was 14.6(±1.3). The majority were females (48.1%) and schooled in urban LGAs (70.8%). The prevalence of intention to use tobacco was 11.7%. Some (2.2%) were past tobacco users, 9.8% owned a tobacco-branded item, and 22.5% were against banning tobacco adverts. Some had low tobacco harm perception (40.9%), perceived that it was easy to buy tobacco (22.5%), had poor attitude to tobacco use (35.3%), and 10.5% had smoking friends. Predictors of intention for tobacco use were: schooling in urban areas (aOR:1.95;95%CI:1.40-2.71), male gender (aOR:1.45;95%CI:1.11-1.90), past tobacco user (aOR:3.18;95%CI:1.69-6.00), owning a tobacco-branded item (aOR:1.65;95%CI:1.14-2.40) and being against the ban on tobacco adverts (aOR:1.82;95%CI:1.34-2.38). Others were low harm perception (aOR:1.76;95%CI:1.31-2.25), poor attitude towards tobacco use (aOR:1.69;95%CI:1.30-2.21), perceived ease of buying tobacco (aOR:1.37;95%CI:1.02-1.84), and having smoking friends (aOR:1.71;95%CI:1.17-2.48). The intention of tobacco use among the participants was 11.7%. The predictors included individual, interpersonal, and environmental factors.

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COMMUNITY PERCEPTIONS OF INCENTIVES FOR MINIMALLY INVASIVE AUTOPSY IN CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) IN WESTERN KENYA

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Incentives play an important role in improving participation in research and establishing ethically acceptable incentives is essential to preserving research integrity. Child Health and Mortality Prevention Surveillance (CHAMPS) uses minimally invasive tissue sampling (MITS) and careful diagnostic testing to improve understanding and prevention of child mortality. Incentives offered to participants in Kenya include transportation of the body for burial, a contribution of $40 towards funeral expenses, and payment of mortuary bills for up to 5 days. This study explored how community members perceive CHAMPS incentives. Qualitative key informant interviews (n=29), semi-structured interviews (n=11), and focus group discussions (n=5) were conducted with community members, community leaders, healthcare workers, and caregivers. Participants provided verbal consent prior to discussions. Data were analyzed using a thematic approach. Participants reported positive perceptions towards the incentives they believed were appropriate within their cultural context. While some respondents perceived them as a motivating factor, others expressed more preference for non-monetary forms of incentives and indicated that the aim of finding a child's cause of death was an adequate incentive alone. CHAMPS incentives were perceived to be well-aligned with the cultural values attached to burial-related practices and expectations. Respondents believed the educational status of the participating family influences the perception of the incentives; better-educated parents were believed to be less suspicious and view the incentives positively. Some respondents believed that research incentives could raise suspicion among community members about the true intention of the research. Overall, the findings suggest that CHAMPS has achieved a positive balance of both cultural value and financial value for participation incentives. Increased community sensitization may be needed to address negative perceptions or rumors that may be associated with research incentives.

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BLOOD PRESSURE VARIATIONS AND THEIR ASSOCIATION WITH SOCIAL DETERMINANTS AMONG MEN AND WOMEN IN BANGLADESH

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Hypertension (HTN) is a leading risk factor for cardiovascular disease, and it is increasing in Bangladesh. Therefore, this study aimed to see blood pressure (BP) variations and their association with social determinants among Bangladeshi adults. This study performed a secondary analysis of the Bangladesh demographic and health survey 2017-18 data. A total of 20,250 households were selected and from these households, one-fourth of the households were randomly selected for BP. All adults (18 years of age or older) living in these households were invited to participate in measuring BP. Among 14,704 eligible women and men, about 90% participated. Hypertension cutoffs classify a person as hypertensive with an SBP/DBP of 140/90 mmHg or more. BP status was categorized as normal, pre-HTN, stage I HTN, and stage II HTN. This study investigated age, gender, education level, marital status, wealth quintile, body mass index, and residence as potential determinants. Sample characteristics were examined and stratified by gender because of established gender differences in HTN prevalence and compared characteristics among men and women using chi-squared tests for categorical variables. Results were considered statistically significant at P values <0.05. A total of 13,128 participants were included; the mean age (±SE) was 39.7 (±0.07) years and 56% were female. Thirty-three percent of them had pre-HTN, 14% had stage-I HTN and 7% had stage-II HTN. In terms of social determinants, stage II HTN was significantly associated with older age whereas pre-HTN was associated with younger people, and males were more likely to be affected (P<0.001). Males who were married, overweight, and from the richest families suffered mainly from stage II HTN (P<0.001). A female with poor education who lives in rural areas was significantly associated with stage II HTN and pre-HTN (P<0.001). It is crucial to lower HTN prevalence and improve control among older adults and men. Lowering the incidence of overweight may lessen the long-term burden of HTN and any associated problems. It is essential to create awareness among younger people and to prioritize rural areas.

5831

THE URGENT NEED OF MOLECULAR DIAGNOSTICS IN LOW RESOURCE SETTINGS. CASE STUDY: CURE CHILDREN'S HOSPITAL OF UGANDA

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Hydrocephalus is a major indication of neurosurgery in infants worldwide. Post-Infectious Hydrocephalus (PIH), the most common form of hydrocephalus in Uganda, is a sequela of neonatal sepsis. Its diagnosis is largely based on clinical history, radiological imaging, or surgical findings because microbiological investigations using traditional culturing of CSF for microbial organism detection and identification have been largely unsuccessful. In a prospective cohort study to discover the cause of PIH at CURE Children's Hospital of Uganda, we recruited 208 consecutive PIH patients below 3 months of age and subjected their CSF samples to on-site conventional culture and PCR testing (in the USA). PCR identified virulent Mbale strains of Paenibacillus Thiaminolyticus in 47% of the processed samples while on-site conventional culture recovered no organisms. This highlights the urgent need for molecular diagnostics at point-of-care in such settings. Unfortunately, these techniques although important, are not readily available in low-resource settings like Uganda due to the high costs of setting up the infrastructure, and training personnel to perform these tests. This has limited our ability to effectively treat neonatal infections leading to the large number of PIH cases we observe at our hospital. To

bridge the gap between microbiological diagnosis and treatment of PIH at CURE Hospital, efforts have been undertaken to set up a molecular laboratory to facilitate diagnosis. An experienced laboratory technologist was recruited and trained in molecular diagnostic techniques at Penn State University, USA. Benchmark for the design of a molecular laboratory was done in collaboration with Penn State University, Yale University, and Harvard University with support from the NIH. The major challenges include: outsourcing the required equipment and reagents as they are expensive locally leaving us with no option but to purchase them from abroad. When fully functional, this laboratory will aid in the point-of-care diagnosis of causes of PIH in infants, enabling targeted and optimized treatment and clinical trials to improve patient outcome.

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SPATIOTEMPORAL CHARACTERIZATION OF CONGENITAL MYELOMENINGOCELE IN UGANDA

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Myelomeningocele (MMC) is the commonest form of spina bifida and the most severe congenital disability of the central nervous system. Without surveillance, Uganda lacks accurate data on incidence, prevalence or geographic variation in MMC risk to guide prevention. Characterization of MMC distribution in Uganda based on treated cases and knowledge of the effect of environmental factors that directly affect crop yields or natural folate availability on MMC occurrence would guide prevention. Here, we examined; the distribution of MMC in Uganda, the presence or absence of clustering within MMC cases compared to controls (under the hypothesis of uniform distribution in space) and, the association between MMC and selected environmental factors (village elevation, temperature, rainfall, and vegetation index) using secondary data from 2916 consecutive infant cases of MMC and controls between 2018 and 2001. The environmental factors 3 months before pregnancy and the first month of pregnancy were accumulated into sums giving a single value for every patient. We created Relative risk maps for being a case compared to control using village location mapped onto the Ugandan map. We examined clustering within cases compared to controls using Ripley's K function Plots with Chetwynd and Diggle method for global clustering and, explored associations between MMC and, environmental factors in terms of odds ratios using Generalized linear Mixed Models. We found a high relative risk of MMC in the Eastern and Southwestern subregions compared to other regions. Vegetation index (OR=0.13 p-value <0.001) had the biggest effect on the odds of being a case. A high vegetation index in the months studied was strongly protective. Other environmental factors with notable effects on the odds of being a case were elevation (OR= 1.14, p-value=0.008), and temperature (OR=0.87 p-value=0.009). These findings show that MMC is neither a random event nor uniformly distributed across space in Uganda. In the absence of surveillance, seasonal risk maps based on vegetation index can guide prevention.

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IMPACT OF CONFLICT ON THE HEALTH SERVICES: OPPORTUNITIES FOR RESILIENCE IN NORTH SHEWA ZONE, ETHIOPIA

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Recurrent conflicts pose threats to health systems, creating disruption in service provision. The conflict which occurred in northern Ethiopia, escalated to additional parts of the country affecting the health system operations, resulting in fatalities, disruption of livelihoods, widespread food insecurities, and displacement of residents. Through a qualitative approach, this study aims to assess the impact of conflict on health service provision, particularly maternal and child health services, and explore areas of resiliency that may be strengthened to mitigate the risks of conflict in the future. Data were obtained from community and facility key informants through in-depth interviews and focus group discussions to understand the challenges during the recovery period with suggestions on potential solutions. Total five overarching themes were explored: disruption in health services, social consequences, psychological implications, health system response for community support, and mitigation strategies to improve health system resilience. Results indicate shortage of staff and transportation, increased home/forest deliveries, rapes and sexually transmitted diseases, theft and destruction of property, lack of funds and resources, and insufficient and delayed support from government and other organizations were some of the reasons for poor health service provision during and immediately after the conflict. There is a need to acknowledge the requirement for additional outreach, IDP sites and temporary clinics to manage the caseloads during conflict crises and to strengthen the collaboration with community and other organizations for disaster management/preparedness to ensure that the health system is capable of absorbing shocks under future stress situations.

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EVIDENCE GENERATION FOR TOOLS FOR SEVERITY TRIAGE OF FEBRILE PATIENTS IN LOW-RESOURCE SETTINGS: A MIXED-METHODS STUDY

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The screening and triage practice that offers severity assessment of a patient is a crucial initial step in any healthcare cascade. Effective utilization of triage could help direct resources for life-saving procedures, and improve the distribution of resources for patients. Much less is understood about the triage process in healthcare settings of low- and middle-income countries (LMICs). The main objective of this study was to describe and evaluate the triage process in an emergency room (ER) of Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Nepal. The mixed-methods observational study has commenced at the ER of TUTH. The study will review ~1500 randomly selected emergency tickets from Jan to Dec 2022. The retrospective review entails collating data from recorded information on the emergency tickets including the demographic characteristics, vital signs, symptoms, triage categorization, primary diagnosis, and discharge of patients. Qualitative methods will be used to document 'patient journey mapping' through in-depth interviews (IDIs) with patients attending the ER. A total of 15 febrile participants will be interviewed upon receiving written informed consent. The interview will explore the decision-making process on pre-visit, visit, and post-visit exploring details on barriers and facilitators related to patients' journey to the ER. In addition, 15 direct observation notes will be collected at the ER that will document the triage practice. Descriptive statistics will be used to present recorded information on emergency tickets and the association between the triage category and specific symptoms or vital signs will be explored using regression analysis. All transcripts and observation notes will be collated into NVivo and analyzed using thematic synthesis. The evidence generated through this study would inform the improvement in the triage process echoing the concept of the 'learning health system' and 'universal health coverage'.

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COMMUNITY-LEVEL USE OF ANTIBIOTICS IN RURAL BURKINA FASO: A HOUSEHOLD-BASED SURVEY USING THE DRUG BAG METHOD

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In Burkina Faso, little is known about antibiotics' use (ABU) outside the formal health system. Assuming that ABU at community level might be overlooked, the purpose of this study was to generate knowledge about the types of antibiotics commonly used at community-level and their purpose. The survey was conducted from June to September 2021 in the rural health district of Nanoro in Burkina Faso. 423 households were purposively selected based on socio-economic status. An electronic questionnaire was used for data collection through the drug bag method, consisting of purchasing locally available antibiotics for respondents to identify and specify their use. Descriptive analysis was performed in R version 4.2.1. Households' main sources of drug procurement were the primary health care facilities (76.8%) and informal drugs sellers (61.5%). Among the 33 antibiotics inventoried, amoxicillin tablets (93.4%) and oxytetracycline tablets (86.5%) were the most recognized by the study participants. Descriptive features were their color and the diseases they were believed to treat, combined with locally shared names. Amoxicillin and oxytetracycline remained the most frequently used antibiotics. There was greater use of antibiotics for gastrointestinal disorders, wounds, musculoskeletal and connective tissue disorders and skin and subcutaneous tissue disorders. However, oxytetracycline (79.9%), metronidazole tablets (57.1%) and metronidazole suspension (56.7%) were largely used for gastrointestinal disorders while amoxicillin tablets (29%) and ampicillin tablets (34.9%) were used to treat wounds. This study provides an overview of the categories of antibiotics people identified as being valuable for domestic use. Access to and use of these medicines are facilitated by the influence of informal drugs providers coexisting with formal health care providers in the community. This raises concerns about people's access to quality medicines and the inadequacy of the health system.

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IMPACT OF THE COVID-19 PANDEMIC ON THE SURVEILLANCE AND CONTROL OF NEGLECTED TROPICAL DISEASES (NTDS) IN BRAZIL

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The Covid-19 pandemic led healthcare services to adopt contingency protocols and direct their attention to suspected and confirmed cases of Covid-19. In addition to measures to restrict people's movement, patients also avoided seeking healthcare services for fear of becoming infected. This led to a reduction in care for other health problems. We sought to quantify the impact of the pandemic on the detection of some NTDs (dengue, chikungunya, leprosy, visceral leishmaniasis, trachoma, and lymphatic filariasis) in Brazil, in the pandemic period (2020 - 2021) compared to the previous period (2015 - 2019). The number of reported cases in the pandemic years was compared to the mean number of cases in the 5-year previous period. The number of reported dengue cases fell 5.7% in 2020, in comparison to the previous period, followed by a sharp reduction in 2021 (-48%). Chikungunya cases fell 42% in 2020, and 32% in 2020. Leprosy cases fell 35% in 2020, and 33% in 2021 Visceral leishmaniasis cases fell 41% in 2020, and 49% in 2021. The national trachoma prevalence survey detected a TF prevalence <1% in all evaluation units in non-indigenous population, and below 5% in four evaluation units in indigenous people surveyed so far (national survey is ongoing). No new cases of lymphatic filariasis were detected in the last remaining focus of transmission in the country. The reduction in the number of dengue and chikungunya cases may be related to changes in services resulting from the pandemic, but it may also reflect the reduction in transmission associated with reduced mobility of people. NTDs in the final phase of elimination, such as trachoma and lymphatic filariasis, seem not to have been affected by the pandemic. The decrease in leprosy and visceral leishmaniasis seems to be related to the disruption of primary care services due to the pandemic. The Brazilian public health needs to carry out additional efforts to recover the ground lost in the pandemic.

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SYMPTOMOLOGY, OUTCOME AND PATTERN OF RISK FACTORS OF CORONARY ARTERY DISEASE IN TANZANIA CLUSTERING AND STRATIFICATION APPROACH

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Coronary artery disease is a significant public health concern worldwide. Its burden is alarming, mainly in Low- and middle-income countries, with 75% of premature deaths and 164 million disability-adjusted life years (DALYs). Tanzania has deployed various interventions to combat disease risk factors and their aftermath, however, its burden is still high. Here, a retrospective study is conducted to identify and evaluate the distribution of symptoms and risk factors of coronary artery disease (CAD) in Tanzania to recommend appropriately tailored interventions.1673 patients who underwent coronary angiography at Jakaya Kikwete Cardiac Institute (JKCI) are analyzed based on four clusters. The lesion was defined as luminal stenosis >50% by invasive angiography. Clusters were determined by the k prototype and stratification analysis was done. The findings indicate that the prevalence of CAD was 51.3% with 56% of patients over 60 years old. Male patients composed 63% and hypertension (92%) was the commonest risk factor. Four clusters of patients are identified with a) hypertensive, diabetes, and dyslipidemia symptoms of chest pain and a higher chance of double vessel lesion, b) prior myocardial infarction (MI) and percutaneous coronary intervention (PCI) with age above 60 years old that contributed to higher prevalence and risk of triple vessel disease, c) dominant risks of alcohol use, family history and smoking resulting to triple vessel disease more than other groups and d) more female patients with a higher level of obesity and smoking. Apart from patients above 60 years old, there is a percentage of premature coronary artery disease, patients below 45 years old with modifiable risk factors. Therefore, the interventions targeting youth and women should focus on reducing unhealthy diets, physical inactivity, smoking, and alcohol abuse- this is the same for the older generation. However, adding proper patient management and counseling may result in better outcomes, reducing repeated PCI and MIs.

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A QUALITATIVE EXPLORATION OF WOMEN PERCEPTIONS AND EXPERIENCES OF ANTENATAL CARE ACCESS IN MOZAMBIQUE

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Despite numerous efforts, maternal and newborn mortality rates in Mozambique are among the highest in sub-Saharan Africa. Poor access to health services and antenatal care (ANC) and low rates of institutional delivery are associated with maternal and newborn deaths. This study aims to understand pregnant women's perceptions and experiences of access to ANC in Manhiça and Quelimane Districts, in Southern and Central Mozambique respectively. A qualitative rapid assessment was conducted in June and July 2022. Data was collected through in-depth interviews of pregnant women recruited from health facilities and communities. Interviews were digitally recorded, transcribed and systematically coded

in inductive and deductive categories. Data were thematically analyzed. A total of 18 in-depth interviews were performed. Almost all participants explained that pregnancy is not a disease and can be quietly managed at home; this influenced the low uptake for ANC in the early stage of pregnancy. Nevertheless, participants recognized the importance of ANC during pregnancy, mainly to protect the baby's health. Pregnant women highlighted the need to prioritize labor activities such as cultivating on farms and selling in markets over going to the healthcare facility for ANC. Further, participants stated the need to "hide their belly" to avoid the threat of the evil eye and witchcraft to their pregnancy. These factors led women to delay seeking ANC until the late stage of pregnancy. Long distances and waiting times during ANC were also mentioned as factors that influence access and the experiences of pregnant women. Participants perceive pregnancy as an easily managed condition at home, and this has impacted their ANC-seeking behavior, although they recognize its importance. Education is needed to improve women's knowledge of the importance of ANC at the first stage of pregnancy and mitigate beliefs about witchcraft in order to improve ANC-seeking behavior.

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ASSOCIATIONS BETWEEN MATERNAL AND PATERNAL STRESS, MATERNAL DEPRESSION, MATERNAL EXPOSURE TO INTIMATE PARTNER VIOLENCE, AND CHILD STRESS

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Globally, many women experience intimate partner violence (IPV), depression, and stress, which have long-term maternal and child health consequences. We assessed the potential associations between maternal and paternal perceived stress, maternal depressive symptoms, and maternal exposure to cumulative lifetime IPV, and child stress biomarkers (urinary F2-isoprostanes, salivary alpha-amylase (sAA) and cortisol, blood pressure, heart rate, and NR3C1 methylation status) in rural Bangladesh. We estimated associations using generalized additive models, adjusting for potential confounders. We measured 686 mother-child dyads at Year 1 and 1,494 dyads at Year 2, overlapping with replacement. F2-isoprostanes outcomes yielded two opposing results: a negative relationship with maternal exposure to IPV and a positive relationship with maternal depression. In the sympathetic adrenomedullary axis, we observed a negative association between paternal stress and child mean arterial pressure (MAP), and positive associations between maternal perceived stress and post-stressor sAA; maternal depression and sAA reactivity and MAP; and paternal perceived stress and resting heart rate. In the hypothalamic pituitary adrenal axis, we observed a negative association between maternal depression and post-stressor cortisol and a positive association between paternal stress and pre-stressor cortisol. The negative relationship between maternal IPV and child F2-isomers, although counterintuitive, reveals possible alternative functional roles, which reactive oxygen species might play. Maternal depression was associated with the largest and most variable number of child stress biomarkers indicating the importance of this exposure in shaping stress responses. Future studies in different geographical contexts quantifying the multigenerational implications of such stressors to determine typical and atypical child stress responses during early life are critical.

5840

UTILIZATION OF PANTOGRAPH AMONG NURSES AND MIDWIVES IN LABOUR WARD AT EDWARD FRANCIS SMALL TEACHING HOSPITAL

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Partograph is a graphic record of progress of labor, maternal and fetal condition plotted against time for intrapartum monitoring (Mathai 2009). Its aim is to provide a pictorial overview of labor, to alert obstetric care providers about deviations in maternal, fetal condition and progress of labour (Lavender et al 2008). The study aimed to describe the utilization of partogram among nurses and midwives, in the labour ward at Edward Francis Small Teaching Hospital (EFSTH). A descriptive quantitative research design to gather information on utilization of the partogram among nurses and midwives in the labour ward of Edward Francis Small Teaching Hospital was employed using a convenient sampling procedure. All the nurses and midwives in the labour ward were selected who were willing to participate in the study and consent was sought from both EFSTH and the participants. Questionnaires were used to collect data and analysis was done using spss version 21. The results indicate that 80% of all of respondents knew what a partogram was. The knowledge on the function of the action line and alert line was poor amongst nurses and midwives who participated in the current study. Only 40% (N=4) of the respondents could explain the function of action line on the partogram. There was poor utilization in labour monitoring. Only 40% (N=4) were found to properly use the partogram while 60% (N=6) were found to not properly use the partogram. The findings confirm the problem of shortage of nurses and midwives with only (N=10) covering the labour ward of EFSTH for all shifts. The recommendation includes deployment of nurses and midwives to EFSTH, training of nurses and midwives on the utilization of the partogram.

5841

A NOVEL VIRULENCE MODIFYING EXOTOXIN SECRETED BY PATHOGENIC LEPTOSPIRA MEDIATES DISEASE PATHOGENESIS AND IS A PAN LEPTOSPIROSIS VACCINE CANDIDATE

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Leptospirosis, a globally neglected zoonotic disease caused by pathogenic Leptospira, affects >1 million people annually, with a 20% case fatality rate. Clinical pathogenesis mechanisms have not been known until the present work and there is no safe/effective vaccine for humans. We recently reported that Leptospira-secreted Virulence Modifying (VM) proteins, comprised of N-terminal ricin B domains and C-terminal DNase/toxin domains, mediate cellular cytotoxicity on HeLa and primary pulmonary endothelial cells; the latter cell type is likely to be involved in lung hemorrhage in severe leptospirosis. VM protein vaccination of two rodent models (mouse, hamster) that recapitulate human disease manifestations protects from lethal challenge infection. We hypothesized that anti-VM protein immunity is mediated by antibodies, given the premise that Leptospira, an extracellular pathogen, causes systemic disease via the circulation of secreted VM protein exotoxins. Polyclonal and monoclonal antibodies both neutralized VM cellular toxicity (HeLa cells). High-affinity anti-VM mAbs 5F8, 6A5, and 5G10 reacted with homologous VM proteins and cross-reacted with the VM protein family. Epitope mapping showed that mAbs and polyAbs recognized linear epitopes that are highly conserved among species and serovars. Serovar Copenhageni showed upregulation of multiple VM proteins, which are present in the serum of infected hamsters at nanogram/ml levels as determined by capture ELISA. This latter finding is

the first time, to our knowledge, that a secreted exotoxin can be detected and quantified in the blood of any infectious disease. Discovery of vaccine-induced, anti-VM antibody-mediated neutralization of VM activity will justify clinical development of a novel leptospirosis vaccine. Future experiments will test whether passive anti-VM protein antibody transfer will protect animals against lethal leptospirosis. Our findings are sufficiently compelling to put leptospirosis on the WHO's Neglected Tropical Disease list which is needed to enable the development of VM protein-based leptospirosis vaccines, diagnostics, and therapeutics.

5842

VILLAGE COMMUNITY BANKING: POTENTIAL OF COMMUNITY-BASED FINANCING SYSTEM FOR HOUSE IMPROVEMENTS AND VECTOR CONTROL IN RURAL TANZANIA

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House improvement has consistently been associated with remarkable reductions in indoor bitingmosquitoes and disease incidences even in typical rural houses, however, its exploitation remainsextremely poor in Tanzania and other endemic countries due to limited financial resources. Nevertheless,the village community banks (VICOBA), practiced in Tanzania for nearly two decades, have proven toprovide financial services to rural communities who would otherwise not be able to get financial servicesfrom formal financial institutions. This study was conducted to explore the views, opinion andwillingness of VICOBA members on using VICOBA platforms as source of finance for improving localhouses and eventually control of mosquito borne diseases.A mixed method approach was used in this study, whereby a survey was administered to 150 participantsand twelve focus group discussion were done in three villages of Ulanga district rural Tanzania. TheFGDs comprised of 8 participants each with equal representation of males and females. The FGD guidewas used to probe the opinion of study participants on malaria transmission, housing conditionimprovements and financial resources.About 99% of all participants indicated the urgent need to improve their houses for preventing themselvesfrom mosquito bites and were willing to utilize VICOBA for improving their houses. In focus groupdiscussion majority of people who participated they were also in need of improving their houses. Allparticipants confirmed that they were at highest risk of getting mosquito borne diseases and they werewilling to use money that was either saved or borrowed from their VICOBA.Going forward with malaria elimination and economic growth agenda as stipulated in the SDG 3 and 8,self-sustaining financial system destined at house improvement and related interventions against malariaand other mosquito-borne diseases are crucial. The community members were willing to use VICOBA assource of finance for house improvement and disease control, however there were limited knowledge andsensitization on how they could utilize VICOBA for disease control.

5843

INNOVATIVE FINANCE FOR NEGLECTED TROPICAL DISEASES

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Neglected tropical diseases (NTDs), impact more than a billion people globally and pose a significant barrier to economic and social development in low- and middle-income countries. Insufficient funding and limited research have caused critical gaps in prevention, diagnostics, and treatment. In the past decade, only ten drugs were developed to treat diseases affecting 2.5 billion people. Six out of 20 NTDs identified by WHO have no tests, while others are not fit-for-purpose or accessible in the necessary areas. These challenges hinder progress towards agreed targets, as evidenced by the WHO NTD Road Map gap assessment. Funding for NTD product development is inadequate to address the need of new and better tools that could make the elimination of several NTDs a reality –it is imperative to explore financing options that have not yet been applied to the NTD space. The post-COVID-19 global health architecture has provided an opportunity to assess new financing models for health initiatives and disease programs. In 2022, GLIDE led a six-month technical exercise with a core group of 20 experts to identify innovative finance mechanisms (IFM) for NTDs through i) condensing existing evidence, ii) stimulating cross-sectoral discussions, and iii) gathering expert input. Through literature and desk reviews, several IFM were assessed across the NTD value chain for scope and applicability to specific diseases. Financing mechanisms were qualified as innovative if they met the four criteria of catalytic, additive, complementary, and sustainable. Shortlisted mechanisms were then prioritised based on their perceived impact versus ease of implementation profiles and mapped into quadrants. This exercise resulted in the identification of four financing instruments to consider for NTDs: (i)debt swaps, (ii) milestone-based funding, (iii) impact bonds, (iv) and pooled procurement. The next steps will be to identify disease-country-mechanism opportunities for investment by public and private stakeholders. By leveraging IFM, innovative finance offers a new and dynamic approach to mobilize resources and drive greater impact in NTD elimination efforts.

5844

MICROBIOME ANALYSIS OF PREGNANT WOMEN AND CHILDREN FROM AMANHI FECAL COHORT

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Characterization of the human microbiome can provide valuable insights to the status of human health and disposition to disease. There is an interest in understanding the role of the human microbiome in maternal, newborn and child health (MNCH). Gut microbiome shifts physiologically during pregnancy and appear to differ in women with pregnancy-associated complications, such as, Adverse Pregnancy Outcomes (APOs). For example, dysbiosis of microbial communities is implicated in a variety of adverse MNCH outcomes including preterm birth (PTB), cardiometabolic complications of pregnancy and childhood, and neonatal complications like necrotizing enterocolitis. Furthermore, the maternal microbiome is a key contributor in the initial microbial colonization and development of the infant microbiome which may have long-term implications for the child's physical growth, nutrition, and neurocognitive development. In this proof-of-concept study, we sequenced by shotgun metagenomiucs 750 trios (250 maternal and 250 infant fecal samples of two time points, postnatal 42 days, and 12-18 months of age) to generate the microbiome profiles of pregnant women in Pakistan collected as part of AMANHI cohort. This study will guide our university to plan further as lead analytical lab for clinical intervention studies focusing to observe the effects on gut microbiome, and to provide insights into complex health problems in maternal, newborn and child health, along with their nutritional status.

5845

UNDERSTANDING HEALTH WORKER AND COMMUNITY ANTIBIOTICS PRESCRIPTION ADHERENCE PRACTICES FOR ACUTE FEBRILE ILLNESS: A NESTED QUALITATIVE STUDY IN THE SHAI-OSUDOKU DISTRICT OF GHANA, AND THE DEVELOPMENT OF A TRAINING AND COMMUNICATION INTERVENTION

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Most health facilities in sub-Saharan Africa, including Ghana, lack the diagnostic capacity to identify the cause of acute febrile illnesses. This leads to presumptive diagnosis and contributes to the inappropriate prescription of antibiotics. Hence, the evolving agenda towards implementing interventions to ameliorate inappropriate antibiotic prescription and consumption. We explored the social and contextual behavior determinants of adherence to prescription and communication of prescription adherence messages for patients with acute febrile illness. The outcome was used to develop a Training and Communication intervention which was delivered as part clinical trial. This was a qualitative study of a randomized controlled trial with the objective to assess the impact of an intervention package consisting of diagnostic tools, clinical algorithms, training, and communication on antibiotic prescriptions, compared with routine practices for patients presenting with acute febrile illness. Data was collected from 39 healthcare prescribers and 66 caregivers in primary healthcare facilities and communities in the Shai-Osudoku district in Ghana. We undertook a content analysis of primary, qualitative data collection using in-depth interviews and focus group discussions, informed by the Capability, Opportunity, Motivation theory of behavior, the Theoretical Domains Framework, and the Behavior Change Wheel approach. Health workers perceived factors that influence what and how prescribers and dispensers communicate include: patients' education level; existing disease condition; health worker's workload; patient's religion; language barrier between health worker and patient; the outcome of laboratory results, and medicine availability. Community members' adherence to prescription was influenced by: the availability of money and affordability of medicine, the severity of the condition, work schedule, and forgetfulness. Our study contributes to knowledge in qualitative methods nested in a clinical trial and reveals factors that affect antibiotic prescription with the communication process.

5846

SEVERE ACUTE MALNUTRITION IN CHILDREN UNDER FIVE

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Acute malnutrition is a rapid onset condition characterized by bilateral pitting edema, sudden weight loss caused by a decrease in food consumption or illness. Severe Acute malnutrition is when weight for height is less than -3 z scores with MUAC less than 11.5cm, bilateral pitting edema and marasmic -kwashiorkor (both wasting and edema). The study was carried out to identify factors that contribute to prevalence and effects associated with Severe Acute Malnutrition(SAM) in children below five years in a Nutritional Unit in Mbale Regional Hospital, Eastern Uganda. This was a prospective study that involved use of different questionnaires that were answered by health workers on duty, mothers and care takers of children with SAM on nutrition unit respectively. Anthropometric measures at two weeks and on monthly basis were taken and compared to mean difference in weight, height, Mid upper arm circumference (MUAC.) The study was carried out from 1st of December 2022 to 14th of March 2023.A total of 1000 respondents were interviewed. Children between 3-4 years (46.7%) had the most effects due SAM and 2-3 years (13.3%) had least effects due SAM. Poverty at(33.3%) was the major contributing factor to SAM, building its roots from family level. The study further showed us that (50%) were fortune to get discharged and (6.7%) died. My findings indicate that, hypoglycemia, impaired growth and development were the commonest complications and effects observed. SAM is still a neglected tropical disease in Uganda. Recruitment of more health workers for easier identification of effects due to SAM among children and multisector intervention that can provide various support in management and prevention of SAM under-fives are some of the recommendations laid out. Also, retaining of health workers that work in lower health facilities was highly emphasized as this would enable easy identification of these children with this type of malnutrition, girl child education should be paramount in communities as way to halt early marriages. As it is said that when you educate a girl child you educate a nation.

5847

PARTICIPANT ACCEPTABILITY OF AN ANCILLARY CARE POLICY DURING AN EBOLA VACCINE TRIAL IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Providing ancillary care (AC) for participants' medical conditions during study participation is an ethical responsibility of clinical researchers. During an Ebola vaccine trial (clinicaltrials.gov: NCT04186000) conducted in the remote area of Boende, DRC, the Universities of Antwerp (Belgium) and Kinshasa (DRC) developed a policy to medically and/or financially support concomitant medical events. By means of two short surveys, we assessed participants' acceptability of this approach. First, 152 participants with a self-reported medical event filled in a short quantitative questionnaire (6 questions; grading 1-5) regarding their experience with the AC policy. Second, at the end of the trial, 307 participants with and without self-reported medical events participated in a short telephone survey (3 questions; grading 1-3 and option for comments) that explored their endorsement of the policy, their experience on how the policy addressed their medical needs, and their opinion on the importance of the policy. Descriptive statistics were used to analyze the surveys and recurring themes from the comments were identified. The majority (89%) of participants with self-reported medical conditions gave a positive to very positive evaluation. All respondents of the telephone survey, with or without self-reported medical conditions, were in full support of the policy and emphasize its importance; 91% indicated that the support addressed all medical needs. Some limitations or constraints were mentioned, e.g. pharmacy stock-outs, conditionalities for financial coverage, the lack of specialized care facilities, etc. Despite limitations and contextual challenges, most participants assessed the policy to be beneficial on a personal and medical level. As clinical trials are increasingly conducted in resource-constrained settings, clinical research sponsors and teams should consider to systematically implement a AC package that is co-designed with representatives of the trial community and Ethical Committee, and tailored to the local health care system, research budget and duration.

5848

EVALUATION OF THE PANBIO™ COVID-19 RAPID TEST DEVICE (ABBOTT) AT THE VIROLOGY LABORATORY OF THE ARISTIDE LE DANTEC UNIVERSITY HOSPITAL IN SENEGAL

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The management of the COVID-19 pandemic requires the widest possible access to diagnosis. To make this diagnosis available to populations, especially in countries with limited resources, it is important to have fast but reliable technologies that are less expensive than RT-PCR, which is the reference technique. For this reason, we evaluated the detection

performance of Panbio™ COVID-19 Ag Rapid Test Device (Abbott Molecular) antigen tests on nasopharyngeal and nasal swabs compared to the Abbott Real Time SARS COV-2 Assay (Abbott Molecular) RT PCR technique. After obtaining free and informed consent, 2 nasopharyngeal swabs (NP) and one nasal swab (NS) were taken from each participant. The NP and NS samples were tested with Panbio Ag and the results were compared with those of RT PCR obtained on the nasopharyngeal swab of the patient considered. Performance analysis included calculation of sensitivity (Se), specificity (Sp), positive (VPP) and negative (VPN) predictive values, and degree of agreement by Cohen's Kappa coefficient. A total of 179 patients were included, including 150 participants recruited from travellers attending the Bacteriology Virology Laboratory of the CHNU Aristide le Dantec and 29 patients from the Hospital Treatment Center. The mean age was 33 years and 40 years and the sex ratio was 0.85 and 1.2 respectively for travellers and COVID-19 patients.Of the travellers, 21 (20%), 13 (8%) and 11 (7.3%) tested positive by RT-PCR, Panbio NP and NS respectively. For CT values <31, Se and Sp were 91% and 100% for NP and 86% and 100% for NS. The VPP was 100% and the VPN was over 96% for the NP and NS. Similarly, the degree of agreement was over 90% for NP and NS. In conclusion, this study showed excellent agreement between the Panbio test and RT PCR on both NP and NS samples. This good performance and ease of use of the Panbio test confirm the interest of its use in the diagnosis of COVID.

5849

APPLICATION OF THE THREE DELAYS MODEL TO UNDERSTAND HOW THE INTERACTION OF COMMUNITY, FAMILY AND HEALTH SYSTEMS CONTRIBUTE TO CHILD MORTALITY IN CHAMPS-KENYA; MAY 2017 - JUNE 2022

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Sub-Saharan African countries continue to bear the greatest burden of mortality in children under the age of 5 (<5's). The 3-delays model provides a useful framework for examination and interpretation of the complexity in the intersection of community, family and health systems factors and their contribution to <5 mortality. These delays include (1) a delay in deciding to seek care; (2) a delay in identifying and arriving at a health facility; and (3) a delay in receiving quality care at the health facility (i.e., suboptimal care).The Child Health and Mortality Prevention Surveillance (CHAMPS) in Western Kenya investigates <5 deaths by conducting extensive data collection and laboratory investigation using minimally invasive tissue sampling, verbal autopsy and data abstraction. Qualitative data routinely collected includes clinician narratives and verbal autopsy and was used to identify the delays. We reviewed cases from 2017-2022 to categorize and describe deaths using the 3-delays model. Nearly all <5's experienced one or more delays prior to death: whereas only 7.5% of those aged 0-1 day-olds had no delays, only 2.3% of neonates aged 1-28 days old had no delays (Figure 1).Delayed decision-making to seek care (Delay 1) co-occurred with suboptimal care received (Delay 3) in over one-third of all deaths, with this overlap greater among infants and children (64.4-68.9%) than stillbirths and neonates (32.7-44.4%). Cases with delays between the decision to seek care and arrival at a facility (Delay 2) co-occurred with Delays 1 and/or 3 for nearly all deaths. Suboptimal care (Delay 3) was observed in 83.6% of all deaths: Delay 3 was observed with no other delays in over half of stillbirths and neonates, and less than one-third of infants and children. Poor clinical care contributes to nearly 9 of 10 <5 deaths, and mothers of older infants and children are more likely to delay in seeking health care than are mothers of neonates. The 3 delays framework is useful. Further reduction in <5 mortality will require multi-level interventions especially earlier health seeking behavior by parents, and adherence to clinical guidelines by healthcare providers.

5850

IMPACT OF MESSAGES ON MATERNAL CONDITION LEADING TO CHILD DEATH AND ON ANC SEEKING PRACTICES AMONG PREGNANT WOMEN IN RURAL BANGLADESH

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Child Health and Mortality Prevention Surveillance (CHAMPS) Program in Bangladesh identified intrauterine hypoxia resulting from maternal health issues as one of the major causes of stillbirth and early neonatal deaths. Quality antenatal care (ANC) is needed to prevent these maternal conditions. This information was communicated and explained to pregnant women and their female family members at the community level through courtyard feedback sessions in Baliakandi, a rural sub-district of Bangladesh. The messages emphasized the benefits of recommended ANC visits to qualified physician on healthy development of the fetus and to identify maternal conditions, major danger signs during pregnancy and after delivery. From December 2021 - November 2022, female team members facilitated 138 courtyard sessions. We assessed the impact of conveyed messages by comparing ANC seeking behavior among 632 pregnant women (aged 14-45 years). In the 60 days following the session, 247 pregnant women (39%; 247/632) received ANC. The proportion of pregnant women who received ANC in the 60 days after the session (100%; 247/247) was 38% higher than in the 60 days before the session (62%; 153/247). When pregnant women's in-laws or maternal family members joined them at the sessions, the number of pregnant women who received ANC increased by 60% (148/247). Besides, the majority of the pregnant women (85%; 126/148) received ANC within 60 days following the session when their in-law's family members learned about the causes of child deaths and prevention strategies from the same session with them as opposed to (15%; 22/148) when they did not attend the session. The messages on main causes of death and understanding about the maternal conditions during pregnancy, likely facilitates in-law's family members to decide on ANC seeking of pregnant women. To improve maternal and child health, it is important to educate pregnant women along with their in-law's families, about the specific causes of maternal conditions that can lead to child death. Additionally, explaining the importance of antenatal care linking with potential risk as a preventive measure can increase its uptake.

5851

A SYSTEMATIC REVIEW OF PREVALENCE AND RISK FACTORS OF TRANSFUSION TRANSMISSIBLE INFECTIONS AMONG BLOOD DONORS, AND BLOOD SAFETY IMPROVEMENTS IN SOUTHERN AFRICA

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Blood and blood products are listed as one of the essential medicines by the World Health Organization (WHO). In addition to inadequate supply, most sub-Saharan Africa (SSA) nations fail to meet blood needs because many donated units are discarded due to contamination with transfusion-transmitted infections (TTIs). We sought to estimate the prevalence of TTIs, identify the risk factors for TTIs among blood donors, and identify

interventions to improve blood safety in southern African nations, particularly the nations of the South African Development Community (SADC).
We investigated prevalence and risk factors for TTIs, and blood safety improvements in the SADC region from PubMed/MEDLINE, Cochrane Library, and HINARI databases from January 1, 2011 to April 31, 2021. All investigations followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). In meta-analysis, we estimated the pooled TTIs prevalence and summarized using forest plots. A total of 180 articles published from the sub-Saharan Africa region were identified covering our three targeted themes. Of these 180 articles, only 27 (15%) focused on the SADC region. The overall pooled TTI prevalence estimate was 2.0% (95% CI: 1.0-3.0) and hepatitis B was the most prevalent TTI in the region (prevalence = 3.0; 95% CI: 2.0-5.0). The prevalence of HIV, HCV, and syphilis was 2.0%, (95%CI:1.0-4.0) 1.0% (95%CI:0.0-2.0), 2.0% (95%CI: 0.0-8.0) respectively. In general, replacement donors and first-time donors were more likely to be infected with TTIs than repeat donors. 12 articles explored blood safety in the region however, they vary greatly highlighting the need for more comprehensive research. Few publications were identified that were from the SADC region, indicating lack of research or resources towards improving quantity and quality of blood donation. TTI prevalence remains one of the highest in the world and blood safety recommendations vary across the region. More effort should be directed towards developing a cohesive regional blood transfusion policy and effective blood monitoring and evaluation strategies.

5852

THE REMOTE EMERGING DISEASE INTELLIGENCE NETWORK (REDI-NET): PREPARING FOR ZOONOTIC SPILLOVER THREATS

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Spillover and zoonotic disease outbreaks of known and novel emerging infectious pathogens are becoming more frequent worldwide due to climate change, globalization and increased interaction among humans, domestic animals and wildlife within a shifting landscape. These outbreaks will inevitably continue into the foreseeable future. The Remote Emerging Disease Intelligence NETwork (REDI-NET) is a multisectoral, multidisciplinary Consortium with the overarching goal to quicken the timeliness in collecting and processing data from across a wide range of ecologies to guide appropriate response options. The REDI-NET is founded on a multi-year, phased approach to leverage pre-existing and real-time long read shotgun metagenomic sequencing surveillance outputs in a flexible, scalable data repository and computing platform to support detection of pathogens, estimate risk of exposure and guide policy-decisions on animal, environmental and public health. Our core objectives focus on leveraging partner expertise to fill gaps in existing surveillance efforts to include 1) strengthening infrastructure where capacity may need to be built and/or enhanced (remote research stations); 2) standardizing sample collection, storage, and testing processes for assurances in data rigor and big data management; 3) leveraging existing networks and health data to widen the global surveillance footprint; and 4) transferring knowledge on surveillance system activities and providing actionable data. Here we will present program successes to date from early phases and describe next steps in expanding the operational framework with broad applicability across international regions.

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KNOWLEDGE OF COVID-19 SYMPTOMS, TRANSMISSION, AND PREVENTION: EVIDENCE FROM HEALTH AND DEMOGRAPHIC SURVEILLANCE IN SOUTHERN MOZAMBIQUE, SEPTEMBER 2021-JANUARY 2022

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Over 230,000 COVID-19 cases and 2,200 deaths have been reported in Mozambique though March 2023. Understanding community members' knowledge and perception of SARS-CoV-2 transmission and prevention is essential for directing public health interventions to reduce disease spread and improve vaccination coverage. We describe knowledge of COVID-19 transmission, prevention, and symptoms among community residents in Mozambique. We conducted a cross-sectional survey among all households (n=33,087) in a Health and Demographic Surveillance System in Manhiça, Mozambique, at the tail end of the Delta variant wave in September 2021 to the peak of Omicron cases in January 2022. Principal components analysis was used to create scores representing knowledge of COVID-19 symptoms, transmission, and prevention. Multiple imputation and quasi-Poisson regression were used to examine associations between demographic characteristics and sources of COVID-19 information, and knowledge of COVID-19 symptoms, transmission, and prevention. Across this rural community, 98.2%, 97.0%, and 85.1% of household respondents reported knowing how COVID-19 could be prevented, that SARS-CoV-2 can cause disease, and how SARS-CoV-2 is transmitted, respectively. Most recognized symptoms were cough (51.2%), headaches (44.9%), and fever (44.5%). Most cited transmission mechanisms were droplets (50.5%) or aerosol (<5 μm diameter) (46.9%) from an infected person. Most cited prevention measures were handwashing (91.9%) and mask-wearing (91.8%). Characteristics associated with greater knowledge of symptoms, transmission, and prevention included having at least primary education, older age, employment, greater wealth, and Christian religion. Respondents who had had COVID-19 symptoms were also more likely to have knowledge of symptoms, transmission, and prevention. Community public health measures to reduce infectious disease transmission are contingent upon perceptions of risk and knowledge. These findings support the need for outreach and for community-engaged messaging to promote prevention measures, particularly among people with low education.

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DEVELOPMENT OF SINGLE DOMAIN ANTIBODY-BASED LUMINEX ASSAY FOR THE DETECTION OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS-2 IN CLINICAL SAMPLES

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Viruses from the genus Betacoronavirus have emerged in the 21st century. These viruses have high morbidity and mortality, starting with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2002, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012, and SARS-CoV-2, which is the causative agent of coronavirus disease-2019 (COVID-19) in 2019. Thus, there is a critical need for rapid, low cost, sensitive, and reliable diagnostic assays for these emerging viral diseases. The ideal assay format would be rapid and multiplexed, enabling the processing of many samples and simultaneously providing information on the presence

of known diseases, while also giving a warning for the possibility of a new emerging disease. High-throughput MagPlex assays have the advantage of being relatively fast and simple in comparison to PCR based formats, while providing the additional capability to be multiplexed. Single domain antibodies (sdAbs) provide an economical means to perform multiplexed assays which can be expanded to include additional assays as desired or tested in a serial manner. Here, we developed a bead-based assay using sdAbs against SARS-CoV-2 nucleocapsid (N) protein. Additionally, we also used SpyTag/SpyCatcher system to improve the sensitivity of the assay. The sdAb-coated beads were able to detect N protein down to 10 ng/mL, however by using SpyTag/SpyCatcher system to orient the sdAbs on the beads, we were able to increase the sensitivity 10-fold to 1 ng/mL. We further assessed the sensitivity and specificity of the assay by using COVID-19 and seasonal coronavirus clinical samples. Both regular sdAb-coated and SpyTag/SpyCatcher sdAb-coated beads were able to specifically detect SARS-CoV-2 in the samples with SpyTag/SpyCatcher sdAb-coated beads performing better. In summary, we provide a proof-of-concept that bead-based assay to detect SARS-CoV-2 is feasible and future research by combining it with other sdAb-coated beads that can detect other coronaviruses may be a useful tool in responding to future pandemics.

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COVID-19 SELF-TESTING: A PROMISING OPPORTUNITY FOR LOW AND MIDDLE INCOME COUNTRIES, YET A REALITY CHECK OF GLOBAL INEQUALITIES

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The widespread use of antigen-detection rapid diagnostic tests has revolutionized the decentralized testing and self-testing of COVID 19. However, the full extent of AgRDT utilization for self-testing remains largely unexplored. To provide vital information for the development of the recently released global guidelines on COVID 19 self-testing, we conducted a cross-sectional survey targeting policy makers, researchers, and implementers worldwide. The survey was shared through professional networks via email and social media. We used questions related to policy and program information concerning the regulation, availability, target population, indications, implementation, benefits, and challenges of COVID 19 self-testing. Descriptive summaries, cross-tabulations, and proportions were used to calculate outcomes at the global level and by World Bank region and income classifications. Between 01 and 11 February 2022, 844 individuals from 139 countries responded to the survey . 504 respondents from 101 countries reported policies supporting COVID 19 self-testing for a range of use cases, including symptomatic and asymptomatic populations. Significantly, more respondents from low-and-middle-income countries than high-income countries reported a lack of C19ST policy (61 vs 11 countries) and low population-level reach of C19ST. Respondents with COVID 19 self-testing experience reported that the tests were mostly acceptable to target populations, provided significant programmatic benefits, and highlighted several key challenges to be addressed for increased success. While the widespread global interest, policy support, and implementation of COVID 19 self-testing demonstrate an opportunity for bridging the testing gap experienced by LMIC populations, the unequal access exposes the realities of global inequalities. There is urgent need for Global Health actors to sustainably address unequal access to lifesaving interventions especially during high consequence epidemics. Benefits, challenges and opportunities shared by respondents should inform development of national and global policy.

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ENVIRONMENTAL HYGIENE FOR HOSPITAL INFECTION PREVENTION AND CONTROL MANAGEMENT IN BANGLADESH: EDUCATING HOSPITAL CLEANING STAFF REQUIRES PRIORITY

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Cleaning staff is a critical part of the hospital infection prevention and control (IPC) program. Despite involvement in environmental hygiene management including patient care, cleaning staff are often overlooked in education and training, resulting in a lack of optimal IPC and hygiene knowledge. This study assessed the existing knowledge and practices regarding IPC and environmental hygiene among cleaning staff at tertiary hospitals in Bangladesh. Between July and December 2022, a cross-sectional study was conducted at six tertiary hospitals among randomly selected 259 cleaning staff involved in hospital environmental cleaning and waste management. Data was collected through face-to-face interviews using a semi-structured questionnaire, and descriptive statistics were used for analysis. The mean age of participants was 36.7 years (SD 10.1) and the majority (65.6%, 170/259) were outsourced workers. None of the cleaners had obtained any formal orientation or training on hygiene from the hospital. Four-fifths (78.4%) of those polled had not received any basic IPC training in the previous two years. Only 7% (18/259) of respondents were aware of the standard cleaning agent-to-water ratio for environmental cleaning. Approximately 15% of respondents correctly identified specific color-coded waste disposal bins. As precautionary measures for IPC management, one-third (35.9%, 93/259) mentioned hospital waste management and environmental cleanliness. Less than half (46.3%, 120/259) of cleaning personnel considered performing hand hygiene (HH) required after contact with patients and surroundings, but 17% (44/259) reported practicing HH in hospitals for these purposes. Only about one-third (29%) of cleaners weekly disinfected high-touch areas, but once a month for low-touch areas of the hospital. The cleaning staff lacked basic knowledge and standard practices on IPC and environmental hygiene in Bangladesh. Establishing environmental hygiene guidelines, hands-on orientation, and refresher training including routine monitoring can enhance the level of skilled cleaning staff for hospital IPC management.

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ONE HEALTH BIOSECURITY: DEVELOPING RECOMMENDATIONS TO ADDRESS LEGISLATIVE GAPS IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Strong whole-of-government biosecurity systems are critical for supporting biological threat reduction efforts. Legislative and regulatory frameworks ensure successful implementation, sustainability, and alignment of these systems with international agreements, including the International Health Regulations and the Biological and Toxin Weapons Convention. The extent to which legislative support for biosecurity systems is successful can vary based on national or regional governance structures, stakeholder capacity and available resources, which itself requires a robust understanding of a country's existing legislative landscape prior to any capacity-strengthening efforts. In support of the Global Partnership's Signature Initiative to Mitigate Deliberate Biological Threats in Africa, we developed a methodology for assessing national legislative landscapes with respect to a broad definition of biosecurity, through a One Health lens, which we then piloted in the Democratic Republic of the Congo (DRC). Through implementation of the methodology, we mapped and analyzed existing national and sub-national

legislation, regulations, and other applicable policy documents, and also engaged key informants to provide additional contextual information relating to awareness and implementation of key legislation. We convened national stakeholders, together with regional and international experts, to validate the analysis findings, and to develop recommendations and an action plan for strengthening DRC's biosecurity legislative structures. We demonstrate that our methodology is an effective approach to biosecurity legislative assessment, which can be adapted for use in other countries, thus making it a useful contribution to global health security scholarship and practice.

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BURIAL SITE SURVEILLANCE TO MONITOR EXCESS MORTALITY DURING THE COVID-19 PANDEMIC IN KARACHI, PAKISTAN

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Population death rates are an important measure of health status and Pakistan is among those countries which has a poor functioning national system of registering deaths and determining their causes. In the context of the COVID-19 pandemic, accurate documentation of fatalities became even more critical. Without accurate data on the number of fatalities and their distribution, it becomes a challenge to track the progression of the pandemic and determine the effectiveness of interventions such as lockdowns, social distancing, and vaccination programs. In this regard, our study aims to identify and monitor disparities in COVID-19 fatalities and their causes by using burial site surveillance in Karachi, Pakistan, which involves collecting both retrospective (2016-2021) and prospective (2022 onwards) data which will be collected till June 2023 from graveyards and morgues. Surveillance process includes data from graveyard registries and verbal autopsy using the WHO verbal autopsy questionnaire. The study's results indicated that among the total deaths (N=161,142), mortalities observed in the year 2021 were 37,778 followed by 2022 (36,719), 2020 (35,858), 2019 (27,018) and data observed between 2016-2018 were 24,119 with work in progress. Majority of fatalities occurred in individuals aged 65-74 (age adjusted mortality ratio = 0.1960) and that among the seven districts of Karachi, Karachi Central had the highest mortality proportion (1922/100,000). Further we found 1612 fatalities attributed to COVID-19, and males exhibited a greater prevalence of mortality than females (64% vs. 36%). Also, 469 cases were recorded in individuals aged between 65-74 indicating elderly population was more vulnerable to COVID-19 related deaths. As compared to pre-surveillance mortality data, there was an increase of 2-4 standard deviation in mortalities during COVID-19 pandemic. In conclusion, most of the deceased in Pakistan are buried as part of religious and cultural norm. Hence mortality data can be a good indicator to understand increase in mortality rates during COVID-19 pandemic and can be used to measure the burden of mortalities during pandemic.

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AN ETHNOGRAPHIC APPROACH TO UNDERSTAND THE FEASIBILITY OF GRAVEYARD SITE SURVEILLANCE TO ASSESS EXCESS MORTALITY IN A RESOURCE CONSTRAINT SETTING

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Population mortality is a crucial statistic that combines data from several risk factors to provide a single measure of public health. This study provides insights related to ethnographic data collection of major graveyards in Karachi, Pakistan from November 2021 to April 2022. The main objective of this study was to understand the process of death to burial in graveyards belonging to various religious and ethnic groups. Qualitative interview guides were developed to interview various stakeholders, including graveyard caretakers (121), ethnic groups (46), Karachi Metropolitan Corporation officials (15), funeral bus/ambulance services staff (9), family members of deceased individuals (4) and NGOs (2). We found that burial of the deceased was the most commonly practices and culturally accepted method in different religions e.g., Muslim, Christianity and Hinduism. We found that obtaining death certificates and registration involved providing a copy of the deceased individual's National Identity Card. However, the process was faster for deceased children which led to incomplete documentation. For obtaining death registration and certificate, union council facilitate urban areas and union committee for peri-urban areas. We found different perspectives related to the cause of death (COD) e.g., parents expressed their curiosity to know the COD of their children, and hospitals shared this information as well. However, it was deemed unethical to disclose the COD when it occurred at community setting. The data explored the concept of doubling graveyards and reasons were lack of space and desire to be buried near ancestors and ease in visit. Data identified the potential graveyards, stakeholders, and information about death records. Further, confidentiality of death record was found as major obstacles among few communities and civilians. In conclusion, this is a unique ethnographic information related to graveyard and burial process in a resource constraint setting. Further the study will also help in exploring social/cultural context related to a mortality surveillance in a community setting.

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THE RELATIONSHIP BETWEEN PRE-EXISTING COMORBIDITIES AND IN-HOSPITAL CARDIOVASCULAR EVENTS AMONG COVID-19 PATIENTS IN BANGLADESH: A PROSPECTIVE COHORT STUDY

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The first case of SARS-CoV-2 was detected on 8 March 2020 in Bangladesh just before 03 days of the announcement of coronavirus global pandemic by World Health Organization. As of March 16, 2023, a total of 2,037,947 cases have been confirmed, resulting in 29,445 deaths. Cardiovascular disease (CVD) and diabetes are scientifically recognized as major risk factors for poor prognosis and fatalities. Bangladesh has the highest prevalence of CVD risk factors among South Asian countries. Majority of the studies on Covid-19 conducted in Bangladesh were related to clinical symptoms, mental health and impact on health systems and scarcity in data exists on the CVD risk factors and outcome of the hospitalized Covid-19 patients. Therefore, a prospective cohort study was conducted as a part of multi-country project to explore the relationships between cardiovascular risk factors and preexisting comorbidities to the cardiovascular in-hospital events of covid-19 patients. Data were collected from 897 adult Covid-19 PCR positive patients of 3 hospitals at the time of hospital admission and at 30 days, discharge or death. Statistical analysis was done using epicalc R package, Descriptive analyses and multivariable log-binomial regression models, adjusted for age, sex, risk behavior and clinical events were performed. Mean & maximum age was 18 and 96 respectively, 52.1% female, 54.8% patients with cardiac comorbidities and the most common preexisting comorbidities were hypertension (54.1%) and diabetes (44.1%). Almost one fifth of the patients developed cardiac events including Myocarditis (0.7%), Myocardial Infarction (3.5%), Pericarditis (0.6%), Acute Heart Failure (6.1%), Endocarditis (0.4%), Atrial Fibrillation (0.2%), Cardiac Arrest (8.0%), Shock (1.0%) and Cardiac Blocks

(0.8%). The predictors of overall in-hospital cardiac events included male sex, overweight, lower education level (<college/university), former smoker, heart rates and low SPO2 ($p < 0.05$ for each). This study provides robust evidence on COVID-19 in-hospital cardiac events which guides future health care preparedness on cardiac emergency for the pandemic globally.

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PATTERNS OF DATE PALM SAP HARVESTING AND TRADING PRACTICES AND RISK OF NIPAH VIRUS TRANSMISSION AT COMMUNITIES IN BANGLADESH

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Bangladesh has been experiencing a nearly annual Nipah virus (NiV) outbreak through drinking contaminated raw or fermented date palm sap (RDPS) with bat excreta since 2001. RDPS harvesting practices and trading patterns have not been explored extensively. Hence, we conducted a study to understand RDPS collection, consumption, and selling practices and the risk of NiV spillover at the community level. We performed an explorative qualitative study in two NiV outbreak districts, Rajbari and Naogaon, between 2021 and 2022. We recorded participant observations (n=14) and conducted ethnographic interviews (n=31) with RDPS collectors (Gacchi) on collecting and selling practices and using diversity of protective apparatus. The interview data were analysed using coding and thematic analysis based on the grounded theory approach. Gachi prefers selling RDPS more than making molasses due to time consumption, fuel costs of preparing it, and the high demand for consuming RDPS. They informed RDPS selling is not limited to their local community and sale distends location of non-harvesting areas based on customer demand through a middleman, which increases the transmission risk of NiV and other bat-borne diseases in wider geographical areas. We observed, and participants reported that Pteropus and non-Pteropus bats and rodents visited the trees and drank RDPS. They are replacing clay pots with discarded plastic pots, due to the free cost. They also prefer to use non-conventional protective apparatuses like jute bags, plastic bags, and nylon nets due to the time and resources to prepare bamboo skirts. Moreover, they reported that bats scratched out bamboo skirts and trunks to lick sap. We recommend adopting a culture-sensitive intervention, including efficacy tests of bat access protection on several apparatuses with economic outcomes of the date palm sap harvesting practices to prevent spillover of NiV and other bat-borne emerging viruses in Bangladesh.

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UNDERSTANDING VACCINE HESITANCY IN BOENDE, WESTERN DR CONGO: A MIXED-METHODS STUDY

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In 2019, WHO identified vaccine hesitancy as one of the top 10 global health threats. Reports following the SARS-COV-2 pandemic indicate a general decline in trust in vaccines, including routine childhood vaccination. The Democratic Republic of Congo (DRC) has a low childhood vaccine coverage (around 50%) and one of the world's highest mortality rates of children under 5 at 79 deaths per 1000 live birth. While previous studies showed a good level of confidence in the safety and importance of vaccines in the country, they relied on data that was mainly quantitative and/or focused on urban areas. To address this gap, we conducted a mixed-method study in Boende, Tshuapa province (western DRC), and surrounding villages in the Boende health zone. The region was hit by an Ebola outbreak in 2014 and witnessed COVID-19 restrictions between 2020 and 2022. Boende was the site of the EBL2007 Ebola vaccine trial between 2019 and 2022. Alongside this vaccine trial, we aimed to explore perceptions and attitudes towards childhood and adult vaccination through individual interviews and focus groups with people living in Boende (mostly non-participants of the trial), as well as a 30-cluster survey covering the entire health zone of Boende. Our analysis revealed that adult vaccines appear to be less trusted than childhood vaccines, with Covid-19 vaccines being the least trusted, most likely due to the low number of related hospitalizations and deaths in the region. The majority of interviewees in Boende stated that their children are vaccinated. Nonetheless, over half of the interviewees expressed concerns about the common side effects of childhood vaccines or had doubts about the storage conditions of these vaccines, others believed that vaccines were given only to people living in Africa and not White people. These reasons were found to deter some study participants and their acquaintances from vaccinating their children. These findings could be used to inform future vaccination and sensitization campaigns in the region by addressing common concerns and misconceptions about vaccines, particularly for adults, to increase trust in and uptake of vaccines.

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PERCEPTIONS ON ACCEPTANCE AND BARRIERS RELATED TO MORTALITY SURVEILLANCE FOR DRY NASAL SWAB PROCEDURE RELATED TO COVID-19 IN PERI-URBAN SETTINGS, PAKISTAN

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COVID-19 is a major public health threat, declared a pandemic by WHO in January 2020. Understanding community perceptions of the disease and its associated mortalities is crucial for protection and planning in LMICs. The objective of the study was to investigate the community perceptions about dry nasal swab procedure for COVID related mortality surveillance in peri-urban settings of Pakistan. This exploratory study design was used to conducted eleven focus group discussions (FGD)with various Muslim ethnicities residing in Ali Akbar Shah, an urban slum area on the outskirts of Karachi, including parents, religious leaders, community leaders, graveyard caretakers, traditional birth attendants, bathers, and community health workers. Three qualitative main themes were identified, namely the community's health-seeking behavior towards COVID-19, the understanding of death rituals in Muslim ethnicities and feasibility of obtaining dry nasal swab samples. Various perceptions were reported on COVID-19 spread e.g. getting vaccination and follow COVID-19 SOPs, while others remained unsure and stated "Covid-19 is there in the entire world, there is no doubt in this, but it is not here in our area .We have never seen it in two years, so we consider it all a lie" (Graveyard caretakers). Further, we explored that in Muslim communities before burial, a body is ritually washed which involves using cotton to clean the nostrils of the deceased and taking a dry nasal swab sample at the time of burial bath would be religiously and contextually acceptable. The findings revealed that the approach to the family elder and parents prior to the sample collection would be a better strategy to implement mortality surveillance, to overcome perceived barriers such as pain to the body, unethical and disrespectful to deceased and grief amongst families. In conclusion, Mortality surveillance studies within community setting is difficult to execute however, community buy-in and liaison with key stakeholders are essential. In addition, community grief support and counselling after death would be beneficial.

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METAGENOMIC DETECTION OF PATHOGENIC BACTERIA IN TICKS FROM ISIOLO AND KWALE COUNTIES IN KENYA

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Ticks are arachnid ectoparasites that are second only to mosquitoes in the transmission of human diseases including bacteria responsible for anaplasmosis, ehrlichiosis, spotted fevers, and Lyme disease among other febrile illnesses. Due to paucity of data on bacteria transmitted by ticks in the Kenya, the present study undertook a bacterial metagenomic-based characterization of ticks collected from Isiolo, a semi-arid pastoralist county in Eastern Kenya and Kwale a county in coastal Kenya. Bacterial 16S rDNA PCR amplicons obtained from the above samples were sequenced using the MinION (Oxford Nanopore Technologies) platform yielding 547,780 reads with a median length of 1.54kb. The resulting reads were demultiplexed in Porechop, followed by trimming and filtering in Trimmomatic before clustering into OTUs using Qiime2-VSearch. A SILVA database pretrained naïve Bayes classifier was used to taxonomically classify the OTUs. A total of 2,918 ticks belonging to 3 genera and 10 species were screened in the present study. The pathogenic bacteria detected in pooled tick assays were as follows: Rickettsia spp. 59.43% of pools, Coxiella burnetii 37.88%, Proteus mirabilis 5.08%, Cutibacterium acnes 6.08% and Corynebacterium ulcerans 2.43%. These bacteria are responsible for spotted fevers, query fever, urinary tract infections, eye infections and diphtheria-like infections respectively. P. mirabilis, C. acnes and C. ulcerans were detected only in Isiolo. Metabarcoding was carried out on the tick species from which bacteria were detected showing that from Isiolo Hyalomma truncatum had the highest number of bacterial species at 12 while from Kwale Rhipicephalus boophilus decoloratus had the highest number of bacterial species at 6. The detection of Cutibacterium acnes, commonly associated with human skin flora suggests that the ticks may have contact with humans thus exposing them to infections caused by the identified bacteria. The findings in this study highlight the need for increased surveillance of tick-borne bacteria to discern their public health burden.

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ENGAGING ANTHROPOLOGY IN NIPAH OUTBREAK: FACTS BEHIND THE HUMMING

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Anthropological approaches play a pivotal role in outbreak investigation by bringing forth sensitive, tabooed, or stigmatized practices, behaviors, and contexts interconnected with the disease paradigm. Unanticipated situations such as the spread of rumors, public panic, uncontrolled prevalence of obscure and misinterpreted information in the community, cause psychological and emotional tensions during an outbreak. In the 2023 Nipah Virus (NiV) outbreak in Bangladesh, a combined team of anthropologists from the Institute of Epidemiology Disease Control and Research (IEDCR) and icddr,b embedded the rumor management method concurrently to tackle unforeseen situations. Alongside functioning anthropological approaches, we especially focused on documenting the 'rumors' spread from social media and communities. We included both human experts and human-computer methods. This year the situation started off with 2-3 Nipah cases similar to other years, and no one was alarmed considering the situation as 'normal'. However, with the increasing number of cases, people's reactions and perceptions changed. Old-aged people were prone to dismiss the linkage between NiV and drinking raw date palm sap (DPS). The young generation apprehended drinking raw DPS as a challenge and started representing this as a trend on social media. Some business groups capitalized on the idea by promoting people through advertising on various social platforms. In some communities, people barely perceived the connection between drinking raw DPS with bats and disease transmission, as they are more used to seeing the abundance of bats in the lychee season. Besides, there was diversion and reluctance among community people to talk about this due to the presence of the media. In this context, along with documenting the then-prevailing rumors, beliefs, and perceptions, we followed the 'slow science' method and invested quality time to observe, listen, build rapport, and then collected data. Sharing the experiences gained through anthropological methods during outbreak investigation in the global forum can generate new risk communication and prevention initiatives.

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SURVEILLANCE OF ACUTE FEBRILE ILLNESS IN JORDAN DURING THE TIME OF PANDEMIC OF COVID-19

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Surveillance of Acute Febrile Illness (AFI) during the pandemic is important to understand the burden of the infectious diseases presenting with fever, which is also a common presentation of COVID-19 cases. In Jordan, AFI surveillance started in June 2020, in 2 tertiary care hospitals in the north, and south of the Kingdom. It was expanded to a third hospital in the middle in September 2021 and to 2 other hospitals in the northwest in June 2022. Cases that require hospitalization presenting with current or history of fever (≥ 38Co) within 10 days before admission with no identified origin, were enrolled, and leftovers of their clinical samples of blood were tested at the Central Public Health laboratory using a multiplex qrt-Polymerase Chain Reaction of 15 pathogens, in addition to PCR testing for SARS-CoV2. Blood culture results were recorded if requested. Through January 2023, a total of 890 patients were enrolled. Male gender constituted 55.2 % (491/890) of cases and median age was 3 years old. Median duration of hospitalization was 4 days. Eight cases died during hospital admission with 0.9 % mortality rate. Out of 890 samples, a total of 157 pathogens were detected in only 15.8% (141/890) of the samples. Of the 157 pathogens detected, Epstein Barr Virus was most frequently detected (42 %) followed by Cytomegalovirus (21.7%) and Human Adenovirus (12.1%). Arboviruses were detected in 8 samples (West Nile virus 6 samples, and one sample of Dengue and Rift Valley virus each). None of the samples tested positive for Zika virus. SARS-CoV2 was detected in only four samples. Other pathogens including Salmonella (6 samples), Leptospira and Brucella (2 cases each), Rickettsia Spp. and Coxiella burnetii (one sample each) were also identified. Expanding the surveillance to mild to moderate cases (e.g., outpatients) is planned to comprehensively describe the epidemiology of AFI in Jordan. Integration of the results with other surveillance programs such as vector surveillance is implemented to provide enhanced data to improve public health and accompanying health risk mitigation knowledge, as well as augment national control measures in Jordan and the region.

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IMPLEMENTING A "TEST AND TREAT" STRATEGY FOR COVID-19 IN BOLIVIA AND PARAGUAY: LESSONS AND CHALLENGES

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Prompt diagnosis of COVID-19 is a key intervention for COVID-19 clinical care and control. The ECO project was designed to enhance the coverage of diagnosis of COVID-19 in Bolivia and Paraguay. We carried out a formative assessment of the national capacities to implement, scale-up and track the use of Rapid Diagnostic Tests (RDTs). When oral treatments became available, this was further built into a 'test and treat' strategy for implementation in selected districts in each country, in collaboration with district leaders, clinics, and the Ministry of Health. The formative assessment identified factors associated with community hesitancy to access COVID-19 diagnostics, but also others that could facilitate diagnosis, including the impact of availability of effective treatment to prevent progression in high risk patients. Catalytic implementation in each country with distribution of 20,000 RDTs to health facilities and health posts afforded the opportunity to track how the supply chain was managed, distribution prioritized, obtaining timely data between first symptom, testing and results to the patient, status of training, and patient follow-up. The findings were built into an implementation strategy, along with enhanced data reporting and visualisation, and carried out in parallel with a communication campaign co-created with the community and the health centres. Despite the delays in access of COVID-19 treatments such as Tocilizumab and subsequently oral drugs, these have begun to reach both countries. The systems to diagnose, identify high risk groups, and deliver drugs have been put in place. We will present the evaluation data on planned endpoints for tracking acceptability and uptake of diagnosis and medicines, including time from diagnosis, which is critical for use of the new oral drugs. In addition, significant progress was made on systems for data capture and visualization, community engagement and communication strategies, and pandemic preparedness, which might extend beyond the duration of the project. Finally, we will summarize lessons learned in the midst of the COVID-19 pandemic in two LMIC Latin American countries.

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COVID 19 KNOWLEDGE, ATTITUDES, PRACTICES (KAP) AND MENTAL HEALTH BEHAVIORS IN LIBERIA: FINDINGS, IMPLICATIONS AND FUTURE DIRECTIONS

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Evidence from the WHO revealed that age, comorbid medical conditions, gender, and occupations are risk factors for CoVID 19. Limited information exist in Liberia on population-based risks. The CoVID 19 outbreak led to the implementation of public health guidelines by the Ministry of Health to protect the health and welfare of the general population. However, risk reduction messaging and risk communication strategies were inconsistent, unclear and non-compliance. Also, there existed significant community distrust in CoVID 19 public health information dissemination channels, limited integration of community structures in the national mitigation strategies and significant increase in public perceptions about conspiracy theories in the country. We conducted a cross-sectional study with multi-stage sampling frame among 250 adult males and females from primary CoVID 19 hotspots in Liberia based on the WHO's Conceptual Framework for Action on Social Determinants of Health. The specific aims were to determine the prevalence of (1) CoVID 19 related knowledge, attitudes, practices and behaviors, (2) CoVID 19 risk factors, and (3) mild-to-moderate mental health related disorders, and (4) the involvement and integration of urban and rural community structures in the primary epicenter in the mitigation of public health outbreaks in Liberia. The study findings revealed a mean age of 34 years, 60% urban and 40% rural, equal proportion of males and females, and majority single and employed, with evidence of formal education. The findings clearly demonstrated that CoVID 19 negatively affected health and social services, employment and lost wages, especially in rural settings; that there was no correlation between CoVID 19 Knowledge and Practices; that rural residence and women were better predictors of CoVID 19 Knowledge, and that depression and anxiety were associated with lower adherence to CoVID 19 prevention practices. We recommend that future research studies may be warranted in post-conflict Liberia to better understand the social determinants and effects of disease outbreaks, and its related impacts, on health equity.

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COMMUNITY ENGAGEMENT IN EPIDEMIC MANAGEMENT: AN ANALYSIS OF THE EBOLA VIRUS DISEASE AND COVID-19 RESPONSES IN BOENDE, WESTERN DR CONGO

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In 2020, the WHO identified several challenges to the simultaneous management of Ebola virus disease (EVD) and COVID-19 in low and middle-income countries, including health systems' overload, international coordination, and communication between response teams and affected communities. Between 2020-2022, the Democratic Republic of Congo (DRC) faced 6 EVD outbreaks while also battling the COVID=19 pandemic. Recent publications highlight that the experience gained during EVD outbreaks has facilitated the implementation of prevention and control measures against COVID19. These publications primarily focus on national-level management and are often narrative reviews. To better understand how DCR's response to COVID-19 built on previous experiences of EVD management, we conducted a qualitative study in Boende (Tshuapa province, western DRC), which faced an EVD outbreak in 2014, hosted the EBL2007 Ebola vaccine trial between 2019-2022, and is currently dealing with COVID-19. We reviewed relevant literature, including official documents, and interviewed healthcare providers, health authorities, political authorities who were actively involved in managing both diseases in Boende, as well as members of the affected community. We found that community leaders (local authorities, religious leaders, teachers, and the relais communautaires, community members trained in health surveillance and communication) played a central role in community-based surveillance, both during the EVD management and in the fight against COVID-19. However, during the EVD response, community leaders were extensively trained on EVD and risk communication and provided with bicycles, communication material, and a financial motivation. During the COVID-19 response, their involvement was rather limited to informing communities of the existence of the disease. This may partially explain the low level of community engagement in the fight against COVID-19. These findings suggest that the role of community leaders should be reconsidered in order to gain community engagement in community-based surveillance and thus improve future outbreak management.

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PERCEPTIONS OF PREVALENCE, IMPACT, AND MANAGEMENT OF POST-ACUTE SEQUELAE OF SARS-COV-2 INFECTION AMONG HEALTHCARE WORKERS IN KWENENG DISTRICT, BOTSWANA

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Since March 2020, over 760 million confirmed cases of COVID-19 infection have been identified, with 9.5 million recorded in Africa. Post-acute sequelae of SARS-CoV-2 infection (PASC) affects an estimated 32% to 87% of COVID patients globally. Data regarding the current prevalence and impact of PASC in Botswana are limited. Utilizing a cross-sectional survey design, we surveyed healthcare workers about the perceived prevalence of PASC, the duration of and characterization of common symptoms, the impact of PASC symptoms on patients' daily lives, and current management strategies. The survey was disseminated to healthcare workers via pre-existing WhatsApp groups and on paper. A total of 79 respondents completed the survey, from an estimated 650 staff meeting eligibility criteria (12% participation). Of these, 91% provided informed consent; 45% were female and 26% were male. The majority (90%) were nurses, with doctors and "other" accounting for 6% and 4% of respondents, respectively; no administrators responded. Over half (70%) worked at primary care facilities, and over a quarter (28%) worked in hospitals. Most (93%) indicated seeing patients with PASC on a weekly basis, though the majority (61%) identified these patients as <10% of total patients. Persistent cough was the most common PASC symptom (64%), followed by fatigue and muscle/body aches (4% each). A substantial proportion of respondents were unsure how to respond to questions regarding the management of common PASC symptoms, with 29% and 36% indicating uncertainty regarding the management of persistent cough and fatigue, respectively. These data indicate that health care healthcare workers frequently encounter patients with PASC at various health system levels across Kweneng, coupled with high levels of uncertainty regarding the best management for this syndrome. Key informant interviews will be conducted to further explore these themes and identify existing PASC management strategies. Data will be used to develop standardized PASC evaluation and management algorithms for use in Kweneng District.

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VERTICAL TRANSFER OF HUMORAL IMMUNITY AGAINST NIPAH VIRUS: A NOVEL EVIDENCE FROM BANGLADESH

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Human Nipah virus (NiV) infection is rapidly progressive and highly fatal, which is one of the major barriers to in-depth exploration of the immune response. Bangladesh nurtures the largest cohort of Nipah infection survivors, and through their contribution, significant discoveries have been made that have substantially helped the scientific community understand the interaction between the virus and the human immune system. One such novel finding is described in this abstract regarding the vertical transfer of immune properties against NiV. In January 2020, a mother and her four-year-old daughter were infected with NiV. Both had a raw date palm sap consumption history and were diagnosed as confirmed NiV-positive cases. Unfortunately, the child succumbed during the course of the infection, while the mother survived with significant residual neurological impairment. Struggling through post-infection physical challenges and psychological trauma, the couple conceived a year and a half later. Per the mandate of national Nipah surveillance, thorough antenatal follow-up and routine Nipah survivor follow-up were done. The pregnancy was uneventful, and a healthy male baby was born. Being the baby of a NiV infection survivor, to exclude the possibility of vertical transmission of NiV infection, specimens were collected from the newborn and tested at the reference laboratory of the Institute of Epidemiology, Disease Control and Research (IEDCR) and icddr,b. While anti-Nipah IgM and PCR tests for NiV were negative, a high titre of anti-Nipah IgG was detected. From mother to neonate, the transfer of humoral immunity against the Nipah virus was confirmed for the first time. This finding will serve as a reference for further research on the transfer of NiV-specific antibodies and warrants further exploration of its effectiveness in virus neutralization and its potential to protect newborns. This will also serve as a resource for future research on vaccine recommendations for pregnant or young women against NiV.

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SURVEILLANCE OF OPERATIONALLY RELEVANT VIRAL HEMORRHAGIC FEVER AND RICKETTSIAL VECTOR BORNE INFECTIOUS DISEASE THREATS, INSECTICIDE RESISTANCE, AND ASSESSMENT OF VACCINE EFFICACY TO PREDICTED T CELL EPITOPES AND B CELL ANTIGENS IN AFRICOM

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Crimean Congo hemorrhagic fever (CCHV), Yellow Fever Virus (YFV), and rickettsial diseases are important emerging or reemerging vector borne infectious diseases of public health concern in Africa and Europe. Expanded vector surveillance, increased insecticide resistance studies, and novel vaccine development efforts for CCHV, YFV, and rickettsial infections in AFRICOM and EUCOM are needed to better detect and prevent disease. While an inactivated vaccine for YFV has been administered prophylactically for decades and is required for AFRICOM entry, there is no licensed vaccine currently available for CCHV or rickettsial species despite recent progress in vaccine research and development for these pathogens. Multiplex PCR panels now provide convenient mobile forward deployable surveillance tools to rapidly detect host, YFV, CCHV, and rickettsial genes in real time and can streamline identification of new strains, variants of concern, or resistance genes. Naval Medical Research Unit-Three (NAMRU-3) sites in Ghana, Egypt, and Djibouti routinely conduct or manage vector-borne infectious disease surveillance in support of AFRICOM. Expansion of vector surveillance sites and sample sequencing to better characterize insecticide resistance, viral hemorrhagic fever, and rickettsial risk within the NAMRU-3 area of responsibility is needed. We expect that broadened surveillance will identify conserved coding sequences in the bunyavirales families, flavivirus families, and rickettsial species that align with immunodominant epitopes and antigens of novel vaccine candidates. Monitoring vector borne pathogen strains will help assess existing vaccine efficacy against operationally relevant infectious diseases in the NAMRU-3 area of responsibility and predict strain-dependent variation in immunological recognition of linear epitopes and surface antigens of vaccines currently in development. These collective activities and network of analyses will have implications for immunization and insecticide spray policies.

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THE REMOTE EMERGING DISEASE INTELLIGENCE-NETWORK: ENHANCING BIOSURVEILLANCE USING WATER AND SEDIMENT SENTINEL SAMPLES FROM BELIZE, CENTRAL AMERICA

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The past decades have seen a dramatic increase of emerging and/or re-emerging infectious diseases worldwide. More outbreaks are foreseen for the future, yet proactive surveillance remains limited due to many challenges including lack of technical expertise and characterization of reliable sentinel sample types for accurate detection of circulating pathogens reflecting potential zoonotic spillover threats. The Remote Emerging Disease Intelligence-NETwork (REDI-NET) is a phased initiative project which aims to enhance current surveillance efforts to detect, predict and contain potential emerging infectious diseases in an efficient and timely manner. Partners have established robust standard operating procedures, including those for standardized field sample collection, storage and metagenomic next-generation sequencing (mNGS) to capture a broad spectrum of pathogens circulating in REDI-NET early phase surveillance sites of Belize, Kenya, and Florida. In Belize, active biosurveillance sampling was performed monthly from ten permanent water bodies, in the Corozal, Orange Walk, Stann Creek and Toledo Districts from November 2021-March 2022 and incorporating two additional permanent water bodies in the Cayo and Belize Districts in November 2022-March 2023 to determine effectiveness of water and sediment samples to serve as sentinels for circulating pathogens. Here we report mNGS outputs on viral and non-viral (e.g., bacterial, parasitic) pathogens using MinION/GridION sequencers (Oxford Nanopore Technologies) to inform on whether both water and sediment sampling are needed, or if one sample type could be used to inform pathogen presence effectively. Findings are meant to provide guidance to field collection efforts in order to streamline resource allocation which is often a limitation in surveillance efforts.

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CAUSE SPECIFIC MORTALITY FROM VERBAL AUTOPSY FOR UNDER FIVES IN WESTERN KENYA, 2019 TO 2022

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Verbal autopsy remains the most widely used and feasible method for measuring cause of death, especially in low and middle in-come countries, which still lack reliable information on pediatric causes of death. Child Health and Mortality Prevention Surveillance (CHAMPS) network that includes Health and Demographic Surveillance Systems (HDSS) in urban (Manyatta) and rural (Karemo) settings in Western Kenya, conducts verbal autopsy (VA) to help investigate and monitor causes of death. We examined U5 cause-specific mortality rates and fractions using VA data from the two CHAMPS HDSS sites for the period 2019 - 2022. VA data were collected using the 2016 WHO form and processed using the InterVA5 probabilistic model in R software. A total of 3642 U5 deaths were recorded, of which 3273 (90%) had VAs conducted. Overall under-five mortality rate in the rural site 14.2(13.3, 15.2) per 1000 live births was higher than the urban site 10.1(9.4, 10.7) per 1000 live births. Neonatal mortality rate was 21.8 per 1000 live births for rural and 23.7 per 1000 live births for urban. Infant mortality rate in the rural site of 24.5(19.6, 29.4) per 1000 live births was higher than the urban site of 16.7(14.5, 17.5) per 1000 live births. Child mortality rate 6.3 (6.0, 6.6) per 1000 live births for rural and 2.3 (2.2, 2.4) per 1000 live births for urban. The leading specific causes of death according to VA were birth asphyxia (141, 13.0%), prematurity (142, 13.1%), stillbirth (136, 12.6%), diarrheal diseases (104, 9.6%), meningitis & encephalitis (80, 7.4%), and malaria (58, 5.4%). The under-five cause-specific mortality rates generated using the InterVA-5 model reflects prevailing knowledge on the under-five disease burden in western Kenya, but better correlation is needed with CHAMPS findings generated using minimally invasive tissue sampling and specific diagnostics. Though U5 survival has increased in recent years, a lot more needs to be done to alleviate under-five deaths in the two sites.

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PUBLIC HEALTH DECISION-MAKING DURING COVID-19 PANDEMIC: A DETERMINANTS FRAMEWORK

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Public health governance and decision-making processes during the Coronavirus disease 2019 (COVID-19) pandemic were constrained by ambiguity about the rapidly evolving epidemiological situation, urgency of response and paucity of robust scientific evidence. Among recent analyses on governance during the pandemic, few studies have focused on the process of decision-making. Comprehensive frameworks for understanding the process and determinants of public health decision-making at different levels are needed for effective future pandemic preparedness and response. Through a series of key informant interviews and focus group discussions with national officials, academic experts and civil society representatives from Singapore, we developed a framework describing the determinants of public health decision-making during the pandemic in Singapore. In this framework, we draw from crisis management theories and present three key determinants of decision-making: centralization, agility and adaptability. Centralization refers to concentration of decisional power with a limited number of executives. Agility refers to timely action and quick redirection of resources towards priority issues. Adaptability refers to modifying existing structures and processes or establishing new structures and processes to respond to the existing crisis. We highlight that these determinants are further shaped by three factors. First is the availability of human, material and information resources. Second by is by political, social and economic context. Third by the governance values of accountability, transparency, equity and trust. We present five key characteristics for each determinant, which we suggest should be strengthened for future pandemic preparedness efforts. Further work is needed to assess generalizability of our results. However, we hypothesize that this framework can be applied across different contexts and governance systems.

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INVESTIGATION AND MANAGEMENT OF A STREPTOCOCCUS PNEUMONIAE MENINGITIS EPIDEMIC IN DJADOUBANGO, IVORY COAST

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On January 21, 2023, the Tanda health district, in the East of the country, was alerted by the general hospital following the death of 2 schoolchildren from Djadoubango, who presented with headaches & a stiff neck. A team from the health district immediately went to the village. The objective of this work is to describe the phenomenon, identify the cause & propose control measures. This multidisciplinary team, made up of doctors, nurses & biologists, reviewed the consultation registers of the health facilities,

interviewed the populations, examined the patients, looked for other patients in the community & collected blood & cerebrospinal fluid samples. From this investigation, the following points emerged: (i) 14 registered patients whose age varies between 6 & 16 years old. They were all from Djadoubango, with family ties & all from the primary school of the village but with no notion of travel during the previous month, (ii) 05 deaths including 03 during evacuation to hospital & 02 during hospitalization, (iii) No information was found on the vaccination status of the children, (iv) cerebrospinal fluid samples were collected from 6 children & sent to Pasteur institute laboratory in Abidjan, (v) 9 patients were hospitalized & treated free of charge at Tanda General Hospital, (vi) the results of the analysis of the samples showed cases of malaria & 2 cases of Streptococcus pneumoniae meningitis. One of the 2 cases died while the other recovered after treatment with antibiotics. These pneumococcal meningitis cases show the change in the ecosystem of the cerebrospinal meningitis germ following vaccination campaigns against meningococcus A & C. Indeed, meningitis epidemics were until then due to Neisseria meningitidis. Vaccination of contact subjects with pneumococcal vaccine was carried out to contain the epidemic. Promiscuity in the classrooms & climatic factors such as the harmattan marked by drought & dust may have favored the occurrence of the disease. Reinforcing pneumococcal vaccination in the Expanded Immunization Program is necessary.

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UNDERSTANDING THE USE OF UTEROTONICS BY COMMUNITY HEALTHCARE PROVIDERS DURING HOME DELIVERY IN RURAL BANGLADESH

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In Bangladesh, uterotonics, e.g. oxytocin, are widely used to augment uterine contractions during home delivery, which may increase the risk of asphyxia leading to stillbirth or neonatal death. A pregnancy surveillance system in rural Baliakandi, Bangladesh systematically identified pregnant women and followed them to identify the care received through their birth outcome. We conducted a mixed-method study to identify the frequency and extent of use of uterotonics during home delivery. Among the 5337 completed pregnancies during September 2021 to December 2022, 23% (1186/5337) delivered at home with a birth attendant. In 47% (563/1186) of deliveries a uterotonic was given to increase contractions. We conducted 14 interviews with birth attendants and six mothers, recently delivered at home. All the birth attendants reported that almost in every case they provided an uterotonic, mainly to increase uterine contractions for normal delivery and usually give the first ampule (5 IU/ml) oxytocin when the water breaks or/and baby's head moves into the vaginal canal and commonly continue to give up to three ampules. Most mothers also shared the same experience. If a mother does not deliver within 30 minutes of the third ampule, birth attendant referred mother to hospital. They also give this drug in some critical conditions, such as when the baby's head is in the birth canal but the mother does not have contraction. A few skilled attendants reported using oxytocin to decrease postpartum bleeding, to discharge placenta and uterus involution. Birth attendants noted, families often pressured them to provide this drug for a quicker delivery. Half of them remarked that if the cervix was not opened but the injection was given, it creates pressure in the uterus and could lead to baby's death, though they rarely experienced it. Among the 563 deliveries in which oxytocin was given, 98% reported to a livebirth outcome compared to 97% livebirth when it was not given. Although the results of our study found a livebirth outcome after frequent use of oxytocin during labor, further follow-up of those livebirths may provide more definitive evidence of adverse outcome of such use.

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ROUTINE CHILDHOOD IMMUNIZATION IN BURKINA FASO: IDENTIFYING AND REACHING ZERO-DOSE AND UNDER-VACCINATED CHILDREN IN A SECURITY CHALLENGED COUNTRY

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WHO-UNICEF estimates and coverage survey data show about 10% of children miss vaccination in Burkina Faso yearly. These children, often from marginalized groups, are susceptible to vaccine-preventable diseases and maintain avoidable outbreaks in the country. Defining Zero-dose (ZD) children as those who have not received a first dose of the combined Diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b (DTP-Hep-Hib) vaccine at 8 weeks, we conducted a secondary analysis of five years of administrative data (2017 - 2021 DHIS2) to map ZD children and prioritize strategies to reach them. We triangulated administrative data with survey data (2020 Demographic health survey, 2020 vaccination coverage survey). To reduce the limitation of coverage survey data at the district level, we created a correction factor (f) using the ratio of regional coverage and applied it to the district level. The determining factors of ZD children and successful immunization strategies were assessed using the Immunization Equity Survey, the Gender Action Plan, the 2021-2025 National Immunization Strategy, the Immunization Strategy for Security Challenge Areas and post-vaccine introduction assessments. Overall, there were an estimated 45,193 (5.6%) ZD children in 2020 and 32,023 (3.8%) ZD children in 2021. From 2020 to 2021, fourteen (14) health districts accounted for 85.4% of the ZD children. The highest number of ZD children were found in Djibo, Dori, Gorom Gorom and Barsalgo districts in 2020, all areas affected by insecurity, while urban districts (Boulmiougou, Bogodogo Sigh Nonghin) and districts dealing with significant security challenges (Diapaga, Barsalgo Djibo et Titao) accounted for the largest number in 2021. The key determining factors for ZD and under-vaccinated children included insecurity, availability and accessibility of health services and poverty, yet there was an upward trend of ZD children in the richest wealth quintiles (from 2.8% in 2010 to 4.4% In 2020).

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ASSESSING KNOCK DOWN RESISTANCE MUTATIONS IN THE DENGUE VECTOR, AEDES AEGYPTI, IN POSADAS, ARGENTINA

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The control of adult populations of the arboviral vector, Aedes aegypti, is mainly based on the application of insecticides, and the widespread use of pyrethroids led to the selection of genetic resistance to insecticides on a global scale. The increased frequency and distribution of non-synonymous knock down resistance (kdr) mutations in the voltage gate sodium channel gene (Nav), impose a threat to the success of mosquito control programs. In this work we investigated the presence of two kdr mutations (V1016I and F1534C) in the Nav gene across four neighbourhoods in Posadas, Argentina. Alleles at both loci were interrogated using TaqMan SNP genotyping assays in DNA extracted from 100 adult females. We report the presence of pyrethroid resistance alleles, kdr 1016I=29.08% and kdr 1534C=70.70%, among adult females. The combined kdr genotypic frequency reveals that approximately 67% of local adult females have an enhanced resistance to pyrethroids, carrying at least one kdr allele at each locus. Genotyping is an invaluable tool for kdr resistance monitoring in vector control campaigns. This is the first report of kdr mutations in Ae. Aegypti in the Northeast of Argentina, a region with recurrent dengue

epidemics. Our results emphasise the need to extend the kdr frequency assessment to other cities alongside with arboviral and entomological surveillance.

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USING TRANSCRIPTOMIC DATA TO IDENTIFY POTENTIAL MARKERS OF TRANSFLUTHRIN INSENSITIVITY IN ANOPHELES GAMBIAE SS

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The emergence of resistance to pyrethroids, threatens the efficacy of insecticide treated nets (ITNs) and necessitates the development of complementary tools. Spatial repellents (SRs), are a promising new intervention that reduce human vector contact, thereby breaking transmission by creating vector-free spaces. Although they are structurally different from insecticides used on ITNs, insecticides used in current SRs such as transfluthrin are pyrethroid insecticides raising the possibility of SR insensitivity among vector populations with high levels of resistance to pyrethroids. We used a high throughput screening system to determine the spatial activity index(SAI) of three strains of An. gambiae s.s. (Kisumu, susceptible; Bungoma, local resistant; Pimperena, resistant) to transfluthrin-treated surfaces. A whole transcriptome analysis approach was used to determine differentially expressed genes and identify potential markers for transfluthrin insensitivity. The SAI analysis showed a heterogeneous response based on mosquito population. Bungoma (12.515 ug/ml : SAI - 0.069), Kisumu (0.0025 ug/ml : SAI - 0.117) and Pimperena (125.15 ug/ml : SAI - 0.111). The differential expression analysis in non-responders relative to responders showed an over-expression of primarily members of the cytochrome P450 monooxygenases. CYP12F12 was the most overexpressed with a fold change (FC) of 36.64 in Bungoma and 43.80 in Pimperena relative to responder Kisumu strain. Olfactory-related genes were mostly globally down-expressed in all test populations. This study provides pertinent background for understanding the effects of transfluthrin pressure on Anopheles gambiae ss and the first evidence of differential gene expression linked to behavioral insecticide resistance in malaria vectors. The roles of these genes in transfluthrin insensitivity need to be validated to further substantiate their involvement in behavioral responses to transfluthrin, in order to provide a basis for the development of molecular surveillance tools for early detection of transfluthrin failure.

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IMPACT OF SUGAR DIET ON THE SENSITIVITY OF INSECTICIDES-RESISTANT MOSQUITOES

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The resistance of mosquitoes to insecticides is a rapidly growing problem. While resistance has a strong genetic basis, the environment also affects the extent of resistance. However, we know little of how, for example, the mosquitoes' diet affects their resistance. Our aim was to see how different types of sugar found in nectar influence the sensitivity of strongly insecticide-resistant mosquitoes. To do so field-collected larvae of Anopheles gambiae s.l. from Tiassalé were reared to adults then, their offspring (F1 generation) reared were used for the experiment. We provided adult female sugar meals consisting of sucrose, glucose, fructose or trehalose dissolved in distilled water at concentrations yielding 1.97 or 19.7 kcal/100ml. After five days we measured their knockdown rate and their mortality within 24 hours of exposure to 0.5% deltamethrin with WHO tube tests. We found that there was a positive correlation between the rate of knockdown and mortality for all sugar meals. Mosquitoes fed on the lower concentration were 1.4 to 2 times more likely to die than the better fed mosquitoes, but that the type of sugar had no effect on resistance. Results indicate that the amount of calories provided by sugar is a potential determinant of mosquito susceptibility to insecticides. Sugar meal containing fewer calories may provided less energy to mosquitoes, making them less vigorous and more sensitive to insecticide. Further studies will consider other components of nectar in an attempt at using plants in an integrated approach to manage infection resistance of mosquitoes.

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EFFECTS OF AGRICULTURAL PESTICIDES ON THE SUSCEPTIBILITY AND FITNESS OF MALARIA VECTORS IN RURAL SOUTH-EASTERN TANZANIA

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Agricultural pesticides may exert strong selection pressures on malaria vectors during the aquatic life stages and may contribute to resistance in adult mosquitoes. This could reduce the performance of key vector control interventions such as indoor-residual spraying and insecticide-treated nets. The aim of this study was to investigate effects of agrochemicals on susceptibility and fitness of the malaria vectors, across farming areas in Tanzania. An exploratory mixed-methods study was conducted to assess pesticide use in four villages (V1-V4) in Tanzania. Larvae were collected from agricultural fields in the same villages and their emergent adults examined for insecticide susceptibility, egg-laying, and wing lengths. These tests were repeated using laboratory-reared An. arabiensis, one of which was pre-exposed for 48hrs to sub-lethal aquatic doses of agricultural pesticides found in the villages. Farmers lacked awareness on the links between public health and agriculture sectors but were interested in being more informed. Agrochemicals usage was reported as extensive in V1, V2 & V3 but minimal in V4. Similarly, mosquitoes from V1-V3 but not V4 were resistant to pyrethroids, and either pirimiphos-methyl, bendiocarb or both. Adding the synergist, piperonyl butoxide, restored potency of the pyrethroids. Pre-exposure of laboratory-reared mosquitoes to pesticides during aquatic stages did not affect insecticide susceptibility and fecundity (except in organophosphates) in emergent adults of the same filial generation. Wild mosquitoes were smaller than laboratory-reared ones, but fecundity was similar. In conclusion, in this study, susceptibility of mosquitoes to public health insecticides was lower in villages reporting frequent use of pesticides compared to villages with little or no pesticide use. Variations in the fitness parameters, fecundity and wing length, marginally reflected the differences in exposure to agrochemicals. Pesticide use may exert additional life-cycle constraints on mosquito vectors, but this likely occurs after multi-generational exposures.

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SUSCEPTIBILITY OF ANOPHELES GAMBIAE SENSU LATO TO FOUR CLASSES OF INSECTICIDES AND THE ALLELIC FREQUENCIES OF GENES KDR L1014F AND ACE 1 G119S IN TWO VILLAGES OF THE CIRCLE OF KATI IN MALI

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The multiple resistance situation in Anopheles gambiae sensu lato found in Mali with the concomitant presence of the kdr L1014F and ace-1 G119S mutations constitutes a major threat to the success of current malaria control strategies (LLIN and IRS). While it is obvious that with the different

uses of insecticides (controlled or not) it is difficult if not impossible to avoid the installation of resistance at any time, it is crucial to accompany malaria vector control strategies with an efficient insecticide resistance monitoring system. The present study aims to evaluate the susceptibility of Anopheles gambiae sensu lato to the four classes of insecticides commonly used in public health for vector control and the allelic frequencies of the kdr L1014F and ace-1 G119S genes. The study took place from June to October 2021 in Ouassorola and Sogolombougou, two villages in the Kati circle, Koulikoro region. Bioassays were performed according to WHO standard procedures, identification of Anopheles gambiae sensu lato species and detection of kdr L1014F and ace-1 G119S mutations were done by PCR. The mortality rates were respectively in Ouassorola and Sogolombougou of : 100% and 91.25% for fenitrothion; 97.5% and 92.5% for bendiocarb; 67.5% and 50% for DDT; 8.75% and 0% for deltamethrin 3.75% and 0% for permethrin and 10% and 0% for lambda-cyalomethrin. The allelic frequencies of the kdr L1014F mutation were 72.93% in Ouassorola and 79.67% in Sogolombougou and those of ace-1 G119S were 25% in Ouassorola and 46.15% in Sogolombougou. Anopheles coluzzii and Anopheles gambiae were the only members of Anopheles gambiae sensu lato identified in both study sites. This study showed strong resistance of An. coluzzii and An. gambiae to deltamethrin 0.05%, lambda-cyhalothrin 0.05%, permethrin 0.75%, DDT 4% and bendiocarb 0.1%. Anopheles gambiae sensu lato was susceptible to fenitrothion 1% in Ouassorola. A high frequency of genes kdr L1014F and ace-1 G119S was observed in both villages. The species of the Anopheles gambiae sensu lato complex found were Anopheles gambiae and Anopheles coluzzii.

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ASSESSING INSECTICIDE RESISTANCE PROFILE OF ANOPHELES GAMBIAE S.L. FOR STRATEGIC VECTOR CONTROL DECISION MAKING IN GUINEA

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Mass and continuous distributions of insecticide-treated nets (ITNs) are the main malaria vector control strategy implemented in Guinea. To support the strategic selection of the most appropriate ITN to deploy across Guinea, vector susceptibility to insecticides used in WHO-recommended ITNs was assessed between July and December 2022 in seven prefectures located in the four natural regions of the country. Wild Anopheles gambiae s.l. larvae were collected from development sites, reared into adults, and exposed to the diagnostic dose of pyrethroids (deltamethrin 0.05%, alpha-cypermethrin 0.05%, and permethrin 0.75%) and chlorfenapyr (100 µg/bottle) using the WHO tube test and bottle bioassay respectively. When pyrethroid resistance was confirmed at the diagnostic dose, intensity test (i.e., exposure to 5× and 10× the diagnostic dose) and piperonyl-butoxide (PBO) synergism tests (i.e., PBO pre-exposure followed by exposure to 1× pyrethroid) were conducted. Pyrethroids resistance was observed at all tested sites with mean mosquito mortalities ranging from 3% to 22% at the diagnostic dose, and the intensity was generally high with less than 90% mortality at the 10× diagnostic dose. Pre-exposure to PBO increased the mortality of all three pyrethroids (between 10% to 50%) but did not result in absolute mortality greater than 70%. Mortality of An. gambiae s.l. after exposure to chlorfenapyr was 100% at all seven prefectures. Hence, there is a high frequency and intensity of pyrethroid resistance in An. gambiae s.l. in Guinea, PBO partially increases susceptibility to pyrethroids, and, at the time of this study, there was complete susceptibility to chlorfenapyr. Based on these results, the scale-up of dual active ingredients or PBO ITNs could help mitigate pyrethroid resistance and improve the impact on malaria vectors in the country. Insecticide resistance monitoring should continue in Guinea, including the identification of mechanistic markers of insecticide resistance.

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IDENTIFICATION OF INSECTICIDE RESISTANCE MARKERS IN ANOPHELES ARABIENSIS AND AN. GAMBIAE FROM KENYA AND BENIN USING WEIGHTED GENE CORRELATION NETWORK ANALYSIS

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Indoor Residual Spraying (IRS) and Insecticide-Treated Nets (ITN) are the two main methods used to control mosquito populations for malaria prevention. Currently, efficacy of these strategies is threatened by the appearance and the spread of insecticide resistance (IR), limiting success of malaria control. Studies of the genetic evolution leading to insecticide resistance could enable identification of molecular markers that can be used for IR surveillance and an improved understanding of the molecular mechanisms associated with IR. This study aimed to use a Weighted Gene Co-Expression Network Analysis (WGCNA) algorithm, a systems biology method, to identify genes with similar co-expression patterns and hub genes that can potentially be used as molecular markers for insecticide resistance surveillance in Kenya and Benin. Anopheles arabiensis and An. gambiae from Kenya and Benin were phenotyped for resistance to alphacypermethrin, permethrin and deltamethrin insecticides. RNA was extracted from unexposed, susceptible and resistant samples followed by Illumina sequencing. WGCNA was conducted to evaluate co-expression patterns of genes to identify modules, hub genes and generate a gene co-expression network. A total of 20 and 26 gene co-expression modules (sft:20,18) were identified via the average linkage hierarchical clustering from An. arabiensis (Kenya) and An. gambiae (Benin), respectively. The top modules based on the number of genes in An. arabiensis and An. gambiae were identified to be salmon (n=3197) and blue (n=3839) modules. The genes with the strongest connection (hub genes) were found in all modules. Serine protease, E3 ubiquitin-protein ligase, cuticular protein RR2 and leucine-rich immune protein were identified as hub genes in both species. This was the first study to conduct WGCNA based on IR transcriptomic data. Four biologically relevant hub genes shared between the two species were identified as potential markers for insecticide resistance. The next phase will be to undertake in vitro and in vivo studies to functionally validate these genes as IR markers.

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POPULATION GENOMICS OF THE INVASIVE MALARIA VECTOR ANOPHELES STEPHENSI IN ETHIOPIA

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Anopheles stephensi has been identified as a major threat to malaria control and elimination efforts in the Horn of Africa (HOA). The species, native to South Asia, is a highly competent vector in urban areas and can transmit both Plasmodium falciparum and vivax. Since An. stephensi

was first identified in Dijbouti in 2012, the country has seen malaria cases skyrocket. Integrated vector management is often the primary strategy used to interrupt disease transmission, but levels of insecticide resistance are growing and could severely impact malaria control. Very little is known about the population genetics of this invasive species spreading in the HOA. In this study we aim to better understand the population genetics of this vector and help better inform vector management programmes. Twenty-eight An. stephensi samples collected from a central Ethiopian town, were whole genome sequenced. Average coverage was ~30-fold per sample, with 14930416 SNPs identified across the genome. We found one known mutation associated with insecticide resistance: A296S, or the rdl mutation. The SNP was found in 46% of the Ethiopian samples analysed, and results in resistance to the insecticide dieldrin. Other putatively novel non-synonymous SNPs were found in genes associated with insecticide resistance: ace-1 and GSTe2.In addition, we examined the population structure of the Ethiopian isolates in the context of publicly available WGS data from Colony Pakistani and wild-type Indian An. stephensi mosquitoes. Pre-liminary ancestry analysis using admixture indicates genetic distinctness between Ethiopian and Indian populations of An. stephensi. Significant Fst was observed between pairwise analysis of these two populations. Phylogenetic analysis suggests a closer relationship between SDA500 Pakistani strains and Ethiopian An. stephensi isolates.Here we have identified an insecticide resistance marker and given insight into the population genomics of Ethiopian isolates of An. stephensi, in the context of native South Asian populations of this invasive vector.

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CHARACTERIZATION OF A NEW LABORATORY COLONY OF ANOPHELES FUNESTUS MOSQUITOES ESTABLISHED IN IFAKARA, TANZANIA

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Anopheles funestus carries most malaria in east and southern Africa. However, it has been challenging to study this species because it is difficult to colonize inside laboratories. Our team was able to successfully colonize a strain of this species from Tanzania (FUTAZ) for >20 generations. We compared the FUTAZ strain to two other strains of mosquitoes: a strain of An. funestus from Mozambique (FUMOZ) and a strain of Anopheles arabiensis. We examined the differences in fitness between these strains through measures like body size and mating success. We also looked at the genetic makeup of the mosquitoes using PCR analysis of mitochondrial clades and restriction fragment length polymorphisms (RFLP) on the 28S ribosomal DNA. We found that the FUTAZ strain had a decline in mating success and body size in the first six generations, but then they adapted, and these measures improved. By the ninth generation, the FUTAZ strain had similar fitness measures to the FUMOZ strain. Fecundity was similar across all strains tested. It took twice as long for the FUTAZ and FUMOZ strains to mate compared to the An. arabiensis strain. The genetic analysis showed that the FUTAZ strain was similar to the wild-caught Tanzanian An. funestus strain, but it was different from the FUMOZ strain. Our study shows that it's important to have a large founder population when starting a new colony to ensure that the mosquitoes can adapt to laboratory conditions.

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CO-OCCURRENCE OF MULTIPLE KDR MUTATIONS (F1534C, V1016I, V410L) IN AEDES AEGYPTI FROM COASTAL AREAS IN GHANA AND ASSESSMENT OF THE ROLE OF MOSQUITO COIL IN CAUSING PYRETHROID RESISTANCE

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The rapid spread of knockdown-resistance kdr mutations in Africa calls for monitoring and investigation into the cause of pyrethroid resistance to inform management strategies. This study investigated the pyrethroid resistance profile of Ae. aegypti from coastal towns in Ghana and the impact of mosquito coils, a popular household pyrethroid-based anti-mosquito tool, on the development of pyrethroid resistance. Susceptibility to deltamethrin and the presence of kdrmutations were determined in adult female mosquitoes reared from larvae. Furthermore, a laboratory colony was exposed to a sub-lethal dose of a mosquito coil once per generation for six generations (F6). The susceptibility of the exposed colony to deltamethrin (0.05%) was determined using WHO protocols. The Ae. aegyptipopulations from the coastal towns were resistant to deltamethrin with co-occurrence of F1534C, V1016I and V410L kdrmutations. In the experimental study, the LT50 (95% CI) of the exposed colony against the coil rose from 8 minutes (95% CI; 6-9) at F0 to 28 minutes (95% CI; 23-34) at F6. Nonetheless, deltamethrin caused similar mortalities in the exposed and control colonies. The resistant allele frequencies of 1534C and 410L were identical, but 1016I was higher in the exposed colony than in the control. However, the increased tolerance to the coil and high resistant allele frequency of 1016I in the exposed colony did not affect the mosquito's resistance to deltamethrin insecticide. Further study is needed to elucidate the role of pyrethroid-based mosquito coils in developing insecticide resistance in mosquito vectors.

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TEMPORAL RESISTANCE ESCALATION AND N1575Y MARKED DETECTION IN ANOPHELES GAMBIAE S.L POPULATION IN ATATAM, AN EXPERIMENTAL HUT STATION SITE IN SOUTHERN GHANA

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Major malaria vectors in Africa are increasingly developing high intensity of resistance to approved used in vector control. This threatens to impact efficacy of insecticides-based tools necessitating the need to monitor resistance in vector populations to support insecticide resistance management. This study reports the temporal aggravation of resistance and significant detection of N1575Y-Kdr marker in the primary malaria vector Anopheles gambiae s.l at Atatam, a rural Ghanaian community. Indoor resting blood-fed Anopheles mosquitoes were collected twice each year coinciding with the peaks of the major and minor raining season between 2021-2022 were forced to lay eggs to generate F1 adult mosquitoes. Insecticides susceptibility bioassays, PBO synergist assay and cone assays with pyrethroid-only nets and PBO-based nets were performed on the F1 adults. Furthermore, molecular basis of resistance were characterized in F0 populations using TaqMan genotyping. An. gambiae s.l consisted of An co.luzzii and An. gambiae s.s. These displayed high levels of resistance to Permethrin, Deltamethrin, Alpha-cypermethrin and DDT with moderate resistance recorded against Bendiocarb in contrast to full susceptibility

recorded for Pirimiphos-methyl. PBO synergist assays with Permethrin and Deltamethrin induced only a marginal recovery of susceptibility in An.gambiae population (6.2% to 43% and 2.2% to 37.1% mortality, respectively). The high pyrethroid/DDT resistance in An. gambiae correlated with high frequency of 1014F, N1575Y knockdown resistance allele (91% and 50%) and GSTe-I114T resistant allele (59.6%). The G119S allele was detected at low frequency (1.7%) indicative of the increased susceptibility to Bendiocarb and full susceptibility to Pirimiphos methyl. Cone assays reveal loss of efficacy against pyrethriod-only based nets and a reduced efficiency against PBO based nets against these resistant An. gambiae s.l population. These results highlight the escalation of insecticide resistance and the challenges that control programmes face to maintain the continued effectiveness of existing insecticide-based interventions.

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INSECTICIDE SUSCEPTIBILITY OF ANOPHELES ALBIMANUS IN THE TWO MAIN ACTIVE MALARIA FOCI OF HONDURAS

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Malaria cases in Honduras have increased over the previous four years, rising from 386 in 2019 to 3,601 in 2022. Around 90% of cases are reported in Puerto Lempira and Villeda Morales municipalities, in the department of Gracias a Dios. Vector control in Gracias a Dios employed the use of pyrethroids-impregnated bednets, with occasional indoor spraying with bendiocarb. The Ministry of Health in collaboration with other partners has conducted insecticide resistance surveillance over the last 5 years in one sentinel site at Gracias a Dios, however, no fine scale evaluations per foci have been carried out thus far. The aim of this work was to evaluate insecticide susceptibility status in the two main malaria transmission areas using both a phenotypic and genotypic approach. Adult entomological collections were carried out at Kaukira, Puerto Lempira and Raya, Villeda Morales in Gracias a Dios. Deltamethrin and Bendiocarb phenotypic status were assessed using CDC bottle bioassays with diagnostic doses. Sequencing analysis was used on a selection of 50 Anopheles albimanus individuals (30 from Kaukira and 20 from Raya) for target-site mutations detection at 995 and 280 positions in the Voltage-Gated Sodium Channel (VGSC) and the Acetylcholinesterase (Ace-1) gene, respectively. Between September and December of 2022, a total of 701 mosquitoes were collected, with An. albimanus (87%) as the most common specie across the sites, however, secondary species as An. vestitipennis and An. crucians were also identified. Deltamethrin and Bendiocarb show 100% mortality in susceptibility assays. Sequencing analysis revealed that all populations had the wild-type genotype, TTG at 995 (VGSC) and GGC (Ace-1) at 280 positions, respectively, supporting the phenotypic results. Altogether, this data provides current evidence of An. albimanus susceptibility to the insecticides employed by the MoH in vector control and supports their use in routine interventions. Further studies are required in other foci as well with secondary species on a routine basis to drive future vector control operations

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ENTOMOLOGICAL STUDY OF MALARIA TRANSMISSION PARAMETERS AS A PRELUDE TO A PHASE III CLINICAL TRIAL OF ATTRACTIVE TOXIC SUGAR BAIT STATIONS IN THE KOULIKORO REGION, MALI

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Despite the use of prevention and control tools, malaria remains a major public health problem in sub-Saharan African countries, including Mali. Parasite resistance to anti malaria drugs and vector resistance to insecticides are undermining prevention and control efforts. In addition, mosquito biting behavior is shifting from predominantly indoor biting to more outdoor biting. New control methods are therefore urgently needed. It is in this context that the attractive targeted sugar baits or Attractive Toxic Sugar Bait (ATSB) based on the “attract-kill” principle have emerged, trapping mosquitoes with a sugar bait containing an oral toxin. ATSB have had many successes after their use in numerous experimental studies in the control of Anopheles vectors, Aedes and other insect vectors. We therefore conducted this study with the aim of evaluating the entomological parameters of malaria transmission before an epidemiological phase III trial. It took place in five villages in the district of Kangaba and two villages in the district of Ouélésséboungou; all in Koulikoro region of Mali. It was a longitudinal study with monthly mosquito collection from July to December 2021. We used three trapping methods: human landing catch (HLC), daytime capture by pyrethroid spray catch and CDC UV light trap. We are here reporting only the data for HLC outdoor where we caught 3289 An. gambiae s.l. They had completed 1 or 2 gonotrophic cycles. Their longevity was greater than or equal to 50 days except for Solonkorein and Balala. The maximum infection, 0.17 infectious bites/person/night was observed in Balala. Our findings will inform the randomization of clusters for epi trial aiming at demonstrating an effect of ATSB on malaria incidence.

5892

PHENOTYPIC INSECTICIDE RESISTANCE STATUS AND MOLECULAR DETECTION OF RESISTANCE MUTATIONS IN ANOPHELES GAMBIAE SENSU LATO IN THE GAMBIA

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The use of long-lasting insecticide treated bed nets (LLINs) and indoor residual spraying (IRS) in high burden areas has played a major role in the reduction of malaria cases and deaths in The Gambia. Widespread resistance of Anopheles gambiae sensu lato to pyrethroids, scale-back of IRS, high costs, and suboptimal compliance to vector control interventions threaten these gains and have led to the adoption of the WHO insecticide rotation plan by the National Malaria Control Programe (NMCP). This study aimed to describe phenotypic and molecular resistance of An. gambiae s.l. to pyrethroids to guide the NMCP’s selection of insecticide for IRS in The Gambia. From July-October 2021, An. gambiae s.l. larvae were collected and reared to adults from 7 sentinel sites: Brikama, Essau, Farafenni, Njabakunda, Georgetown, Basse, and Gambisarra. Using the WHO tube bioassay, a total of 3,237 An. gambiae s.l. were exposed to Deltamethrin 0.05%, Deltamethrin 0.25%, or Pirimiphos-methyl 0.25%. A total of 195 mosquitoes were genotyped at 7 loci for 11 SNP mutations associated with insecticide resistance. Resistance to Deltamethrin 0.05% was confirmed in all sites, with mortality ranging from 30% in Bakau to 73% in Georgetown. Moderate to high resistance to Deltamethrin 0.25% was observed in 6 sites (81%-97% mortality) and low resistance in one site (Georgetown; 99% mortality). An. gambiae s.l. from all sites were susceptible to

Pirimiphos-methyl. Sequencing detected 8 SNPs: kdr-1014S, kdr-1014F, Coeae1d, A296S rdl, T345S rdl, Cyp6jS, Gste2-119V, and Gste2-114T with allele frequencies varying between 0.03 and 0.54. One to 6 SNPs per mosquito were identified with over 80% with 1-3 SNPs. An. gambiae s.l. in The Gambia are susceptible to Pirimiphos-methyl 0.25%, resistant to Deltamethrin 0.05%, and exhibited moderate to high resistance to Deltamethrin 0.25%. The lowest and highest frequencies were observed for Cyp6jS and Coeae1d, respectively. Since no resistance was confirmed for Pirimiphos-methyl 0.25%, the NMCP will continue using this insecticide for IRS in The Gambia, while also adhering to the insecticide rotation plan to delay expansion of resistance.

5893

OVEREXPRESSING IMMUNE SIGNALING PROTEIN VAGO RESTRICTS DENGUE VIRUS INFECTION IN AEDES AEGYPTI MOSQUITOES

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Aedes aegypti is the principal vector for pathogens like, Dengue virus, Zika Virus, and Chikungunya virus. The lack of effective vaccines and drugs against these pathogens has led to severe economic and healthcare burdens in developing countries, leading to the need for new control measures. The four major pathways through which Aedes mosquitoes mount an immune response are, the JAK-STAT, RNAi, IMD, and Toll pathways. Recent publications have indicated that there is a crosstalk between these pathways during viral infections. The Vago gene which encodes for a cysteine-rich 18Kd polypeptide has been shown to be involved in antiviral activity. In Culex quinquefasciatus mosquitoes, Vago has been shown to be involved in crosstalk between the JAK-STAT, RNAi, and IMD pathways upon West Nile Virus infection. The potential of the Aedes orthologue of Vago to connect immune pathways has not yet been studied and its mode of action is still unknown. In the present study, we have created two transgenic lines that overexpress Vago in the fat body and the midgut, using the PiggybacTM transposon system. A significantly lower titer of Dengue virus was observed 14 days post-infection in transgenic lines overexpressing Vago in the midgut. We also aim to study the role of Vago in connecting immune pathways and its potential anti-viral activity when overexpressed in the fat body.

5894

DEFINING THE ROLE OF JUVENILE HORMONE AND ITS RECEPTOR, METHOPRENE-TOLERANT, IN ANOPHELES GAMBIAE REPRODUCTION AND PLASMODIUM TRANSMISSION

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Controlling the reproductive cycle in Anopheles mosquitoes can serve as a critical tool for vector control and contribute towards the overall goal of malaria elimination. Our previous studies have demonstrated a functional role for the insect steroid hormone 20-hydroxyecdysone (20E) in Plasmodium falciparum development in its main vector Anopheles gambiae, where blocking 20E activation resulted in reduced parasite survival but faster parasite growth through the insect stages. In the adult female mosquito, the vitellogenic phase that is governed by 20E regulation temporally follows the post-eclosion (PE) development phase (day 1-3 PE) that is regulated by another insect hormone, Juvenile Hormone (JH). JH is responsible for initiating the cascades responsible for tissue maturation that are required to prime the female reproductive machinery prior to the acquisition of a blood meal. Here, we analyzed the role of the JH binding receptor, Methoprene-tolerant receptor (Met), in An. gambiae reproduction and P. falciparum development. After characterizing the gene expression pattern of Met and two down-stream transcription factors (Kruppel homolog-1 and Hairy), we demonstrate that JH has an important functional role in regulating gene expression during the PE period by artificially inducing the JH-mediated pathway through the topical application of Methoprene. Next, we administrated dsRNA targeting the Met receptor to block the JH response and subsequently measured vector reproductive fitness and parasite transmissibility. Our results indicate that blocking JH activation results in both reduced mosquito egg development and parasite survival, but also leads to faster parasite growth. It is likely that blocking JH activity results in alterations in mosquito immunity and nutritional status that need to be further explored to understand its full impact on Plasmodium transmission. These data unveil a key role of JH in regulating Anopheles-Plasmodium interactions, and suggest a critical cross-talk between 20E and JH in regulating reproductive processes that also impact the survival and growth of the deadliest human malaria parasites.

5895

COMPOSITIONAL DIVERSITY IN THE EARLY-DEVELOPMENTAL MICROBIOME OF AEDES ALBOPICTUS LEADS TO HETEROGENOUS IMMUNE EXPRESSION OF ADULT MOSQUITOES

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Mosquitoes rely on a community of symbiotic microorganisms to sustain biological processes.Variation in the diversity of the microbiome has profound impacts on mosquito physiology thatscale up to host phenotypes. Of special interest are phenotypes permissive to sustained diseasetransmission. We examined the immunological responses of Aedes albopictus mosquitoes to assess how exposure to compositionally different microbial communities during earlydevelopment impacts adult responses to infection. We sourced water from three differentenvironments—bromeliad axils, artificial containers, and purified laboratory water—to createlarval habitats. The water sourced from bromeliads and artificial containers was filtered using30-50 µm, 10 µm, and 0.2 µm filters. Upon eclosion, adults were provided a 10% sucrosesolution and allowed to feed ad libitum for 72 hours. After 72 hours, adults were injected withapproximately 500 live Escherichia coli cells suspended in Luria-Bertani (LB) broth or injectedwith sterile LB broth. At 24 hours post-injection, adults were processed for immune expressionanalyses using quantitative reverse transcriptase PCR. We assayed five gene markers in total:relish 1 (REL1), relish 2 (REL2), STAT, cecropin A (CEC-A) , and defensin C (DEF-C). REL1, REL2,and STAT are transcription factors unique to the three innate immune pathways; CEC-A andDEF-C are antimicrobial peptides. Using generalized linear mixed models, we found thatexposure to compositionally different microbial communities during early mosquitodevelopment impacted the immune response of adult mosquitoes when infected with E. coli.Immune expression patterns varied across treatments and by gene; however, the general trendshowed that mosquitoes from lower filtration habitats (highest microbial diversity) hadincreased upregulation of immune activity. Our results suggest that exposure to diversemicrobial communities in early development may be a significant predictor for the vectorial capacity of Ae. albopictus and that microbial “hotspots” have an important ecological role insustaining mosquito-borne disease transmission.

5896

ALTERNATING CURRENT ELECTROPENETROGRAPHY REVEALS IN SITU BEHAVIORAL CHANGES OF AEDES AEGYPTI BITES ASSOCIATED WITH DENGUE VIRUS INFECTION

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Human infection with dengue virus (DENV) results in significant morbidity and mortality around the world. Observations of infectious blood feeding events of the primary DENV vector Aedes aegypti have identified DENV-associated behavioral changes that may promote DENV transmission. Current methods are largely restricted to video analysis of feeding events outside of the host or microscopic video capture of biting events on thin tissues. To supplement these methods, AC-DC electropenetrography (EPG) was investigated to assess the method's potential to record infectious mosquito bites and quantify the amount of time a mosquito spends in different stages of the feeding process. IFN-αβ receptor-deficient mice and DENV-2 (S-14635) were used to determine the feasibility and utility of EPG for arbovirus research. EPG recordings were made of Ae. aegypti feeding on anesthetized mice under three conditions: mosquito/mouse uninfected, DENV-infected mosquito/uninfected mouse, and uninfected mosquito/DENV-infected mouse. Successful and interpretable EPG recordings were obtained for seven feeding events under each condition. Ae. aegypti with disseminated DENV-2 had significantly shorter probe durations and more probes per feeding than uninfected controls. This group also spent significantly more time in the low-voltage initial skin penetration stage of feeding and switched more frequently between two different vessel locating behaviors within the skin than controls. During the ingestion phase, uninfected mosquitoes fed on DENV-infected mice spent significantly less time in the classic M1 ingestion phase and much longer in the more irregular M2 phase, though overall ingestion lengths were not significantly different. These data suggest that there are quantifiable in situ behavioral changes associated with DENV infection, especially with respect to behaviors between initial skin penetration and the beginning of ingestion. Moreover, these data demonstrate that EPG is a suitable tool for interrogating arbovirus associated behavioral changes during blood feeding events.

5897

TEMPERATURE DEPENDENCE OF ANOPHELES IMMUNE RESPONSE KINETICS AND VECTOR COMPETENCE

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Most studies on mosquito innate immunity responses to malaria parasite infection have relied on rodent Plasmodium berghei laboratory models. However, we and others have shown that the Anopheles immune factors and mechanisms involved in eliminating the clinically relevant human P. falciparum may differ from those against murine parasites. A significant difference between the two malaria species is the fact that P. berghei achieves unnaturally high infection intensities in the vector mosquito, frequently exceeding 200 oocysts per midgut, while median infection intensities for P. falciparum of lower than 3 oocysts per mosquito midgut are usual. Using CRISPR/Cas9-mediated gene knockout and RNAi-mediated silencing of A. gambiae immune factors, we demonstrate that the immune regulation of Plasmodium is dependent on the intensity of infection. Here, we show that the differences in intensity are in part due to the parasite's optimal infection temperature: P. berghei sexual sporogonic development occurs at ~19 °C whilst P. falciparum's is optimal at ~27 °C. We hypothesize that this rather large temperature difference results in a slower rate of development for the rodent parasite than for the human malaria parasite within its vector. Temperature also influences mosquito immune response kinetics and the length of exposure of the parasites to these immune responses. In this study, we predict that temperature variations and climate change may significantly affect mosquito transmission of malaria parasites and other pathogens, by altering the infection kinetics. Our study stresses the importance of conducting malaria laboratory-based transmission studies using clinically relevant species.

5898

DISHEVELLED ACTIVITY DIFFERS IN AEDES AEGYPTI AND CULEX TARSALIS INFECTED WITH RIFT VALLEY FEVER VIRUS

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Aedes and Culex mosquitoes are vectors of Rift Valley Fever Virus (RVFV), a zoonotic virus endemic to Africa that causes episodic outbreaks and has emerged on the Arabian Peninsula. RVFV outbreaks are characterized by abortion storms and occasional death of livestock. The specific mechanisms that underpin differences in efficiency of virus transmission are still not understood. To address this, we sought to better understand mosquito host signaling responses late in RVFV MP-12 infection through analysis of differentially expressed genes (DEGs) in two mosquito strains with marked differences in vector competence, Aedes aegypti (Aae, low competence) and Culex tarsalis (Cxt, higher competence). Mosquito-host transcripts related to three different signaling pathways were investigated. The Wingless (WG, WNT-beta-catenin) pathway is a conserved regulator of cell proliferation and differentiation; changes to FRIZZELED2 (FZ2), DISHEVELLED (DSH), and ARMADILLO (ARM, beta-catenin) were assessed. Importantly, DSH differentially regulates progression/inhibition of the WG and JNK (c-Jun N-terminal Kinase) pathways through interaction with NAKED CUTICLE. A negative regulator of the JNK signaling pathway, PUCKERED, was also assessed. Lastly, Janus Kinase/signal transducers and activators of transcription (JAK-STAT) is a multi-functional signaling pathway important for innate immunity; in this context, we tested DOMELESS levels. Here, individual Aae and Cxt were exposed to RVFV MP-12 in oral bloodmeals and then held for 14 days at 28oC. Robust decreases in expression of signaling transcripts in both Aae and Cxt were observed. In particular, Aae DSH expression, but not Cxt DSH, was correlated to the presence/absence of virus at 14 days post-infection (dpi). This effect was not seen in Culex, perhaps due to its high susceptibility to RVFV. Moreover, there was an inverse relationship between viral copy number and aaeDSH expression that did not occur for any other transcript. Silencing of DSH by dsRNA injection resulted in increases in viral copy numbers compared to controls at 7 dpi, consistent with a role for aaeDSH in antiviral immunity.

5899

MAMMALIAN HEMOPEXIN REGULATES OXIDATIVE STATE IN ANOPHELES MOSQUITOS DURING PLASMODIUM INFECTION

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During mosquito midgut invasion, Plasmodium ookinetes cross the peritrophic matrix barrier bringing pro-oxidant molecules in contact with the midgut epithelial cells. Our previous data show that during midgut invasion hemopexin from mouse blood is enriched in the mosquito midgut epithelium and hemolymph. We hypothesize that the accumulation of hemopexin, an antioxidant molecule that binds free heme, protects the parasite and the mosquito from heme and iron-induced cellular damage. To further investigate the impact of hemopexin on oxidative state in Anopheles mosquitos we measured the concentration of hydrogen peroxide in the hemolymph from mosquitos that fed on uninfected or infected wild type (WT) or hemopexin-null mice. Hydrogen peroxide was increased in the hemolymph in the absence of host hemopexin. Additionally, lipid peroxidation, protein carbonylation and nitration, markers of oxidative damage, were increased in the hemolymph of mosquitos that fed in hemopexin-null mice. We also compared the impact of hemopexin in

Aedes aegypti mosquitos which are known to have a robust system to control reactive oxygen species (ROS) after ingesting blood. In contrast to Anopheles, the absence of host hemopexin didn't increased oxidative damage markers in A. aegypti suggesting an important role for hemopexin in controlling ROS triggered by blood digestion in Anopheles mosquitos. Mosquitoes feeding on hemopexin-null mice had a significant decrease in survival, egg oviposition and egg hatching, which points that human hemopexin is a key molecule for the mosquito adaptation and survival to feeding on blood. Moreover, Plasmodium infection was significantly decreased in mosquitos that fed in hemopexin-null mice and was restored in mosquitos that fed in hemopexin-null mice that had been injected intravenously with hemopexin. Together, these results show that hemopexin is an essential molecule for the survival of Anopheles mosquitos and malaria parasite transmission.

5900

TNF-A SIGNALING MEDIATES MOSQUITO CELLULAR IMMUNITY TO PROMOTE PLASMODIUM KILLING

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Malaria is a devastating vector-borne disease caused by Plasmodium parasites and transmitted to humans through the bite of Anopheline mosquitoes. Therefore, understanding mosquito innate immunity and the mechanisms that influence vector competence are crucial to efforts to block malaria transmission. In vertebrates Tumor Necrosis Factor- α (TNF-α) is a well-defined proinflammatory cytokine with essential roles in regulating immune cells, yet our understanding of TNF-α signaling in invertebrate systems is limited. Here, we characterize a functional TNF-TNFR-like system in the mosquito Anopheles gambiae, comprised of the TNF-α ortholog Eiger and its two cognate receptors, Wengen and Grindelwald. We demonstrate that the direct injection of recombinant TNF-α limits malaria parasite survival and provide evidence that these killing responses are immune cell-mediated. The injection of TNF-α increases granulocyte numbers via Wengen and leads to the reduced expression of oenocytoid-specific genes, implying the role of TNF-α in oenocytoid rupture, with evidence supporting both immune cell phenotypes in malaria parasite killing. Additional gene-silencing experiments confirm the involvement of Eiger, Wengen, and Grindelwald in anti-Plasmodium immunity, with initial experiments suggesting that Wengen and Grindelwald may act interchangeably to promote TNF-α signaling to suppress Plasmodium development. Together, our data support the role of a conserved TNF-α signaling pathway in influencing the cellular immune system of mosquitoes, providing new insight into the mechanisms of malaria parasite killing and mosquito vector competence.

5901

EFFECT OF LOW RELATIVE HUMIDITY OVER MORTALITY AND VIRAL VECTOR COMPETENCE IN AEDES AEGYPTI

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Vector-borne diseases (VBDs) cause over 700,000 deaths every year. The mosquito species Aedes aegypti is a competent vector of multiple viral pathogens including dengue, Zika, chikungunya, and Mayaro viruses. Ae. aegypti was originally distributed in Africa, however, it is currently present in the Americas, Oceania, Asia, and Europe. Because of climate change, it is expected that the distribution of this mosquito species and the pathogens they transmit will change even more. Relative humidity is an environmental variable that affects the mosquito biology and distribution. This variable can differ between indoors and outdoors, and it oscillates over the course of the day and year, thus it is expected that mosquitoes face variations in relative humidity during their lifespan. Low relative humidity can induce dehydration in mosquitoes, leading to alterations in physiological and behavioral responses such as bloodfeeding and host-seeking behavior, which are relevant for pathogen transmission. The aim of our research was to evaluate the short and long-term effects of low relative humidity over mortality and viral vector competence in Ae. Aegypti, using two different experimental designs. Briefly, we tested mosquitoes under three different conditions of relative humidity to induce dehydration, and measured mortality and bloodfeeding rates. Then, we used a cell culture and immunofluorescence-based assay to quantify the viral load in different parts of the mosquitoes at 7 and 14 days post infection. Our results show that under our experimental designs, low relative humidity does not impact the viral loads, nor the infection, dissemination and transmission rates, in mosquitoes infected with Mayaro-L virus. However, we detected a significant difference in mosquito mortality between treatments regardless of whether the mosquitoes were previously exposed to viral infection or not. These findings allow us to further understand the role of relative humidity in vector-borne disease dynamics.

5902

PLAYING SMART: HOW MALE AEDES AEGYPTI MOSQUITOES USE JUVENILE HORMONE TO MAKE FEMALES FITTER FOR REPRODUCTION BY SUPPRESSING THEIR IMMUNITY AND PROMOTING GUT MICROBIOTA EXPANSION

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Aedes aegypti mosquitoes are notorious vectors of diseases, and understanding their reproductive biology is essential for developing effective control strategies. Our research reveals how mating induces midgut growth in female mosquitoes, a response mediated by the transfer of Juvenile Hormone (JH) from males during copulation. In addition, we demonstrate how mating and JH modulate the mosquito's immune response in the gut, leading to the establishment of a core microbiota population that enhances reproductive output. Specifically, we have observed a JH-dependent suppression of Anti-Microbial Peptides (AMPs) in the female gut, resulting in an increase in bacterial load within the midgut. Our findings demonstrate for the first time how mating and Juvenile Hormones influence organ size and immune responses in the mosquito gut, and how this modulation leads to improved fitness in the form of increased egg counts and lifespan. Our results provide new insights into the molecular mechanisms underlying the interplay between nutrition, immunity, and reproduction in the mosquito gut, highlighting opportunities for further study and potential strategies for mosquito-borne disease control.

5903

WHOLE BODY VOLATILOMICS TO COMBAT VECTOR-BORNE DISEASE

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Human scent is a complex blend of hundreds of volatile organic compounds (VOCs) released via breath and skin emissions that guides arthropod disease vectors towards us. To improve our understanding of human scent signatures, we have developed a field-deployable booth-style collection chamber which enables characterization of inter-individual variability in the chemical composition of human body odor. To validate this sampling chamber for whole body volatilomics, we first performed a screen of 20 humans in a laboratory setting to characterize and quantify the most frequent and abundant compounds present in whole body odor headspace across participants using thermal desorption-gas chromatography/mass spectrometry (TD-GC/MS). Application of this method facilitated detection of a range of VOCs including ketones, aldehydes, carboxylic acids,

alcohols, and hydrocarbons, and quantification of their emission rates in whole body headspace across large numbers of humans for the first time. Leveraging this information, we next developed ratio-specific slow-release lure formulations, mimicking the emission rates of the major components of whole body scent signatures, for use as mosquito attractants. In the laboratory, adhesive trapping assays with a synthetic human scent mimic that we developed revealed that An. gambiae are equally attracted to this novel lure relative to human foot odor. We next performed semi-field assays in Macha, Zambia to test the attractiveness of this lure within the context of the CDC-miniature light trap broadly used for surveillance of malaria vectors. The use of our human scent mimic lure supplemented with yeast-generated CO2 significantly boosted the performance of the CDC light trap, capturing almost four times as many mosquitoes as traps baited with yeast-produced CO2 alone. We propose the use of whole body volatilomics has the potential to instruct development of highly attractive synthetic lure blends for enhanced surveillance and control of varied arthropod disease vectors including major malaria vectors such as Anopheles gambiae and An. stephensi which is currently invading Africa.

5904

A MICROSCALE PLATFORM FOR IMAGING NEURAL CIRCUITS IN THE AFRICAN MALARIA MOSQUITO

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The African malaria mosquito Anopheles gambiae is a deadly vector of malaria that detects humans using its sense of smell. We have recently applied CRISPR/Cas9-mediated homologous recombination and transposon-mediated transgenesis to generate transgenic strains of An. gambiae that express neural activity sensors in defined subsets of mosquito olfactory sensory neurons. These include olfactory sensory neuron populations expressing the olfactory co-receptors Ir76b, Ir25a, Orco and Gr22 - each responsible for detecting varied components of human scent. To overcome previous technical barriers for generating viable surgical preparations to image neural activity in the olfactory center of the An. gambiae brain, we have engineered a laser microsurgery apparatus to create precise micron-scale excision windows in mosquito head cuticle to reveal underlying brain tissue. This microscale platform for imaging neural circuits stands to provide significant insights into the molecular and cellular basis of An. gambiae attraction to human scent. By extension this open-source laser microsurgery device may also be used to study other facets of mosquito biology via intravital imaging of previously hidden mosquito tissues occluded by cuticle.

5905

WARBURG METABOLISM IS CRITICAL FOR ANOPHELES MOSQUITOES ANTI-PLASMODIUM IMMUNE DEFENSE

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Warburg metabolism is an inefficient metabolic shift characterized by increased glycolysis and lactate production. This phenomenon has been observed in mammalian rapidly proliferating cancer and immune cells. Anopheles mosquitoes, which are the vectors for malaria, rely on their metabolic system to provide energy and intermediates for their innate immune system, known as immunometabolism. We posited a disruption of Warburg metabolism would impair the immune response of Anopheles mosquitoes to Plasmodium parasites. To test this hypothesis, we treated Anopheles mosquitoes with dimethyl fumarate (DMF), a GAPDH inhibitor, or used CRISPRi to silence the genes coding for GAPDH and LDH, key enzymes of Warburg metabolism. We then challenged the mosquitoes with either P. berghei (Pb, rodent malaria) or P. falciparum (Pf, human malaria). Our results showed that both DMF treatment and CRISPRi knockdowns increased parasite load in both Pb and Pf infections, and DMF-treated mosquitoes had a significant mortality in both infections. These findings suggest that Warburg metabolism is essential for mosquito anti-Plasmodium immunity.

5906

SAMPLING EFFICIENCY AND MOLECULAR SCREENING OF YELLOW FEVER VIRUS IN AEDES MOSQUITOES IN NIGER DELTA REGION OF NIGERIA

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The vector potential of Aedes mosquitoes in the transmission of the arbovirus responsible for the transmission of yellow fever around the world is well documented. Although Nigeria is a high risk country for yellow fever, there is paucity of information in the Niger Delta region on the distribution of Aedes mosquito vectors and molecular detection of the virus in infected mosquitoes. This study was carried out to breach the gap. The mosquitoes were sampled in four communities (Otolokpo, Ute-Okpu, Umunede and Ute Alohen) in Ika North-East Local Government Area, Delta State, Nigeria. The efficacy of various methods of sampling the mosquitoes (Odour baited traps (BG sentinel), CDC light trap with attractant, CDC light traps without attractant and modified human landing catch (mHLC) were assessed for 12 weeks. Collected mosquitoes were transferred into a holding cages, killed by freezing at -4oC for 20 minutes. They were morphologically identified as Ae. albopictus using standard identification keys. A total of Seven hundred and Twenty-five (725) mosquitoes were obtained from the various traps. They were then preserved in RNAlater by pooling 10 mosquitoes per Eppendorf tube. The preserved mosquitoes were transported to National Arbovirus and Vector Research Centre Institute, Enugu Nigeria for screening of the virus strain using yellow fever primers and probes. Two samples (made up of 10 mosquitoes each) for every sample location were analyzed. It was observed that mean abundance of the mosquitoes was highest in mHLC (42.9 and the difference was highly significant ($p< 0.0001$). The mean abundance of mosquitoes was lowest in CDC light traps without attractant (0.29) compared to other means in other sampling techniques. It was also observed that no yellow fever virus strain was detected in all the mosquitoes sampled at the four locations. The possibilities of not encountering viral strains in mosquitoes may be due to the mass vaccination exercise that was carried out the previous year in the study area. Conclusively, adequate monitoring using the mHLC and continuous research are required to avoid resurgence of these virus in these locations.

5907

SURVEILLANCE OF ARTHROPOD-BORNE VIRUSES IN BENIN, WEST AFRICA 2020-2021: DETECTION OF DENGUE VIRUS 3 IN AEDES AEGYPTI (DIPTERA: CULICIDAE)

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The resurgence of arboviruses in recent decades is a major public health issue facing the international community due to the domestication of insect vectors. Aedes aegypti is the most important vector of arboviruses. In West Africa, it is known to transmit dengue virus (DENV), yellow fever virus (YFV), chikungunya virus (CHIKV), and Zika virus (ZIKV). To determine the abundance of arboviruses a longitudinal surveillance study was conducted in three consecutive years in Benin, West Africa. Adult mosquitoes were captured on human bait, Biogents Gravid Trap and BG-Sentinel traps at five ecological different locations in Benin from June 2019 to September 2021. A total of 3749 mosquitoes were collected and tested by RT-PCR

for arboviruses. One pool of Ae. aegypti captured on 7 July 2021 in Porto Novo tested positive for dengue virus. PCR results were confirmed by sequencing and showed the occurrence of dengue virus serotype 3. Our study highlights that there is a need to implement further investigations and surveillance strategies to prevent and control future outbreaks of mosquito-borne viruses in Western Africa.

5908

COMMON PREDATORS AND FACTORS INFLUENCING THEIR ABUNDANCES IN ANOPHELES FUNESTUS AQUATIC HABITATS IN RURAL SOUTHERN TANZANIA

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The role that larval predators play in regulating the population of malaria vectors remains relatively unknown. This study aimed to investigate the common predators that with Anopheles funestus group larvae and evaluate factors that influence their abundance in rural south-eastern Tanzania. Mosquito larvae and predators were sampled concurrently using standard dipper (350ml) or 10L bucket in An. funestus habitats in south eastern Tanzania. Predators were identified using standard identification keys. Habitats were characterized, geo-located and water physicochemical parameters were recorded. Generalised linear mixed effects models (GLMM) using template model builder (TMB) with zero-inflated negative binomial implemented under the glmmTMB package. Result presented as risk ratios at 95% CI and statistical significance considered when P<0.05. A total of 85 identified An. funestus habitats were sampled for larvae and potential predators. A total of 8,295 predators were sampled, with Coenagrionidae 57.7% (n=4785), Corixidae 12.8% (n=1,060), Notonectidae 9.9% (n=822), Aeshnidae 4.9% (n=405), Amphibian 4.5% (n=370), Dytiscidae 3.8% (n=313) being common. There were 5,260 mosquito larvae sampled, consisting of An. funestus group 60.3% (n= 3,170), Culex spp. 24.3% (n=1,279), An. gambie s.l. 8.3% (n=438) and other anophelines 7.1% (n=373). Permanent and larger than 100m2 habitats were positively associated with An. funestus group and predator abundance (P<0.05). Habitats with submerged vegetation were negatively associated with An. funestus group (P<0.05). Only dissolved oxygen positively affected the abundance of An. funestus group (P<0.05). Predators' abundance was not impacted by any physicochemical parameters. The study highlighted six common predators and factors influencing their abundances in An. funestus aquatic habitats. Further studies are needed to demonstrate the efficacy of predators on larval density and adult fitness traits. Interventions leveraging the interaction between mosquitoes and predators can be established to disrupt malaria transmission and survival of the An. funestus mosquitoes.

5909

FINE-SCALE SPATIAL AND TEMPORAL DYNAMICS OF ANOPHELES GAMBIAE SWARMS IN SOUTH CENTRAL UGANDA

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In Africa, and especially in Uganda, sibling mosquito species belonging to the Anopheles gambiae species complex are some of the most widespread and important malaria vectors. New tools to complement existing ones are needed to control and eliminate malaria as progress has stagnated over the last few years, and even reversed in 2020. A number of new approaches for malaria vector control are being explored including population suppression through swarm reductions and genetic modification involving gene drives. These new interventions will involve understanding of the biology and mating behaviour of target vectors in order to be successful. However, Anopheles mosquito swarms have historically been hard to locate in Uganda and only one study documenting swarm collection has been published in the last two decades. This study located, characterised and collected An. gambiae s.l. swarms in study sites in south central Uganda during 2017 and 2018, filling an important gap in knowledge on the mating behaviour of An. gambiae in Uganda. A majority of swarms solely composed of An. gambiae s.s. were collected during this study, however some mixed An. gambiae s.s. and Culex spp. mosquito swarms were also observed. Swarms were larger in the wet season than in the dry season. Mean swarm height ranged from 2.16 metres to 3.13m off the ground and only varied between villages but not by season. An. gambiae mosquitoes were present in all three villages, preferred to swarm over bare ground markers, and could be effectively collected by field collectors. This study demonstrated that An. gambiae s.l swarms could be effectively located and collected in South Central Uganda and contributed to bridging the knowledge gap regarding the mating behaviour of An. gambiae mosquito species in Uganda in terms of swarm species composition, height above ground, swarm sizes, swarm marker preference and swarm distribution. While mixed species swarms have been reported before, this is the first documented instance of mixed genera swarms found in Uganda, and this warrants further study to fully understand the species mating dynamics.

5910

ANOPHELES STEPHENSI: THE EMERGING VECTOR OF MALARIA IN THE REPUBLIC OF DJIBOUTI, HORN OF AFRICA

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The present study investigated mosquito species composition and phenotypic insecticide resistance profile to support decision-making in malaria vector control in the Republic of Djibouti at the Horn of Africa. Adult mosquitoes were collected between December 2016 and December 2017 across 20 sentinel sites established in the 6 regions of the country using both Centers for Disease Control (CDC) miniature light traps and pyrethrum spray catches (PSC). Female mosquitoes were kept aside, for morphological identification to species by an expert entomologist using appropriate taxonomic keys by Gillies & Coetzee and Glick. WHO tube bioassays were also conducted in An. stephensi from Djibouti-ville against nine insecticides used in public health. A total number of 12,538 host-seeking mosquitoes belonging to four genera (Anopheles, Culex, Aedes, Uranotaenia) comprising 12 species were collected. Among these, An. gambiae s.l. and An. stephensi were the two major malaria vectors identified while secondary malaria vectors such as An. nili somalicus, An. dthali and An. azaniae were also collected. Cx. quinquefasciatus was the most abundant mosquito species in the 6 regions. WHO susceptibility tests performed on An. stephensi population from Djibouti-ville showed resistance to pyrethroids, organophosphates, carbamates and DDT. The resistance intensity bioassays indicated low to moderate intensity of resistance with pyrethroid insecticides and the organophosphate pirimiphos methyl. Meanwhile pre-exposure to PBO suggested involvement of P450 detoxification enzymes in pyrethroid resistance.These findings revealed the urgent need to develop and implement a programme for monitoring and managing insecticide resistance in local vector populations with efficient control strategies in Djibouti.

5911

VIRAL INFECTION PROFILE OF AEDES MOSQUITOES IN SOME FORESTED AREAS IN GHANA

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Aedes-borne arboviral infections including Yellow fever (YF), Zika (ZIK), Dengue (DEN) and Chikungunya (CHK) have recently become a major public health concern worldwide and in Africa. Most arboviruses originate from the forest and circulated among non-human primates (NHPs) by arthropods including mosquitoes. Several outbreaks of arboviral diseases such as Dengue have been reported in many West African countries including those that share borders with Ghana. Recently, Yellow fever outbreak was reported in Ghana which resulted in 35 deaths. Although Ghana has not recorded other arboviruses, previous studies have indicated the presence of Dengue serotype-2 antibodies in some febrile patients. This study investigated the viral infection profile of Aedes mosquitoes collected from two forested areas in Ghana. A cross-sectional study was conducted in two forested areas, Achimota and Kakum National Park. The different stages of Aedes mosquitoes (eggs, larvae, pupae and adults) were collected using standard collection methods, identified and analysed. A total of 1,080 adult mosquitoes were morphologically identified. Aedes eggs collected from ovitraps in Kakum National Park yielded 17052 (87.2%) and in Achimota forest yielded 2498 (12.8%). The most prevalent Aedes subspecies collected from both sites were Ae. aegypti formosus, 156 (19.3%) in the Kakum National Park and 164 (60.1%) in the Achimota Forest which had diverse species. Culex fuscocephala were the most abundant Culex species identified in Kakum National Park (648). A total of 80 Anopheles gambiae (29.3%) were identified in the Achimota forest and 3 in the Kakum National Park (0.37%). Using RT-PCR, all 109 pools of Ae. aegypti mosquitoes were negative for YFV, DENV, ZIKV and CHIKV. The Positive Ovitrap Index (POI), a measure the risk of transmission was significantly higher (P= 0.03) in Kakum National Park: POI = 81.5% than Achimota forest :POI = 55.3%. The two forested sites are high risk areas for transmission of Aedes-borne arboviruses and sustained surveillance is needed to prevent future outbreaks.

5912

THE CHANGING ECOLOGY OF LARVAL MALARIA VECTORS IN THE CITY OF ACCRA, GHANA

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There is increasing evidence of malaria vectors adapting to breeding in polluted and other unexpected habitats in Sub-Saharan Africa. Historically, Anopheles mosquitoes breed in clean, unpolluted waters, and have shunned breeding in effluents from households and industries in cities. However, this seems to be changing in urban settings. This study investigated the Anopheles mosquito habitat types, their species composition, and their physicochemical parameters in the city of Accra, Ghana. Larval surveys and collections were undertaken in fifteen sites within the city of Accra (5° 36' 53.3448" N, 0° 12' 21.1464" W), Ghana, using the WHO standard dipping technique. These sites were selected and categorized into five sectors (three sites per category) based on the following: Irrigated Urban Farming (IUF), Lower (LS), Middle (MS) and High (HS) socioeconomic status, and Peri-urban (PU) sites. Physicochemical parameters were measured, and species identification was done using morphological and molecular methods. A total of 727 breeding habitats were found, of which [65.34%, n = 475/727] were positive for Anopheles larvae. Drainage ditches were the most abundant [48.21%, n = 229/475] habitat type. Overall, the abundance of An. gambiae s.l. was highest in IUF sites [6,244/22,919], and in the rainy season (77.01%; 17,650/22,919), (R2 = 3.46, P = 0.000). The highest larval densities of 19.22 and 13.22 larvae/dip were recorded in a swamp and tire track respectively in the rainy season. Malaria vectors were found to breed in much polluted waters including effluents from households. Polluted waters had on average dissolved oxygen of 17.6% compared to unpolluted (26.1%). Other parameters that distinguished polluted breeding habitats from unpolluted were conductivity (7332.5 uS/cm vs 2932.0 uS/cm); total dissolved solids (4567.0mg/L vs 1780.2mg/L); NH4-N (11.9 mg/L vs 4.9 mg/L). An. coluzzii 54.4% (368/677) was the most abundant species. The invasive An. stephensi, which has not yet been reported in Ghana was detected. The findings in this study provide evidence for the consideration of environmental management for malaria control in urban Accra.

5913

"FIGHTING AGAINST MALARIA IS EVERYONE'S CONCERN": A RANDOMISED CONTROL TRIAL ASSESSING THE ROLE OF INCENTIVES FOR ENCOURAGING LOCAL COMMUNITIES TO RECORDING AND UPLOAD MOSQUITO SOUND USING MOZZIWEAR APPLICATION

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Current malaria surveillance methodologies are considered too expensive to scale within resource limited settings, hence new technologies and approaches are necessary to maximize data collection and ultimately design new malaria control tools. Effective mosquito surveillance can be enhanced through the utilization of digital technologies and engagement of citizen to real time data collection. This study was a follow-up research on the use of mobile phone application (mozziewear) for detecting and identifying wild host-seeking mosquitoes using their flight tones. In this particular study, citizens were provided with airtime incentives to encourage them to participate in recording and uploading mosquito sound. This study was randomised controlled trial (RCT) conducted in four villages in rural Tanzania between April and August 2022. Participants were randomised into two groups; 1) control group: nothing was provided to participants and 2) Incentive group: airtime was provided to participants. Both groups were then asked to record and upload mosquito flight tone data once per week for a period of four months. At the end of the study, experience survey was administered to participants in both groups to assess their experience of participating in this study. The results indicate that the participants were willing to record and uploaded mosquito flight tone data even without being paid incentives. They expressed that fighting against malaria is everyone's concern in rural Tanzania. In addition, the participants expressed their interest in being involved in future research efforts related to mosquito surveillance and the fight against malaria. In conclusion, citizens can still play a valuable role in scientific research, even without the promise of incentives. By participating in mosquito surveillance and malaria prevention studies, community members have significant contribution in addressing mosquito borne diseases and improvement of health outcomes

5914

MOLECULAR SURVEILLANCE LEADS TO THE FIRST DETECTION OF ANOPHELES STEPHENSI IN KENYA

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Anopheles stephensi is an invasive malaria vector that is endemic to south Asia and the Arabian Peninsula. Recently reported in the Horn of Africa countries including Djibouti (2012), Ethiopia, Sudan (2019), Somalia (2019) and Nigeria (2020). This mosquito is a competent vector for both Plasmodium falciparum and P. vivax. It is characterized by a high degree of behavioral plasticity and the ability to reproduce in various types of breeding sites including containers and therefore has the potential to propagate malaria transmission in rapidly urbanizing settings with poor drainage and waste disposal containers. The World Health Organization (WHO) has called on all countries to scale up surveillance efforts to report invasion by this vector and institute appropriate and effective control mechanisms. In Kenya, the Division for National Malaria Program (DNMP) and its partners have been conducting entomological surveillance in coastal and northern counties that are suspected to be at risk of An. stephensi invasion as well as counties at risk of malaria. These efforts were supported by molecular surveillance of Anopheles mosquitoes by the Kenya Medical Research Institute (KEMRI) to try and identify An. stephensi. We report the first detection of An. stephensi in Kenya in three sub-counties of Marsabit County in December 2022 and February 2023. Polymerase Chain Reaction (PCR) was used as the primary method of identification in addition to morphological identification with further confirmation of results by amplicon sequencing of the ITS2 region. Out of 566 samples analyzed by PCR 44 were confirmed to be An. stephensi. Sequencing of the ITS2 region was performed on 4 samples, 3 of which clustered closely with isolates from India, Yemen, Iraq, and Nigeria based on phylogenetic analysis. The detection of this vector in Kenya presents an urgent need to re-examine and expand the vector surveillance and control effort to include An. stephensi which is likely to increase transmission in Northern Kenya and spread further to highly populated areas and existing malaria-endemic counties further compounding the problem of malaria control in the country.

5915

ARBOVIRUS SURVEILLANCE AND BLOOD-MEAL ANALYSIS OF MOSQUITOES IN JAMAICA

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Annually, mosquitoes are responsible for over 1 million deaths and 700 million infections. Arboviruses transmitted by mosquitoes are of global public health and veterinary significance, causing disease syndromes such as encephalitis, viral hemorrhagic disease, and sometimes death. Despite identifying several arboviruses across Jamaica, little is known about the non-human hosts that may be involved in the maintenance of these viruses in the different ecological habitats, as well as the contributions of various mosquito species in transmission cycles. Therefore, we aimed to identify blood-feeding patterns of mosquitoes in different ecological niches in addition to characterizing novel or re-emerging arboviruses and their hotspot localities before future outbreaks. Mosquitoes were collected from four ecological habitats (mangroves, forested, rural and peri-urban) using CO2-baited BG-sentinel and CDC light traps. Samples were transported to the laboratory on dry ice, where mosquitoes were identified and pooled into groups of 25 based on species, sex, date and location and stored at -80℃ until used for NGS. All blood-fed specimens were processed and stored on FTA cards for cytochrome c oxidase subunit I (COI) gene analysis. A total of 2,150 mosquitoes were collected belonging to 6 genera Aedes, Culex, Anopheles, Mansoni, Psorophora and Wyeomia. Culex quinquefasciatus, a competent vector for several arboviruses, was the dominant species identified. The information from this study can be used for informed and targeted vector control strategies and also as an early warning system to predict potential future outbreaks.

5916

PHENOTYPIC AND MOLECULAR INSECTICIDE RESISTANCE MONITORING OF ANOPHELES FUNESTUS MOSQUITOES TO GUIDE MALARIA CONTROL EFFORTS IN TANZANIA

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Insecticide-based vector control approaches remain the mainstay of malaria control in Africa. The effectiveness of these tools is however threatened by the increasing vector resistance to the insecticides. In Tanzania, Anopheles funestus is an increasingly important malaria vector mediating most of the transmission in some settings compared to other vectors. Consequently, its routine resistance monitoring is crucial to ensure the continued efficacy of control tools against it. Between November 2021 - December 2022, we used WHO tube bioassays to assess the response of field-collected adult An. funestus to pre-determined doses of insecticides in nine regions in Tanzania representative of geographical variations and malaria transmission intensity. We further genotype the mosquitoes to monitor allele frequencies of three metabolic resistance genes - CYP6P9a, L114F-Gste2, and CYP6P9b; additionally, we analyzed the association between surviving the standard insecticide dose (phenotypic resistance) and these resistant alleles (genotypic resistance) using generalized linear models. We found high resistance to pyrethroids (deltamethrin and permethrin) across the country (mortality range 24-55%); however, susceptibility was fully restored following pre-exposure of the mosquitoes to piperonyl butoxide. Resistance to bendiocarb was mostly observed in the South (Mtwara, Lindi, & Ruvuma) and North (Kagera) of the country (mortality range 57-77%) with full susceptibility to DDT and pirimiphos-methyl. Moderate resistance intensity to deltamethrin was observed in coastal regions (Mtwara, Lindi, & Pwani) with high intensity confirmed in Pwani. Similarly, we detected moderate intensity for permethrin in Katavi and Mtwara. We observed a positive association between CYP6P9b and L114F-Gste2-resistant alleles and surviving lethal insecticide doses. However, carrying CYP6P9a-resistant alleles did not increase the chances of insecticide survival. These findings provide a basis for implementing resistance management strategies to limit the further exacerbation of resistance and its impact on malaria control efforts.

5917

DEVELOPMENT, PILOTING, AND EVALUATION OF AN ENTOMOLOGICAL ADAPTIVE SAMPLING FRAMEWORK (EASF) IN MOZAMBIQUE AND GHANA

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Routine entomological surveillance is important for monitoring and evaluating vector control interventions, however there is no operational guidance for optimizing entomological sampling in programmatic settings. An adaptive sampling framework responds to existing data and can adjust the sampling strategy to maximize representativeness and accuracy of the data across time and space. Applied as part of a malaria control program, this may be able to better capture changes in disease transmission dynamics to produce better data that can guide programmatic and strategic decisions.A spatiotemporal EASF model was developed for Mozambique and Ghana and used to inform adaptive entomological sampling designs across space and time for detecting changes in the three priority indicators: 1) vector species compositions, 2) vector behaviour, and 3) insecticide resistance (IR). The optimal sampling approach suggested by the spatiotemporal model is running in parallel with each country's routine surveillance framework. The EASF will be compared with routine surveillance in terms of the primary outcomes of representativeness, cost-effectiveness, and acceptability. In Mozambique the EASF will run for 2 years while Ghana 1 year. Here, we will present the year one EASF preliminary results from Mozambique and Ghana pilots.The EASF may help programs establish a cost-effective adaptive entomological surveillance strategy that is responsive to changing transmission dynamics and optimizes the use of available resources by obtaining more robust and informative data.

5918

INVESTIGATING THE SIBLING SPECIES DIVERSITY AND BREEDING BEHAVIOR OF THE MAJOR MALARIA VECTOR ANOPHELES GAMBIAE SENSU LATO IN SOUTHERN NIGERIA

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Mosquitoes in the Anopheles gambiae complex are major malaria vectors in Nigeria. However, studies that characterize the diversity and breeding behaviors of sibling species of the group in southern Nigeria are limited. To address this knowledge gap, we inspected water bodies for mosquito larvae in southern Nigeria. Results revealed the presence of Anopheles larvae in 53.49% (23/43) of mosquito breeding sites inspected between September and November 2022 in three southern Nigeria states (Edo, Delta, and Anambra). Molecular analysis identified wild-caught Anopheles larvae as An. coluzzii (89.44%, 95% CI: 84.91, 93.98) and An. gambiae sensu stricto (10.56%, 95% CI: 6.02, 15.09). An. coluzzii occurred in 95.45% (95% CI: 86.00, 100) of surveyed locations, whereas An. gambiae ss occurred in 31.82% (95% CI: 10.68, 42.50) of the same area. The larvae of both species were present in urban and periurban areas, and in puddles, stream margins, and open drains. Anopheles gambiae ss were further discovered in a concrete underground well. The overall average abundance of malaria larvae in water bodies was 1.82 larvae per dip (95% CI: 0.76, 2.89). Logistic regression analyses indicated higher odds of Anopheles larval presence in lowlands, and natural and shallow water bodies. Future work to be completed prior to the meeting include assessing population genetic structure of An. gambiae s.l. across diverse ecological habitats for understanding genetic diversity, vector dispersal, and insecticide resistance spread of the species in southern Nigeria. So far, we show that An. coluzzii are major malaria mosquitoes infesting extensive urban and periurban areas in southern Nigeria.

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MALARIA TRANSMISSION RISK INDICES OF SECONDARY VECTORS FROM COASTAL AND FOREST AXES OF NIGERIA

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We sampled 14,332 female anophelines belonging to seven different species from coastal and forest axes in Nigeria between 2019 and 2022 using both morphological and molecular identification methods (using species specific PCR) to specific level. Major vectors including Anopheles gambiae Giles, An. arabiensis Patton, An. funestus Giles and An. melas represented ~98% of the total anopheline fauna identified. The remaining 2% was composed of An. moucheti Evans, An. coustani Laveran complex, An. leesoni Evans and An. nili (Theobald)(only species habiting both the coastal and forest areas). Enzyme Linked Immunosorbent Assay (ELISA) was used to determine the Circumsporozoite (CSP) infection status of the species of interest. Circumsporozoite (CSP) infection status showed that the mean infection rate of minor vectors (0.82%) was significantly (P=0.7652) lower than that of major vectors (2.36%). Plasmodium falciparum infection was high and repeatedly found in An. moucheti, indicating its contributory role to the total malaria transmission especially in the forest area. EIR indicates a mean of 146 infective bites/year: 51.8 from An. gambiae s.s., 29.2 from An. funestus, 14.6 from An. arabiensis, 29.2 from An. moucheti, 13.7 from An. melas, 7.3 from An. leesoni, 0.2 from An. coustani and 0.00 from An. nili respectively.

5920

AEDES AEGYPTI AND OTHER MOSQUITO SPECIES COHABITATING IN THE CHEKWOPUTOI CAVE, UGANDA

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Aedes aegypti is a major mosquito vector of globally significant human pathogens. Ae. aegypti can transmit viruses such as dengue (DENVs), Zika, chikungunya, and yellow fever. Ae. aegypti exhibits a complex genetic structuring among populations in Africa. Significant knowledge gaps remain pertaining to the sylvatic larval habitats of Ae. aegypti. We opportunistically collected mosquito larvae (n=113) from a rock pool at the entrance to Chekwoputoi cave located in the Kween District, Uganda. This cave is is the known roosting site for a large colony of the African sheath-tailed bat, Colura afra and is regularly utilized by domestic and other wild mammal species. Mosquitoes were reared to adults at the Uganda Virus Research Institute and morphologically identified. This collection comprised eight species: Ae. aegypti formosus (n=5), Anopheles rhodesiensis, and six additional Culex and Aedes species. Species identifications will be confirmed using molecular techniques and documented using high resolution photography. These observations represent unique ecological insight into the larval habitat and mixed-species larval community of medically-important mosquito species in Uganda. We hope to utilize this information to understand mosquito vector ecology in this poorly-studied area, and how these vectors cohabitate with each other.

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ROLE OF MALARIA VECTORS BLOOD-MEAL PREFERENCES ON MALARIA TRANSMISSION RISK IN MASENO AND KOMBEWA, WESTERN KENYA

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Mosquito feeding behavior provides a baseline in understanding malaria transmission risk. Accurate identification of relative proportion of bloodmeals taken from humans and alternative hosts is important in calculating

entomological indexes such as Human Biting Rate (HBR) an important component in calculation of vectorial capacity- a measure of malaria transmission that increases with HBR. A longitudinal study involving collection of Anopheles mosquitoes was carried out from July 2015 to August 2016 in Kombewa and Maseno study sites, Western Kenya using Prokopac aspirator for indoor collections. Microscopy was used to identify An. gambiae sensu l ato (s.l)and An. funestus species. Polymerase chain reaction (PCR) was used to further characterize mosquito species within the Anopheles gambiae s.l into An. gambiae sensu stricto (s.s) and An. arabiensis. Enzyme-linked immunosorbent assay (ELISA) was used in blood meal identification. A total of 573/923(62.1%) Anopheles mosquitoes had blood meals of which An. funestus and An. gambiae s.s were 373/573 (65.1%) and 200/573 (34.9%) respectively. An.arabiensis was rather transient with only 4/309 testing positive of An.gambiae s.l identified . Bloodmeals were inclusive of human 485/573 (84.6%), cow 40/573 (7.0%), dog 7/573 (1.2%), chicken 3/573 (0.5%), goat 1/573 (0.2%), while cat and donkey appeared in mixed sources. Blood meals containing human and alternative sources were 13/200 (6.5%) and 20/373 (0.5%) in An. gambiae s.s and An. funestus respectively. Surprisingly, mixed non-human blood meal sources were observed in An. gambiae s.s at 4/200 (2.0%) contrary to some of the previous studies. An. funestus was majorly anthrophilic as opposed to An. gambiae s.s that showed opportunistic behavior. This marginal shift from normal feeding patterns exhibited by An. gambiae s.s appears to suggest increased risk of malaria transmission in study populations. Additional survey on host feeding preferences is necessary in order to support reciprocal changes in malaria control strategies to contain this enhanced risk.

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BITING PATTERN OF ANOPHELES ARABIENSIS, HUMAN BEHAVIOUR, AND SOCIO-ECONOMIC MALARIA RISK FACTORS IN AN IRRIGATED AGROECOSYSTEM IN WESTERN KENYA

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Knowledge on the biting patterns of malaria vectors, human behavior, and malaria risk factors is important in understanding malaria transmission dynamics, evaluating the effectiveness of vector control interventions, and informing the development of appropriate interventions. This study assessed vector biting patterns, human behavior, and socio-economic malaria risk factors in an irrigated agro-ecosystem in western Kenya. Adult mosquitoes were sampled using human landing catches. The mosquito samples were identified to species using polymerase chain reaction (PCR). Malaria parasites were detected by quantitative PCR. Human behavior data was collected using a questionnaire to understand human night activities and sleeping patterns and how they overlap with vector behavior. In order to investigate the association between malaria prevalence and socioeconomic risk factors, these parameters were also included in the questionnaire. The mean indoor and outdoor host-seeking densities of An. arabiensis varied significantly, with the highest density collected indoors. During the first half of the night (6 p.m.-12 a.m.), indoor biting activity of An. arabiensis showed a peaked plateau between 8 p.m. and 10 p.m. before the local community went to sleep. Data on human behavior and indoor mosquito biting activity showed that there is a high risk of transmission at dusk and dawn when people are not under the protection of bed nets. Outdoor biting activity of An. arabiensis occurred throughout the night; nonetheless, the greater proportion of the human population was indoors from dusk to dawn; therefore, there was a low risk of outdoor malaria transmission. These findings demonstrate that there was a higher risk of malaria transmission due to factors such as sleeping indoors, sleeping late, a lack of bed nets, and low utilization. The study underscores the necessity of complementing the core malaria vector control strategies by integrating larval source management and novel techniques such as transgenic mosquitoes.

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PREVALENCE OF MICROSPORIDIA MB AMONG ANOPHELES MOSQUITOES MAY BE ASSOCIATED WITH MICRO-ECOLOGICAL FACTORS OF BREEDING NICHES

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Microsporidia MB is found associated with Anopheles mosquito vectors and shown to interfere with the development of Plasmodium. In Kenya where this was first reported, Microsporidia MB was widespread in An. arabiensis collected from rice fields. Since then, the symbiont has also been reported in An. gambiae and An. funestus. As a potentially useful tool for symbiont-based disease control, its ecological distribution is still not clearly understood especially since Anopheles mosquitoes have different niches. This study was aimed at determining the prevalence of Microsporidia MB in Anopheles mosquitoes in selected sites across Ghana, and measuring the physicochemical parameters of breeding sites to determine the associated micro-ecological factors. Anopheles larvae and pupae were collected from study sites in northern and southern Ghana between Aug-October of 2021 and 2022. A total of 4195 immature mosquitoes were raised to adults and DNA was extracted from the abdomen. Microsporidia MB was detected by qPCR and mosquito species molecular identification using a SINE and RFLP methods. The overall prevalence of Microsporidia MB was 1.9% (78/4195) with prevalence similar among An. gambiae (41.0%; 78/4195) and An. coluzzii (30.8%; 24/78) (χ;2, P= 0.28), reiterating previous findings from archived samples. Microsporidia MB was observed in only one An. arabiensis (1.3%; 1/78). Male mosquitoes showed predominance in Microsporidia MB infections (χ;2, P= 0.001). Sites in the Savannah ecological zone of Ghana, which had no associations with rice fields, had the highest prevalence of Microsporidia MB (55.1%; 43/78) compared to other sites (χ;2, P= 0.0009). Overall, the study suggests the distribution of Microsporidia MB is most widespread among predominant malaria vectors in a geographical region and their sustainability in the aquatic stages of the host may be influenced by microecological factors. Further analyses on the physiochemical parameters collected will help in our understanding of the distribution of this symbiont among Anopheles mosquitoes in their different breeding niches.

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THE CHANGING LANDSCAPE OF DENGUE AND CHIKUNGUNYA VECTORS IN KENYA – A THREAT TO PUBLIC HEALTH.

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Dengue and chikungunya are a major problem in Africa, causing outbreaks annually. In Kenya, dengue (DENV), chikungunya (CHIKV), primarily transmitted by Aedes aegypti, frequently cause outbreaks mainly in urban coastal (Mombasa, Lamu) and northern (Mandera and Wajir) counties resulting in significant morbidity, associated lost man-hours, enormous socio-economic impact among communities, and burden on health systems. Entomological Surveillance was conducted during dengue

and chikungunya outbreaks in Mombasa to i) determine the presence and densities of Ae. aegypti vectors, ii) identify breeding habitats and iii) identify other potential vector species previously not associated with these viruses. Sampling involved collection of adult mosquitoes using BG sentinel and CDC light traps; and larval collection from affected areas. During the 2013/2014 dengue outbreak, 2,069 adult Aedes mosquitoes were collected: Ae. aegypti (n=2,069) and Ae. vittatus (n=4); while larvae comprised of n=2,510 Ae. aegypti outdoor (n=1,515), indoor(n=995) and Ae. vittatus (n=0). In 2018 chikungunya outbreak, 2,086 adults: Ae. aegypti (n=911), Ae vittatus (n=1,175); and n=528 larvae: n=526 Ae. agypti (indoor, n=280; outdoor, n=246), and Ae. vittatus, (outdoor, n=2) were collected. N=2,511 adult female Culex quinquefasciatus mosquitoes were also collected, and two CHIKV isolates obtained. Ae. vittatus occur in abundance, voraciously bite humans despite being majorly zoophilic. CHIKV has also been repeatedly isolated from them and have been shown to efficiently transmit CHIKV. Therefore, it plays a critical role in Key in sylvatic maintenance; and urban transmission of DENV, CHIKV, YFV, ZIKV whenever it invades urban areas. Although predominantly a rock-pool, tree-hole breeder; it can breed in diverse macro-, micro-habitats. A combination of Ae. aegypti, Ae. vittatus and Cx. quinquefasciatus poses a major challenge in vector control. Therefore, intensive surveillance to identify breeding habitats for Ae. vittatus in Mombasa is instrumental in devising appropriate vector control tools specific to this species.

5925

THE DISTANCE-DENSITY RELATION TO INFORM LARVAL SOURCE MANAGEMENT: HOW FAR IN SUGAR IRRIGATION SCHEMES DO MALARIA MOSQUITOES BREED

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While agricultural production is expanding in low-and mid-income countries, the vast majority of plough able land is too dry to depend only on rain-fed agriculture. Irrigation is the most effective and supplementary system to increase crop production and yields as well as to ensure reduced risk of crop failure. While these large-scale agriculture may enhance local economies and consequently boost livelihoods, some crop systems create and sustain suitable mosquito breeding habitat and hence affect malaria transmission especially where drainage system is poor. We conducted a study in Manhica district in 2020, south of Mozambique to characterize mosquito-breeding habitats along an irrigated sugarcane plantation. Additionally this study aimed at assessing how mosquito immatures change in different environments as well as which breeding types contribute and sustain malaria mosquitoes throughout the year. Here we will present the outcome of this survey in Manhiça district. This study will provide useful information to the programme and significantly enhance understanding of use of focal control of larvae in Mozambique either through aerial spray or manual where applicable.

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DETECTION OF INSECT-SPECIFIC VIRUSES IN MOSQUITOES COLLECTED IN URBAN AND FOREST FRAGMENT AREAS OF NORTHWEST OF SAO PAULO STATE, BRAZIL

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Insect-specific viruses (ISVs) can affect arboviruses cycle transmission, mainly impacting vector competence, and have a great potential to be used as biological control agents or vaccine platforms. From March 2022 to March 2023, we collected 463 mosquitoes (allocated in 273 pools) from urban and forest fragments of Sao Jose do Rio Preto (SJdRP), Sao Paulo, Brazil. The mosquito species belong to different genera, including Culex, Aedes, Psorophora, Sabethes, and Limathus. So far, 136 pools have been submitted to viral isolation and molecular investigation for medically important flaviviruses, alphaviruses, and for insect-specific viruses such as PCLV, HTV, GUAPV, CxFV, and AeFV. We detect HTV in 22 pools (16.17%) of mosquitoes from Aedes, Culex, and Sabethes genera. PCLV was detected in 30 pools (22%) of mosquitoes from Aedes and Culex genera. CxFV was detected in 20 pools (14.70%) of Culex genus. We detect GUAPV in three pools (2.2%) of mosquitoes from Limathus, Culex, and Psorophora genera. PCR products were sequenced by the dideoxy method confirming these results. In addition, we had 15 pools (11%) of mosquitoes from Aedes and Culex genera positive in a pan-Flavivirus PCR. The PCR products of these samples were sequenced by the dideoxy method, and the nucleotide sequences obtained showed similarity with other mosquito flaviviruses. In addition, we have some co-infections: 13 pools of Aedes aegypti and one pool of Culex sp. co-infected with HTV and PCLV; two pools of Aedes aegypti co-infected with FLAV-like and PCLV; one pool of Culex sp. co-infected with PCLV and CxFV; one pool of Culex sp. co-infected with GUAPV and CxFV; and one pool of Aedes aegypti co-infected with HTV, PCLV, and FLAV-like. All pools tested negative for the medically important arboviruses. Our next steps are genomic characterization/biological characterization and electron microscopy. Our findings demonstrate the viral diversity in mosquitoes from SJdRP and open perspectives for further studies of metagenomics, vector competence, and interactions between these ISVs and circulating arboviruses.

5927

A METHODOLOGICAL FRAMEWORK TO UNDERSTAND THE DRIVERS OF DENGUE FOR DESIGNING OPERATIONALLY EFFICIENT AND SUSTAINABLE VECTOR CONTROL POLICIES IN ENDEMIC SETTINGS; A CASE STUDY FROM KALUTARA DISTRICT, SRI LANKA

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Dengue imposes a substantial public health and economic burden on affected populations in endemic countries, including Sri Lanka. Complex interactions among susceptible humans, viruses, and Aedes mosquitoes determine dengue's transmission and spread. Assessments of context-specific climate and non-climate drivers of dengue transmission and the analysis of effectiveness and cost-effectiveness of dengue control interventions are required to develop pragmatic and sustainable dengue control programs. To meet this demand, we developed a methodological framework which is capable of (1) identifying the most vulnerable populations by assessing delayed and non-linear associations between

climate and non-climate drivers of dengue across different geographical settings; (2) evaluating the effectiveness and cost-effectiveness of population-level vector control interventions implemented to address the identified drivers in the above settings. We found that early and targeted interventions, triggered by the evidence generated through the methodological framework, were effective and cost-effective, reducing the burden of dengue by 50% in a highly endemic area in Kalutara district, Sri Lanka. Given the capacity is established, program managers can use this methodological framework to develop a decision-support platform to set up short-, intermediate-, and long-term targets for designing and deploying equitable and efficient operational response to dengue. The inbuilt monitoring and evaluating framework would promote a more informed and transparent public health decision-making process towards attaining the World Health Organization's dengue and other vector-borne disease targets by 2030 in endemic and resource-constrained settings.

5928

COMMUNITY PERCEPTIONS OF NUMBER OF MOSQUITOES AND MOSQUITO BITES AFTER USE OF WOLBACHIA SUPPRESSION AS A CONTROL METHOD FOR AEDES AEGYPTI MOSQUITOES IN PONCE, PUERTO RICO

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Wolbachia suppression (WS) can reduce Aedes aegypti mosquito populations, the main vector of the dengue virus, by decreasing the hatch rate of eggs from crosses of released Wolbachia-carrying male and wild-type female mosquitoes. Because WS involves releasing mosquitoes, understanding community members' perceptions of the number of mosquitoes and mosquito bites after releases are important to inform the acceptability of WS. During 2020-2021, WS was tested in a randomized cluster trial in 8 communities in Ponce, PR. We conducted phone and in-person surveys of adult residents of the 4 release (intervention) and 4 non-release (control) areas during August-October 2022. We compared post-release community perceptions of the number of mosquitoes and mosquito bites in intervention and control areas using chi-square tests of proportion. We also identified factors associated with reporting fewer mosquitoes and fewer or no change in mosquito bites in intervention areas using logistic regression. Of 258 total respondents, 70% were female, the median age was 51 years (range 19-93), 69% were aware of mosquito releases, of whom 75% had supported releases. Demographic characteristics and awareness of and support for WS were similar in release and control areas. While not statistically significant, a higher proportion of respondents in release areas reported perceiving fewer mosquitoes (19% vs. 12%, Chi-square p=0.4) and mosquito bites (27% vs. 16%, Chi-square p=0.06) compared to respondents in control areas. Among respondents in release areas, age, sex, awareness, and support of releases were not associated with reporting fewer mosquitoes; however, women were more likely to report perceiving less or no change in mosquito bites (adjusted OR 3.3 [95%CI 1.4-7.9]) compared to men. Community perceptions of mosquito numbers and mosquito bites were consistent with expected results from implementation of WS, where total mosquito numbers and mosquito bites decrease due to decreased egg hatch rates. Our findings suggest that WS may be associated with perceptions of fewer mosquitoes and mosquito bites, informing the acceptability of WS.

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USING HIGH POWER ELECTRIC FIELDS TO REPEL MOSQUITOES

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To control and prevent existing and (re) emerging mosquito-borne diseases, insecticides are often our only option. Insecticides reduce mosquito population sizes and/or prevent human-vector contact, but their excessive use raises concerns for our environment, our health, and led to the rapid development and spread of insecticide resistance. As a result, the development of novel technologies for mosquito control is urgently needed. One of the new tools in development is the use of high power pulsed electrical fields (EFs) that create an invisible barrier and repel mosquitoes. I will provide an overview of the current knowledge of this first non-chemical insect repelling technology, and present novel data on how EFs generated with cheap over-the-counter insulated conductor wires prevent host-seeking Aedes aegypti mosquitoes from entering spaces, allowing us to protect typical mosquito entry points in houses (such as eaves, windows, and doors) as well as groups of people outdoors.

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ASSOCIATION OF WATER AVAILABILITY AND AEDES AEGYPTI PUPAE AND ADULTS IN AN URBAN/RURAL MOSAIC IN NICARAGUA

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The increase in dengue virus (DENV) epidemics and the latitudinal expansion of Aedes mosquitoes globally has made it critical to understand the ecological and social factors that modulate its population abundance locally. We used multilevel models to evaluate the different life stage abundances of Ae. aegypti collected from October to December of 2022 (rainy season) in 500 households in 21 urban and peri-urban neighborhoods in District 3 of Managua, Nicaragua, as part of an arbovirus surveillance study (A2CARES). A total of 1,194 pupae and 201 adult female mosquitoes (indoor: 129, outdoor: 72) were collected. We used a GLMM and GAMM approach to estimate pupae and adult female indoor and outdoor abundance. The number of pupae found in a home was directly associated with number of containers present (exp= 1.41, SE= 0.09, p< 0.001) and outdoor female specimen abundance (exp= 2.73, SE= 0.47, p< 0.03). We observed that outdoor female abundance increased with frequency of water service interruptions per day (exp= 1.07, SE= 0.02, p< 0.01), total number of pupae found in the household (exp= 1.027, SE= 0.009, p< 0.01) and neighborhood of collection (exp= 0.501, SE= 0.027, p=0.01). The GAMM smooth for water interruptions was also significant, increasing with the number of female mosquitoes outdoors. Indoor female abundance was only associated with the number of pupae found in a home (exp= 1.021, SE= 0.008, p< 0.01). We are currently untangling the fine-scale spatial patterns for mosquito abundance, human density, access to water and services, and most productive containers to evaluate how these variables impact mosquito ecology using a urbanicity mosaic perspective within our study site. Our results suggest that for our geographic setting, pupae can be an adequate proxy for female abundance. More importantly, the inclusion of stakeholders involved in household water container management and municipal services are critical for future intervention projects in the region. Fine-tuning hotspot analysis of mosquito abundance to identify key factors that modulate their population is critical to improve vector control activities in limited-resource settings.

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IMPACT OF STANDARD AND LONG-LASTING IVERMECTIN FORMULATIONS IN CATTLE AND BUFFALO ON WILD ANOPHELES SURVIVAL ON SUMBA ISLAND, INDONESIA

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Sumba Island has some of the highest diversity of Anopheles species in Indonesia, contributing to its high malaria incidence. Southwestern Sumba, the area with highest malaria burden, has small livestock holder systems where the animals (e.g. cattle, buffalo, horses, and pigs) are kept near the owners' house at nighttime, often underneath the house. Anopheles mosquitoes frequently blood-feed on livestock providing an opportunity for vector control by treating the animals with insecticides. Ivermectin is a systemic endectocide used to control helminth and ectoparasites in livestock, and ivermectin-treated hosts are lethal to Anopheles vectors. Both standard (Ivomec) and long-lasting (Ivergen Platinum) commercial formulations of ivermectin were investigated in cattle and buffalo in this study. Four villages were selected to maximize the diversity of Anopheles species. In each village, three cattle and three buffalo were treated with either standard (200 ug/kg), or long-lasting ivermectin (630 ug/kg), or kept untreated as controls. Study animals were placed in net traps, which allowed mosquitoes to enter and blood feed on the animals. Mosquitoes were collected by mouth aspiration. Animals were exposed to mosquitoes before treatment and up to 70 days post treatment. A venous blood sample was collected from the study animals the morning after each mosquito collection for ivermectin quantification. Blood-fed Anopheles were transported to a field insectary where their survival was monitored daily. Each day the dead mosquitoes removed, identified to species, and on day ten of monitoring the mosquitoes were frozen and counted as alive. Ten Anopheles species were frequently collected including: An. aconitus, An. annularis, An. barbirostris, An. flavirostris, An. kochi, An. maculatus, An. subpictus, An. sundaicus, An. tessellatus, and An. vagus. Cattle treated with long-lasting ivermectin were lethal to all Anopheles species through 46 days post treatment. Ivermectin concentrations will be quantified and linked to mosquito mortality to characterize the lethal concentration that kills 50% of the mosquitoes for each species captured.

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AUTOMATING MOSQUITO STERILE INSECT TECHNIQUE (SIT)

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One of the best prevention methods for vector-borne diseases is control of the vector itself. For mosquitoes that transfer a number of viruses and parasites affecting millions, an integrated management approach has proven most effective. Integrated control brings together tools like source control, larviciding and adulticiding. For a subset of species coined as "container breeding" this approach has fallen short. The main difficulty in controlling container breeding mosquitoes is that source control and larviciding are near impossible. One important tool that could close the gap is the sterile insect technique (SIT). SIT works by overwhelming the vector population with sterile males causing the production of unfertilized eggs. SIT has been in use for decades against a couple of agricultural pests and numerous field tests for mosquito vector control have shown great success. As male mosquitoes will seek out females even when humans can't find all their hidden breeding sites, SIT can close the hole in integrated control of container breeders. Mosquito SIT requires accurate sex-sorting to ensure no females are released. Currently, state of the art technologies sort at the late developmental stages. However, as adult mosquitoes have a short lifespan and are fragile, they must be produced near the release site (usually manually). This makes mosquito SIT prohibitively expensive. Uniquely, Diptera.ai can sex-sort mosquitoes and numerous agricultural pests at the larval stage, previously considered impossible. Larvae can be shipped long-distance from centralized facilities, thus allowing for economies of scale and introduction of rearing automation. Our sex sorter utilizes proprietary optics coupled with machine learning algorithms to rapidly and precisely predict and separate larvae sexes. The system is comprised of an array of small autonomous units. This design allows for maximum flexibility and means that units can be serviced without shutting down production. Using the systems described above we successfully controlled the Aedes albopictus population in a small town over an entire season.

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SPATIAL ANALYSIS OF ENVIRONMENTAL DRIVERS AND MOSQUITO SPECIES ABUNDANCE ON MALARIA PREVALENCE IN KENYA FROM JANUARY 2019 TO JUNE 2021

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Over 50% of the global population is at risk of contracting malaria, especially those living in 85 endemic countries- the majority of which are in Sub-Saharan Africa. Climate change is impacting malaria prevalence and mosquito species distribution and densities. Our objective was to estimate the effect of climate parameters (temperature, humidity, rainfall) and mosquito species on malaria prevalence in Kenya from January 2019 to June 2021 We compiled data across 31 counties in Kenya from previous surveillance work: a malaria indicator survey, secondary data from a monthly entomological survey and a household malaria indicator survey. We analyzed the data using linear regression, correlation and used least absolute shrinkage and selection (LASSO) for selection of coefficients. We found that malaria prevalence in Kenya is highest in the lake region with prevalence at 19%, coast endemic at 5%, semi-arid seasonal at 2%, and low risk at 0.9% for 2020. The mosquito species distribution varied across malaria epidemiological zones. In the coastal region, An. Funestus was more abundant, while in the lake region An. Gambiae was more abundant, although significant An. Funestus' presence was also detected. The regression results suggest that a combination of environmental factors (such as temperature, vegetation, and aridity) as well as public health interventions (such as ITN coverage) are important predictors of malaria prevalence. However, the relationship between some of these factors and malaria prevalence is complex and may vary across different regions and time periods.Overall, this study provides insights into the spatial-temporal dynamics of mosquito species and their distribution in relation to malaria epidemiological zones in Kenya and can inform control strategies within specific ecological zones. Further studies are needed to better disentangle the factors influencing the distribution and abundance of mosquito species in different malaria epidemiological zones in Kenya

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STUDY OF THE DIVERSITY OF MACRO INVERTEBRATES ASSOCIATED WITH THE LARVAL HABITATS OF ANOPHELES GAMBIAE COMPLEX IN TWO VILLAGES OF THE KATI DISTRICT MALI

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Target Malaria is a non-profit research consortium, which aims to develop new vector control strategies against malaria using genetic technologies based on population reduction. The aim is to reduce the malaria-carrying mosquito population in the Anopheles gambiae s.l. complex in the long term. Before that, it is important to understand the biodiversity and

abundance of macro invertebrates associated with the larval habitats of An. gambiae s.l. in different ecological environments for risk assessment purposes. It is in this context that this study proposes to inventory macro-invertebrates in mosquito breeding sites. From June 2021 to December 2022. The collection was carried out in two sites by monthly rentals at the level of the previously characterized cottages. Macro-invertebrates have been morphologically identified.Preliminary results show a total of 122 macro-invertebrates. The following species have been encountered: Lestidae, Bactidae, Corixidae, Dytiscidae, Gyrinidae, Hydrophilidae, Nepidae, Notonectidae, Physidae at both sites; Anisoptera, Belostomatidae, Haliplidae, Lestidae, Libellulidae, Lymnacidae, Naucoridae, Noteridae, Veliidae only in Ouassorola. The number varies according to the sites Ouassorola = 66%, Sogolombougou = 34% and over time. Notonectidae were most abundant in Sogolombougou (95%) and Noteridae was the most abundant species in Ouassorola, 97.94%. The rivers had the greatest diversity of macro-invertebrates compared to the other habitats studied (Brick Quarries, Footprints).

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FEASIBILITY AND COMMUNITY ACCEPTANCE OF INSECTICIDE TREATED EAVE NETS AND INSECTICIDE TREATED WINDOW SCREENS IN TANZANIA

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Long-lasting insecticidal nets (LLINs) and targeted indoor residual spray (IRS) are used extensively in Tanzania and have significantly reduced malaria mortality and morbidity across the country. However, malaria remains a public health concern, calling for the development of supplementary intervention tools. This study aimed to understand community perceptions on the installation of insecticide treated eave nets (ITENs) and windows screens (ITEWs) for full house screening against mosquitoes. Fourteen In-Depth Interviews (IDIs) with local carpenters who installed the intervention in 440 households and six Focus Group Discussions (FGDs) with community members in both the treatment (with intervention) and control (without) arms were conducted to gain understanding of feasibility and community perceptions of the intervention against malaria in three villages at Chalinze district in Tanzania. Only two carpenters reported to get nasal congestion and a headache after the working with the intervention on day 1 and related it to the chemicals on the netting. However, none of the community members experienced any adverse effects after the intervention was installed in their houses. Community members reported the intervention reduced mosquito abundance in their houses and also protected them from insects, lizards and snakes. Due to an observed reduction in malaria incidences in their households, some residents reported to stop sleeping under LLINs. A willingness to buy the netting if sold at an affordable price range of TZS 1000-6000 (≤ USD 2.50) per square meter was also expressed among community members. Community feasibility studies provide insights to barriers and facilitators to the adoption of new interventions tools. Therefore, appropriate social behavioral change communication strategies can be developed prior to deployment newer vector control tools to ensure synergy with existing interventions.

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COMBINING PYRETHROID-PIPERONYL BUTOXIDE (PBO) NETS WITH CLOTHIANIDIN-BASED INDOOR RESIDUAL SPRAYING IMPROVES CONTROL OF PYRETHROID-RESISTANT MALARIA VECTORS: AN EXPERIMENTAL HUT TRIAL IN SOUTHERN BENIN

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Coverage of pyrethroid-piperonyl butoxide (PBO) nets and indoor residual spraying (IRS) with the neonicotinoid insecticide clothianidin either as a solo-formulation or as a mixture with deltamethrin is being scaled up to improve control of malaria transmitted by pyrethroid-resistant mosquitoes. Most IRS campaigns are deployed against a background of moderate to high net coverage thus combined use of these tools is already an operational reality in many settings. However, no published trials have evaluated whether combining pyrethroid-PBO nets and clothianidin-based IRS would improve malaria control impact relative to use of either method alone. We performed experimental hut trials to evaluate the impact of combining different types of pyrethroid-PBO net with IRS formulations containing clothianidin both alone and as a mixture with deltamethrin against a pyrethroid-resistant vector population in southern Benin. We compared the impact of the combinations to each intervention alone and combinations with pyrethroid-only nets. The vector population at the hut site was susceptible to clothianidin but exhibited a high frequency and intensity of pyrethroid resistance that partially overcame by PBO pre-exposure. Mortality was significantly higher in huts combining pyrethroid-PBO nets with the clothianidin IRS solo-formulation (75%) and clothianidin-deltamethrin IRS mixture (77%) compared to those where pyrethroid-PBO nets (35–43%) and clothianidin-based IRS (42–48%) were applied alone. All combinations improved blood-feeding protection relative to the IRS alone but higher levels of blood-feeding inhibition were recorded with combinations containing pyrethroid-PBO nets compared to those containing pyrethroid-only nets (78–85% vs. 21–64%). Combining pyrethroid-PBO nets and clothianidin-based IRS shows potential to improve control of pyrethroid-resistant malaria vectors.

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LONG-ACTING FORMULATION OF IVERMECTIN FOR EFFECTIVE MALARIA CONTROL: INSIGHTS FROM AN AGE-STRUCTURED MODELLING STUDY

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Controlling malaria consists of either killing the parasite within the human host or reducing the vector population. These two approaches have allowed to decrease the number of deaths by almost 40% during the 2 past decades. However, a stagnation since 2015 followed by an increase in the last years, highlight the limits of available tools. One of the known limits is the vector tolerance to insecticides. A complementary approach is to render the vector's blood meal toxic by treating hosts with a drug that impairs mosquito survival. Ivermectin (IVM), an endectocide, has been proven to possess such ability. Several studies have modelled the impact of mass drug administration (MDA) of oral ivermectin to human populations and have evidenced a promising effect in reducing malaria clinical cases. However, the mosquitocidal effect of a single oral IVM dose (150-200 µg/kg) is relatively short-lived, requiring multiple mass distribution to significantly decrease malaria prevalence. An original model was developed to investigate the effects of a Long-Acting Injectable Formulation of Ivermectin (LAIF-I) on malaria transmission. This population model considers multiple continuous structural variables: humans age, time since infection, and time post-IVM administration for both humans and vectors. Such an approach

allows targeting a specific human class, e.g. by excluding children under five years and women of childbearing age. Furthermore, the time post-IVM was required to properly capture the longitudinal dynamics of both (i) IVM systemic concentrations in the human bloodstream, and (ii) IVM effects on mosquitoes' life span after a blood meal on LAIF-I -treated human. The long-lasting insecticide treated net coverage associated to different malaria transmission profiles were used as baselines to evaluate the added value of using LAIF-I in realistic life conditions. The detailed effect of the LAIF-I on the reduction of malaria prevalence will be presented during the conference.

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EXPLORATORY ANALYSIS OF THE EFFECTIVENESS OF INDOOR RESIDUAL SPRAYING WITH ACTELLIC 300CS AND FLUDORA FUSION TO REDUCE ENTOMOLOGICAL INDICATORS IN ALIBORI AND DONGA REGIONS, NORTHERN BENIN

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This study explores differences in the entomological indicators after Indoor Residual Spraying (IRS) with Actellic® 300CS (AC; pirimiphos-methyl) and Fludora® Fusion (FF; a deltamethrin-clothianidin mixture) in the Alibori and Donga Department of Benin. After the IRS campaigns with AC in 2019 and FF in 2020, respective monthly mosquito collections were performed over 10 months using both Human Landing Catches (HLCs) and Pyrethrum Spray Catches (PSCs) in Alibori and Donga, and adjacent untreated control areas (Bembèrèkè and Bassila). The Indoor Resting Density (IRD), the Human Biting Rate (HBR), Plasmodium falciparum Sporozoite Rate (SR), and the Entomological Inoculation Rate (EIR) of Anopheles gambiae s.l. were determined. The residual activity of AC and FF on the treated walls was also evaluated. A comparison of the indicators between IRS and control sites was done by calculating the percent reduction (Abbott's formula) and the P-value using poisson test function in R. Overall, the residual activity lasted 5 months for AC and 10 months for FF. The IRD was 0.30 An. gambiae s.l. per room (Ag/room) in AC-sprayed and 2.59 in control areas (Reduction [RD] = 88%, $p < 0.0001$), while the IRD was 0.92 Ag/room in FF-sprayed and 3.25 in control areas (RD = 72%, $p < 0.0001$); the HBR was 6.76 bites/person/night (b/p/n) in AC-sprayed and 19.93 b/p/n in control areas (RD = 66%, $p < 0.0001$), while the HBR was 18.33 b/p/n in FF-sprayed and 26.17 b/p/n in control areas (RD = 30%, $p < 0.0001$); the SR was 0.31% in AC-sprayed and 2.61% in control areas (RD=88%, p =0.0013), while the SR was 0.65% in FF-sprayed and 1.52% in control areas (RD = 61%, p = 0.0034); the EIR was 0.63 infectious bites person per month (ib/p/m) in AC-sprayed and 15.62 ib/p/m in control areas (RD = 96%, $p < 0.0001$), while the EIR was 3.52 ib/p/m in FF-sprayed and 12.00 ib/p/m in control areas (RD = 71%, p = 0.0019). When comparing sprayed and control areas, AC areas had a higher reduction in entomological indicators than FF. However, FF had longer residual activity than AC. More robust analyses and the use of epidemiological data are needed to compare these insecticides.

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MOLECULAR TECHNIQUE FOR THE DETECTION OF WOLBACHIA (WANGA-MALI) WITHIN ANOPHELES GAMBIAE SENSU LATO IN MALI

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Malaria is a major public health problem for sub-Saharan countries including Mali. The progress made in the fight against malaria through the use of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) is threatened by the emergence and progression of resistance of major vectors to commonly used insecticides, hence the need to develop new vector control methods such as the use of the endosymbiotic bacterium called Wolbachia.The aim of this work was to set up in Mali an efficient detection technique of Wolbachia within Anopheles gambiae s.l. as a prelude to the fight against malaria.This was an experimental study, carried out within ICER-Mali in the framework of a collaboration between the University of Science, Technology and Technology of Bamako (USTTB) and the National Institutes of Health of the United States of America (NIH). Mosquitoes were collected in Kenieroba by the "Spray Catch" insecticide spraying method in human dwellings. In order to obtain a good quality of mosquito DNA and the bacteria, two extraction methods were compared, namely the "old" Phenol-Chloroform extraction method and the "MasterPure" extraction kit. The molecular techniques used for the detection of Wolbachia was: quantitative PCR (qPCR) for the determination of the prevalence of Wolbachia in the An. gambiae s.l. population.The highest DNA concentrations and the lowest protein contamination were obtained with the MasterPure kit. This method was also the least toxic for the laboratory technician. The prevalence of Wolbachia infection was 45.16%. This prevalence was lower than previously reported. in the same locality in 2016 but who used a larger sample size. Our study showed that the Wolbachia wAnga-Mali strain of Wolbachia is still present in An. gambiae s.l. in the Kenieroba area, the prevalence of which may vary in time and space. The use of the Wolbachia bacterium remains a promising method in the eradication of malaria worldwide.

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ENDECTOCIDES TO COMPLEMENT THE MALARIA VECTOR CONTROL TOOLKIT: EXPECTED AND UNEXPECTED SIDE-EFFECTS OF IVERMECTIN ON MALARIA VECTORS

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Mass treatment of livestock and/or humans with ivermectin has been proposed as a complementary vector control strategy to combat malaria. However, this strategy requires repeated mass treatments to cover the high transmission period during the rainy season. To overcome this, a Long-Acting Ivermectin Formulation (LAIF) is currently under development and its potential to release mosquitocidal concentrations of ivermectin for more than a month is under evaluation as part of the IMPACT project. Although broader use of ivermectin can pose some anticipated challenges (i.e. potential environmental contamination and effects on non-target organisms, withdrawal times in livestock and implications for milk or meat production, risk of inducing resistance in livestock or human parasites), other side-effects such as the selection and spread of ivermectin resistance in malaria vectors through physiological or behavioral modifications appear to be less obvious. The aim of this review was to decipher how resistance to ivermectin could be selected in malaria vectors and propose a research agenda to study and manage this phenomenon if it appears. We used relevant terms to search databases including PubMed and Web of Science and included studies that describe mechanisms of resistance in arthropods. Results were summarized in terms of resistance mechanism. We also proposed a research agenda that integrates 1) the characterization of resistance and/or pyrethroid-ivermectin cross-resistance mechanisms, 2) the development of molecular and phenotypic assays to monitor ivermectin resistance in the field, 3) the study of potential behavioral changes vis-a-vis to ivermectin-treated subjects, and 4) the study of potential strategies to mitigate ivermectin resistance in mosquitoes. Anticipating the research on physiological or behavioral resistance to ivermectin in mosquitoes will facilitate the development of effective resistance-management plans and

enable preparedness for monitoring and evaluating this strategy after its implementation. Selection of Anopheles coluzzii resistant to ivermectin is in progress in our research team.

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ANOPHELES STEPHENSI IN TURKANA - PRELIMINARY FINDINGS ON THE LARVAL SURVEILLANCE IN TURKANA COUNTY, KENYA

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Anopheles stephensi has been identified by the WHO as a key threat to malaria control. Although endemic to Southeast Asia, it was detected in Djibouti in 2012 and has spread throughout the Horn of Africa. In 2020 it was detected in Nigeria. This invasive vector efficiently transmits both P. falciparum and P. vivax. Unlike other malaria vectors, An. stephensi thrives in urban settings where it can breed in manmade habitats such as tanks, tires and open sewers. In 2020, we established longitudinal larval surveillance in Lodwar, Turkana in the northwest corner of Kenya. We hypothesized that close proximity to Sudan and Ethiopia and the presence of a major transport route from the Horn into Kenya makes this region a likely environment for establishment of An. stephensi. We conducted bi-weekly surveillance in three types of sites - cisterns, river pans along the seasonal river and irrigation canals. Anopheline larval were collected, counted, and transferred to 95% ethanol for transport to the laboratory. Larvae were extracted in pools of 3 and tested by established molecular methods for An. gambiae, arabiensis, funestus and stephensi. In the first 5 months (March-July 2020), the selected sites were active in all collections. 557 larvae were tested by PCR and the major species was An. arabiensis (85%). The second surveillance period ran from November 2022 to March 2023. We collected a high number (2,387) of anopheline larvae across all sites in November-January. Out of 1483 larvae assayed, two pools from one site tested positive for An. stephensi. Larvae (5) from this site were sent for independent confirmation and sequencing at a partner laboratory. An. stephensi was a minority species in this river pan site which also hosted An. gambaie s.s. and arabiensis. Surveillance and testing are ongoing. The confirmation of An. stephensi in Kenya is critical information for malaria control efforts and underscores the need to expand vector surveillance even in parts of the country where malaria is epidemic/seasonal. The presence of An. stephensi could lead to increasing malaria transmission in northern Kenya, spreading further southwards to highly populated urban areas.

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IMPACT OF INDOOR RESIDUAL SPRAYING ON ENTOMOLOGICAL INDICES IN SAKASSOU, CENTRAL CÔTE D'IVOIRE

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Indoor residual spraying (IRS) is a major vector control strategy for malaria prevention. Entomological parameters such as indoor resting density (IRD), human biting rate (HBR), and entomological inoculation rate (EIR) were monitored in Sakassou (sprayed with clothianidin-based insecticide) and Beoumi (unsprayed district) to monitor changes due to three consecutive years of IRS in Côte d'Ivoire. After one year of baseline data collection in 2019, IRS was implemented in August 2020, August 2021, and May 2022 using clothianidin-based insecticides. Adult mosquitoes were collected monthly using human landing catches (HLCs) and pyrethrum spray catches (PSC) from January 2019 through December 2022. Mosquitoes collected were identified morphologically while sibling species were further analyzed using PCR. A subsample of the mosquitoes collected were analyzed for sporozoite infection using ELISA for estimating the EIRs. At baseline in Sakassou, the mean IRD was 15.5 females/room/day (f/r/d), the mean HBR was 296.8 bites/person/night (b/p/n) and the mean EIR was 4.9 infective bites per person per night (ib/p/n). After three years of IRS the mean IRD, the mean HBR and the mean EIR decreased significantly to 5.8 f/r/d (p=0.0003), 142.6 b/p/n (p=0.0002) and 0.919 ib/p/n (p=0.0022), respectively. At baseline in Beoumi, the IRD was 3.8 f/r/d, the HBR was 35.5 b/p/n and the EIR was 0.61 ib/p/n at the baseline collection. After three years, there was a reduction of the IRD (2.2 f/r/d; p=0.0954), the HBR (24.9 b/p/n; p=0.5483) and the EIR (0.474; p=0.6776), but the differences were not statistically significant. Although Sakassou had higher vector density than Beoumi, the relative reduction of malaria entomological indicators post-IRS following three years of IRS was significant. These decreases in malaria transmission are consistent with preliminary findings on malaria case reductions after the 2020 and 2021 IRS campaigns, indicating that IRS was effective in Côte d'Ivoire.

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IS THE UK PREPARED FOR A MOSQUITO-BORNE DISEASE EMERGENCE? A PROTOCOL FOR FIELD WORK

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In 2021, risks to health from vector-borne diseases were highlighted as an area requiring more action in the 3rd UK Climate Change Risk Assessment Technical Report. Currently, cases of mosquito-borne diseases (MBDs) are typically imported to the UK but there is a risk of arbovirus transmission from a number of vector-competent mosquitoes indigenous to the continent, as well as from an increasing number of invasive species establishing in Europe. A "mosquito watch" programme between the UK Health Security Agency (UKHSA) Medical Entomology team and the Chartered Institute of Environmental Health (CIEH) currently provides a portal for environmental health officers (EHOs) to submit samples to UKHSA and partners for identification of species. UKHSA also conduct a range of enhanced surveillance strategies for invasive mosquitoes in the UK at points of entry. The aims of this study are to i) identify current awareness, risk perception and engagement in local authorities, in England, ii) understand more about perceptions on the drivers of MBD and barriers to effective preparedness and iii) determine how they have changed over time. Current surveys distributed to EHOs have been carried out by the UKHSA every 10 years since the 1970s across 374 local authorities and include information on nuisance biting complaints, potential habitats for mosquitoes, local capabilities to control mosquitoes etc to determine two key aspects: experience with mosquitoes and mosquito control preparedness. For this study, additional scenario-specific questions related to potential Aedes albopictus incursions will be added to this survey, for the EHOs based in South-East England and the Greater London Regions, as previous research has forecasted those two regions as hotspots within England. This research will help determine the best survey tools that can be implemented more frequently, in more areas, to prepare for the risk of MBD emergence which is increasing with climate change on a global scale.

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DETERMINING IMPACT OF DENGUE VIRUS INFECTION IN PREGNANCY ON MATERNAL AND CHILD OUTCOMES

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Dengue virus (DENV) is the most common arbovirus globally, with estimated 400 million infections yearly. Dengue in pregnancy has been associated with adverse maternal and neonatal health outcomes including preterm birth, low birth weight and miscarriage. Despite the abundance of literature for DENV in pregnancy, few studies examine this issue in Africa. In this study, we utilized IgG ELISA to identify DENV exposure (seronegative at antenatal visits and seropositive for anti-DENV IgG at delivery) and characterize the epidemiological burden of DENV among a Kenyan cohort of pregnant women. Seroconverted mothers were also tested by PCR to identify timing of DENV exposure and then assessed by logistic regression for any associations between DENV exposure and adverse maternal and/or infant health outcomes. At birth, neonatal development outcomes were assessed and children were followed every 6 months. The studied cohort comprised 454 pregnant women initially part of a 749-maternal child cohort followed for parasitic infections. Median maternal age was 25, primary delivery mode was vaginal (95%), and mean birth weight was 2,991 grams. The cohort experienced significant maternal and neonatal morbidity: one maternal death, 74% of women with anemia at delivery, 75% of women with parasitic infection during pregnancy, 20% preterm birth and 2% stillbirth. Using community-based estimates from our prior work, we expected approximately 18 women to have gestational DENV exposure; however 35 mothers (7.7%) seroconverted during their pregnancy, indicating nearly twice the expected burden of DENV for this vulnerable population. Using Fisher's Exact test, comparisons of DENV+ and DENV- mothers found no association between seroconversion and: Caesarian birth (5.7% vs 4.7%,p=0.68), adverse birth outcomes [Ex: stillbirth, maternal death, intrapartum fever] (0% vs 5.3%, p=0.62), or preterm birth (21% vs 20%, p=0.84). Although it was found that adverse fetal outcomes had no association with seroconversion, next steps are to complete assessments of fetal developmental outcomes, such as APGAR score, to better understand the burden of DENV in pregnancy.

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YELLOW FEVER VACCINATION COVERAGE IN ARID AREAS OF KENYA AN ASSESSMENT FOLLOWING OUTBREAK, 2022

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Kenya reported a Yellow Fever (YF) outbreak in the arid pastoral counties in March 2022 following the confirmation of three cases. A reactive vaccination campaign conducted had a coverage of 52% in Garissa and 58% in Isiolo. However, the precise estimated coverage had not been determined. We sought to estimate vaccination coverage and evaluate strategies used in the campaign. We used the WHO-recommended strategies to conduct a cross-sectional population-based survey involving residents aged 9 months to 60 years. We used a multi-stage proportionate-to-size cluster sampling to determine the number of clusters and randomly selected 7 households per cluster. Data were collected using semi-structured questionnaires and analyzed using descriptive statistics. We visited 118 clusters and 818 households with 5187 eligible participants, of whom 76% (4020/5187) had been vaccinated during the campaign. Participants available for interview were 45% (2355/5187), among whom 81% (1927/2355) had been vaccinated, 60% (1419/2355) were female, and 28% (650/2355) were children aged 1–5years. Garissa county had a coverage of 77% (1093/1412), with 58% (818/1412) having the YF card. Isiolo county had a coverage of 89% (834/943), with 59% (555/943) having the YF card. Respondents who were vaccinated from mobile points were 88% (1696/1927). Community Health volunteers (CHVs) 55% (597/1090), Healthcare workers 56% (615/1090) and religious leaders 16% (170/1090) had the most influence on respondents taking the YF vaccine. Respondents who were aware of the YF campaign were 80% (1886/1927), with CHVs 48% (1135/2355), mobilizer/criers 23% (545/2355) and radios 13% (301/2355) providing the most information on the YF campaign. The respondents who experienced adverse events following immunization were 5% (102/1927). Garissa's overall coverage was below the desired threshold of 80%. CHVs and mobile vaccination points were integral in the vaccination campaign. The use of mobile vaccination points should be adopted in arid-pastoral areas.

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ASSESSING ENTOMOLOGICAL IMPACT OF A LARVAL SOURCE MANAGEMENT PILOT USING AERIAL SPRAYING OF RICE FIELDS WITH DRONES IN TWO DISTRICTS OF MADAGASCAR

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As a complementary vector control intervention in Madagascar, the PMI VectorLink project and National Malaria Control Program conducted a larval source management pilot via drone in 17 fokontany of two mapped districts with high malaria incidence (144/1,000 in Morombe, 120/1,000 in Ankazobe in 2020) and abundant rice fields that are common larval habitats. The intervention occurred during the short rainy season, from February to July 2022, with Bacillus thuringiensis israelensis (Bti) larvicide twice per month (10 spray cycles).To assess the entomological impact of the intervention, larval collections, insecticide susceptibility bioassays, and adult mosquito collections were conducted before, during and after spraying in six sites per district. Bioassays using a range of Bti dilutions demonstrated larval susceptibility, with mortality above 80% after 24h at a dose of 0.07g (1/14 of larval habitat solution sample) and 0.05g (1/20). Larval density decreased by 96% and 97% in Morombe and Ankazobe, respectively, one day post spray. However, recolonization of larval habitats was observed one month after spraying ended with an increase from an average of 0.4 larvae/liter (l/L) one day post spray to 4.6 l/L in Morombe, and from 0.6 l/L to 2.6 l/L in Ankazobe. A reduction in mosquito biting rate was recorded in all sprayed sites compared to baseline. In Morombe, the Anopheles gambiae s.l. human biting rate decreased from 6.3 bites per person per night (b/p/n) at baseline to 1.3 b/p/n indoors, and from 8.4 b/p/n outdoors to 2.6 b/p/n after 10 spray cycles, but then increased one month after spraying stopped to 5.1 b/p/n and 6.4 b/p/n indoors and outdoors, respectively. In Ankazobe, the biting rate significantly decreased through the end of the spraying cycles from 2.1 b/p/n at baseline to 0.3 b/p/n after 10 spray cycles indoors and 2.4 b/p/n to 0.3 b/p/n outdoors, but then increased to 0.5 b/p/n and 0.9 b/p/n indoors and outdoors, respectively, one-month post-spray. This study suggests that biweekly spraying in rice fields reduced larval density and human biting rates and could be beneficial in areas with outdoor biting and seasonal malaria transmission.

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DETECTION OF ANTIBODIES AGAINST SALIVARY PROTEINS OF AEDES ALBOPICTUS AND CULEX QUINQUEFASCIATUS IN NORTHERN CARDINALS IN LOUISIANA

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West Nile virus (WNV) is a mosquito-borne pathogen primarily transmitted by Culex mosquitoes. Since the emergence of WNV in the US in 1999, detecting infection in birds and mosquitoes have become the primary surveillance tools used as precursors for human infection and neuroinvasive disease incidence. WNV is normally transmitted between birds and mosquitoes in the environment; and humans are considered dead end hosts. WNV is transmitted to a vertebrate host through the bite of an infected mosquito during blood feeding. In this process, mosquitoes deposit salivary proteins that elicit antibody responses; previous studies have established that the concentration of such antibodies is directly related to the intensity of exposure to mosquito bites and a good proxy to determine risk of infection in the human population. Since WNV infection in birds has also been used to determine risk of transmission in some areas, we tested the levels of IgY antibodies against whole salivary glands of Aedes albopictus and Cx. quinquefaciatus in more than 700 Northern Cardinals captured via mist nets in Louisiana between 2018 and 2019. Our preliminary data (n=169) showed a significant negative correlation between the sample collection date and the IgY antibody levels against Ae. albopictus in younger hatch year Northern Cardinals (p=0.0375). This correlation was not shown in older after hatch year birds. We did not find significant difference in the antibody levels between males or females from any of the locations. In general, higher levels of antibodies against Ae. albopictus were observed in comparison to Cx. quinquefasciatus. We will discuss the proteins that were identified by immunoblot as the most immunogenic in these two different sets of samples. We are working towards designing new tools to track bird exposure to infective bites to effectively measure risk of WNV transmission.

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ENTOMOLOGICAL SURVEILLANCE STRENGTHENING IN INDIA: MEETING THE CHALLENGES

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India has varying degree of challenges in entomological surveillance and vector control due to six major VBDs, multiple vector's influence and different eco-geographical zones. The core vector control measures include adult mosquito control through Indoor Residual Spraying, Long Lasting Insecticidal Nets and Larval Source Management for urban areas. The technical guidance to implement the VBD programme is based on knowledge on vectors and bionomics. National Programme established 72 entomological zones in 1977 to do entomological monitoring after massive resurgence of malaria in 1976. India has targeted for elimination of Malaria, Visceral leishmaniasis and Lymphatic Filariasis. During elimination phase, entomological monitoring becomes paramount to sustain the vector control impact and prevent re-establishment Shortage of entomologists are the major challenge in entomological monitoring which is highly skilled job. Though efforts have been made to bridge the gap by providing consultants and increasing number of Entomological Zones, high level advocacy is required to fill all sanctioned positions and support by development partners. Gates Foundation is supporting through integrated entomological surveillance in a few areas. Global funds also supporting by provisioning contractual entomologists. Insecticide resistance monitoring and operational research for programme are supported by two premier national institutions viz., NCDC, ICMR and WHO.

5949

EVALUATION OF SPATIAL REPELLENT PRODUCTS AGAINST MALARIA VECTOR SPECIES IN PAPUA NEW GUINEA

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Malaria remains one of the most common and deadly diseases within tropical and sub-tropical countries with an estimated 229 million cases recorded by 2019 across 87 malaria-endemic countries. Papua New Guinea (PNG) accounts for about 80% of the malaria burden recorded within the Western Pacific region and controls vector populations through nationwide long-lasting insecticide treated bednets (LLINs). Early and outdoor biting behavior of vector species and the evidence of substandard LLIN products in PNG compromises the effectiveness of LLINs against the local vector populations. This study explores the potential of alternative vector control tools (VCTs) to complement LLINs and improve the effectiveness of malaria control within the country. A promising VCT are spatial emanators (SE), devices that passively emit insecticide volatiles to provide a protective space for users. This tool has the potential to be used both indoors to complement LLINs, and outdoors, particularly in the peridomestic space. This study aims to evaluate the efficacy of SE products against the Anopheles punctulatus group of mosquitoes in Papua New Guinea under laboratory and semi-field conditions. Secondly, it aims to understand the effects that sublethal exposure to insecticides may have on the local vector populations. Finally, this study aims to assess the feasibility, cost-effectiveness and impact on malaria transmission in a small-scale field study in two malaria-endemic villages in PNG. We will present data on the effectiveness of SEs against malaria vectors in PNG and explore the impacts of SE and spatial repellent insecticides against mosquito landing rates, feeding inhibition and the impacts of sublethal exposure to the local malaria vector species. Finally, we will discuss the effectiveness of SE in a proof of concept field trial that will guide the national malaria control program in consideration of SE products as malaria VCT for future control programmes in PNG.

5950

NON-INFERIORITY EVALUATION OF PERMANET® DUAL TO INTERCEPTOR® G2 AND SUPERIORITY TO PERMANET® 3.0 AT THE 'DALA SUNA' EXPERIMENTAL HUTS IN SIAYA, KENYA

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The rise and spread of insecticide resistance threatens the gains already made in malaria control particularly with long-lasting insecticidal nets (LLINs). The development and evaluation of new generation LLINs is therefore critical in ensuring the constant supply of effective products. This study evaluated the non-inferiority of Permanet Dual against Interceptor G2 (IG2) and the superiority of Permanet Dual (PD) against PermaNet 3.0 (PN3.0) on mortality and blood feeding inhibition. The trial was conducted

at the 'Dala Suna' experimental huts located on the shores of Lake Kanyaboli, Siaya County, western Kenya. The study followed a 7 by 7 Latin square design with treatments employed as unwashed and 20 times washed. Each hut had sleepers daily. Mosquitoes were collected from the huts every morning and categorized based on collection site as roof, wall, net under bed, floor and window exit traps. The mosquito samples from experimental huts were monitored for immediate knockdown and delayed mortality after 24hours, 48hours and 72hours. This study was carried out in an area with high vectors' resistance to pyrethroids. Only An. funestus was used for the experimental hut evaluation due to high densities during the study period. A total of 15144 An. funestus mosquitoes were collected from the experimental huts over the 7 weeks' study period. Mortality at 72 hours was 37% for control net, and higher in the LLINs (washed and unwashed), at 56% for PermaNet 3.0, 66% & 64% for IG2 and 67% & 68% for PD. Blood feeding inhibition was highest with PN3.0 at 33% and 49% unwashed and 20 times washed respectively, and least with PD, at 3% and 12% unwashed and 20 times washed nets, respectively. PD and IG2 had differences in mortality with odds ratio of 1.096 at lower 95% CI: 1.001 – 1.199 and blood feeding odds ratio of 1.176 at upper 95% CI: 1.037 - 1.334. Additionally, PD was found to be superior to PN3.0 on mortality with an odds ratio of 1.805 at 95% CI: 1.654 - 1.969, and inferior in blood feeding, with odds ratio of 1.627 at 95% CI: 1.425 - 1.856. In conclusion, PD was found to be non-inferior to IG2 and inferior to PN3.0 LLINS following WHO efficacy criteria.

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RESIDUAL BIO-EFFICACY OF ATTRACTIVE TARGETED SUGAR BAIT STATIONS TARGETING MALARIA VECTORS DURING SEASONAL DEPLOYMENT IN WESTERN PROVINCE, ZAMBIA

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The primary vector control interventions in Zambia are long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS). Challenges with these interventions includes insecticide resistance and the outdoor biting and resting behaviors of many Anopheles mosquitoes. Therefore, new vector control tools targeting additional mosquito behaviors are needed to interrupt transmission. Attractive Targeted Sugar Bait (ATSB) stations, which exploit the sugar feeding behaviors of mosquitoes may help in this role. This study was conducted to evaluate the residual laboratory bio-efficacy of Westham prototype ATSB stations deployed in communities throughout a 7-month deployment in Western Province, Zambia during the first year of a large cluster randomized phase-III trial (Clinical Trials.gov Identifier: NCT04800055). One undamaged bait stations that had been installed on outside walls of households were collected on a monthly (one per cluster per month) basis from each of twelve randomly selected intervention clusters among the 35 trial interventions clusters. Bioassays utilized mosquitoes from a laboratory reared colony of An. gambiaes.s.s, male and female mosquitoes, from December 2021 to June 2022 (rainy to dry season). In total, the study utilized 71 field deployed ATSB stations plus 12 new ATSB stations for comparability purposes. Field deployed ATSB stations had significant lower bio-efficacy than ATSB stations which had never been deployed in the field, but the field-deployed stations retained high levels of bio-efficacy mortality (over 80%) after more than six months in the field. Duration of deployment was also not associated with lower bio-efficacy. There was relatively little variation in mortality between month rounds for those ATSB stations which had been deployed to the field. Westham prototype ATSB stations can retain bio-efficacy even after deployment in the field for 7 months, provided they do not meet predetermined criteria for replacement.

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IMPACT OF VOLATILE PYRETHROID SPATIAL REPELLANT ON THE ABUNDANCE OF OUTDOOR BITING ANOPHELINES IN A LOW MALARIA TRANSMISSION SETTING, SOUTHERN ZAMBIA

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Residual transmission in the catchment area of Macha Hospital, Southern Province, Zambia, is attributed to outdoor exposure to malaria vectors - spaces and times where indoor interventions are not as effective. This study aimed at evaluating the entomological impact of a volatile pyrethroid spatial repellant (VPSR) product for peri-domestic use (outdoor kitchens) in a semi-field-system (SFS) and in village structures. The transfluthrin-based VPSR tool enables spatial protection against host-seeking mosquitoes. The two phases of this study included 1) a SFS study utilizing replica outdoor kitchens. Here, two VPSR devices were hung from the eaves of each SFS- structure. Release-recapture (using human landing catches (HLCs) experiments enabled the evaluation of the impact of the VPSR device on laboratory reared Anopheles gambiae s.s. Additional secondary endpoints for mortality and reproduction were also collected. 2) a field study conducted in the Macha region during the transmission season. Forty households were selected from two villages for the study. HLCs in VPSR treated and untreated kitchens were conducted to assess the impact on human landing. SFS and filed results demonstrated a significant reduction (40-60%) of mosquito numbers entering VPSR-treated structures. In addition to a reduction in landing, there were also mortality and reduction of fitness impacts with mosquitoes exposed to the VPSR. In conclusion, this study demonstrates that VPSR can reduce the exposure of humans to vectors in both (SFS) and field (village) structures, with additional evidence for community impact through mortality and other impacts seen in transfluthrin-exposed mosquitoes. VPSRs are a potential gap filler as an alternative outdoor malaria intervention.

5953

EXPERIMENTAL HUT AND FIELD EVALUATIONS OF THE THERMACELL® BASED METOFLUTHRIN SPATIAL REPELLENT AGAINST PYRETHROID RESISTANT ANOPHELES FUNESTUS IN SIAYA, WESTERN KENYA

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Spatial repellents (SR) are undergoing epidemiological evaluations with the aim of complementing current vector control tools This study conducted experimental hut and small-scale field trials to evaluate the protective efficacy of Thermacell® based metofluthrin SR against pyrethroid resistant Anopheles funestus in Siaya County, western, Kenya. Phase 1 of the study was conducted in the "Dala Suna" experimental huts located around Lake Kanyaboli, Siaya County, Kenya. The SR product emanator included a cartridge containing metofluthrin attached to liquefied petroleum gas (LPG) cylinder and included two experiments: one to evaluate whether fire from the LPG cylinder increased mosquito density indoors and the second to evaluate the effect of 2, 4 and 12-hour emanation periods had on indoor density and biting rates. Experiment 2 was further modified to include an hour's emanation between 0500-0600HRS the next morning. The second phase: was a field evaluation of an outdoor emanation of the SR product using human landing catches outdoors with volunteers sitting at 5ft,

10ft and 20ft from the emanator. Measured outcomes were deterrence, percentage feeding inhibition, mortality and mosquito landing rates. The SR had an 87.7% deterrence rate and knockdown of 95.5% of Anopheles funestus coming into the huts. Cooking with LPG cooker increased mosquito densities indoors by 52.2%. The 12-hour emanation period reduced Anopheles landing rate indoor by 99.3%. Using 5ft as reference, outdoor mean hourly biting rate were significantly lower than at 20ft (0.33 RR = 9.766(5.351-17.822) P<0.001) but were not significantly different from 10ft (0.025 RR=0.79 (0.349-1.79) P=0.573). SRs almost completely blocked biting indoors and led to 10X lower biting rates within 10ft of the emanator outdoors, the first product to demonstrate such potential. The use of LPG in house could increase exposure to Anopheles mosquito bites.

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APPLICATION OF VECTOR CONTROL OPTIMIZATION MODEL ON EAVE RIBBONS FOR MALARIA VECTOR CONTROL IN KILOMBERO VALLEY, TANZANIA

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Despite significant progress against malaria, the use of two core interventions, namely insecticide-treated nets (ITNs) and indoor residual spraying (IRS), are becoming increasingly vulnerable due to insecticide resistance and outdoor biting by mosquitoes. One representative example is Kilombero Valley in Tanzania where transmission continues despite over 80% of the population using ITNs. Further progress in this and similar African settings will require identifying which supplementary tools combine most effectively with ITNs to reduce mosquito exposure. Using the Kilombero Valley as a case study, the Vector Control Optimization Model (VCOM) was adapted and extended to simulate the impact of adding eave ribbons treated with spatial repellent (ER) as supplementary intervention in an area of high ITN coverage. Simulation was conducted to assess the impact of varying coverage of this supplementary intervention on the entomological inoculation rates (EIR) generated by two common vectors in Kilombero, Anopheles arabiensis and Anopheles funestus. Finally, the impact of introducing this intervention on the combined EIR from An. arabiensis and An. funestus was assessed to identify scenarios in which values fell below 1; the likely threshold required for malaria interruption. ER was predicted to substantially reduce the EIR in Kilombero valley when combined with 80% ITN coverage. However, the nature of the impact varied notably between vector species. ER was predicted to have a much larger effect on transmission mediated by An. funestus than An. arabiensis. Additionally, in the situation where EIR from both An. arabiensis and An. funestus was combined, substantial coverage of this supplementary intervention was predicted to lower EIR to below one. Despite the significant impact ER in combination with ITNs on one of the two vectors (An. funestus or An. arabiensis), this intervention is insufficient when combined with ITNs to reduce the EIR to below one in settings like Kilombero Valley where both species contribute to malaria transmission.

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COMMUNITY-BASED BIOLARVICIDING FOR MALARIA CONTROL IN TANGA REGION, TANZANIA

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Malaria remains a disease of public health importance globally. Prevalence of malaria in Tanzania among under-fives is 8.1% (MIS 2022) and the country accounted for approximately 3% of all malaria cases in 2021 (WHO – World Malaria Report). The country is deploying community-based biolarviciding in enhancing its efforts towards malaria control. Tanzania is conducting routine implementation of biolarviciding in three councils: Handeni DC, Tanga CC and Lushoto DC, representing 'high', 'moderate' and 'low' malaria risk strata respectively as well as representing both urban and rural settings. Implementation follows a community-based approach whereby trained community-owned resource persons (CORPs) identify the habitats and apply biolarvicide at the ground level. Officers at the village/street, ward, council and regional levels using existing local government structures supervise CORPs. The country is using two biolarvicide products produced in-country: Bacillus thuringiensis var. israelensis (Bti) and Bacillus sphaericus (Bs). Biolarvicide is applied to all identified breeding habitats for three rounds per year based on rainfall pattern. Each round comprises of eight weekly cycles of larvae monitoring and application of biolarvicide. The councils collected baseline data in February 2022 for four consecutive weeks. Handeni DC, Lushoto DC and Tanga CC had 12,203, 2,126 and 1,005 breeding habitats respectively. Handeni DC reported an average of 233,515 anopheles larvae per week, while Lushoto DC and Tanga CC reported 79,528 and 3,520 respectively. Two rounds of application have been completed: Jun-Jul 22 and Oct-Nov 22. Handeni DC showed anopheline larval reduction of 99.9% and 96.1% across the eight weeks of application between rounds 1 and 2 respectively. Lushoto DC reported a reduction of 97.2% and 98.5%, while Tanga CC reported a reduction of 84.4% and 89.6%. Programmatic monitoring highlights that biolarviciding reduces anopheline larval in all three councils. Next steps include conducting entomological and epidemiological evaluation to determine the impact of the intervention.

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PILOT STUDY OF BACILLUS THURINGIENSIS ISRAELENSIS IN THE CONTROL OF PERSISTENT DRY SEASON BREEDING MALARIA VECTORS IN MALI

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One of the challenges to malaria elimination is residual malaria transmission. The concept of "residual malaria" expresses the contribution of other factors to the persistence of malaria transmission. Larval control has been poorly applied in African settings because of the huge number and type of larval habitats encountered. However, riverbeds constitute hot spots for maintaining malaria transmission throughout the long dry seasons in Sahelian West African countries with fewer numbers of larval habitats. In this study, we are pilot testing the biological larvicide Bacillus thuringiensis (Vectobac WG®) in malaria vector control along the River Niger during the dry season in Mali. An active search for major larval habitats was conducted during the dry season in localities along the Niger River. In total, 45 main larval habitats, including water pools, puddles, and brick pits were identified and treated with Bti. Just before treatment, the mean larval density was estimated through the standard WHO deepening technique. The mean number of larvae was 22.4 larvae per dip (SD = 32.75, 95% CI = 12.58—32.26). Using the same method 24 hours after treatment, we could not detect the presence of any larvae in all the identified larval habitats. This is except for a mixed Culex sp and Anopheline larval habitat, where the mortality rate was 97%. 48 hours after treatment, this larval habitat became negative. As a result of this trial, Bti has been shown to be effective in reducing larval density in residual riverbed transmission areas in sub-Saharan Africa.

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CHARACTERIZATION OF THE PUTATIVE ANOPHELES FUNESTUS-CYP18A1 ORTHOLOG IN ANOPHELES GAMBIAE

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New targets for vector control are needed to reduce malaria transmission due to the spreading of insecticide resistance. In Anopheles gambiae, a likely candidate for genetic control is the 20-hydroxyecdysone (20E) hormone. Two genes CYP314A1 and CYP18A1 regulate respectively the activation and deactivation of the 20E. Although, CYP314A1 is conserved in all mosquitoes species, CYP18A1 is absent in An. gambiae genome. This work used in silico and an experimental approaches to characterize the putative 20E deactivating enzyme coding gene (Anopheles funestus-CYP18A1 ortholog) in Anopheles gambiae. Basic bioinformatics analyses were done to identify Af-CYP18A1 candidate ortholog in An. gambiae genome. To validate the ortholog, molecular docking was performed to compare the binding affinity of 20E to the candidate gene product in An. gambiae and to Af-cyp18A1 protein. The 20E deactivating ability of the candidate gene product in An. gambiae, was evaluated through loss of function experiment using RNA interference system. Two days old females of An. gambiae COGS colony were blood fed and injected with 138 nL of dsRNA+20E. 72 hours post blood meal, 20E titres was measured by High Liquid Chromatography (HPLC). Bioinformatics analyses revealed the CYP306A1 (AGAP004665) as the putative Af-CYP18A1 ortholog in An. gambiae with 54% and 32% protein sequence similarity and identity respectively. The 20E interaction (docking) showed an hydrogen bond between 20E carbon C3 and the Agap-cyp306A1 residue VAL321. While no 20E titre could be detected in control mosquitoes injected with the dsGFP at 72PBM, HPLC analyses showed that An. gambiae females were not able to successfully metabolize the injected 20E when the expression of the CYP306A1 was silenced. The findings of this study are preliminary results suggesting that CYP306A1 could be the Af-CYP18A1 ortholog in An. gambiae. Further investigations are needed to fully characterize the functional role of this candidate gene in 20E deactivation.

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TRANSCRIPTOME-WIDE DISCOVERY AND QUANTIFICATION OF LNCRNA EXPRESSION IN VARIOUS CONTEXTS IN THE MALARIA MOSQUITO ANOPHELES GAMBIAE FROM RNA-SEQ DATASETS

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Long non-coding RNAs (lncRNAs) are a class of RNA transcripts longer than 200 nucleotides that cannot code for canonical proteins but play various roles in biological contexts. Despite being recognized in mosquito Anopheles gambiae, comprehensive profiling and characterization of lncRNAs remain limited. This study presents a transcript discovery pipeline to identify lncRNA transcripts from RNA-seq datasets in public domains. First, RNAseq reads are mapped against the An. gambiae PEST genome reference using parameters allowing(intron spanning alignment. Then, transcripts from the resulting read mappings are inferred. To identify lncRNAs, non-mRNA transcripts are filtered by the following parameters: a minimum of 10 reads, relative confidence of >10%, a minimum length of 200 nucleotides, and no protein-coding potential. Transcripts that meet these criteria are considered putative lncRNAs. Notably, up to 30% of RNAseq reads are non-mRNA reads. The pipeline predicted thousands of putative lncRNAs. We validated 5 predicted lncRNAs using RT-PCR. The predicted lncRNAs are integrated into the existing transcript annotation to enable simultaneous quantification of mRNA and lncRNA abundance. The lncRNAs identified from different transcriptomes can be merged to update lncRNA annotations. We applied the pipeline to RNAseq datasets in different conditions, such as immune responses to bacterial and Plasmodium challenges and hemocytes, midgut, salivary gland, and whole body. In the datasets of different hemocytes upon bacterial challenges, principal coordinates analysis (PCA) revealed mRNA and lncRNA co-expression patterns. In the dataset that profiled polysome-associated transcripts in the midgut infected with P. falciparum, some lncRNAs demonstrated a differential association with polysomes between the infection and control samples, suggesting that some lncRNAs may encode micropeptides, and/or play roles in regulating protein translation. Our pipeline facilitates lncRNA discovery and quantification to enhance our understanding of transcriptomic response in different contexts.

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ENDOGENOUS NON-RETROVIRAL RNA VIRUS ELEMENTS IN ANOPHELES DARLINGI

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The rise of metavirome research has positioned insects as important virus reservoirs, mainly dominated by insect-specific RNA viruses (ISV). The discovery of the ISVs and the sequencing of a variety of genomes have allowed the identification of RNA virus sequences integrated into genomes denominated non-retroviral endogenous viral elements (nrEVEs). This work aimed to identify nrEVEs in the Anopheles darlingi reference genome (idAnoDarlMG_H_01) and RNA-seq data obtained from An. darlingi natural populations of three regions of Colombia. A database was built with all virus sequences identified in arthropods available in the NCBI-virus repository and a tBLASTn was performed against the An. darlingi reference genome. The detection of nrEVEs in the An. darlingi transcriptome was performed by mapping the RNA-seq reads on the nrEVEs identified in the reference genome; additionally, contigs assembled from RNA-seq data were aligned against nrEVEs. As a result, 44 nrEVEs of negative-strand RNA viruses (ssRNA-) of the families Rhabdoviridae (n= 22), Chuviridae (n= 11) and Phasmaviridae (n= 3) and double-stranded RNA virus (dsRNA) of the families Partitiviridae (n= 6) and Reoviridae (n= 1) were identified in the An. darlingi genome. Thirty-four nrEVEs were detected on chromosome 3, eight on chromosome 2 and two on chromosome X. A differential nrEVE read count was observed in the Colombian An. darlingi metatranscriptomic data. Finally, the multiple alignment showed an identity greater than 98% in three of the sequences assembled from the metatranscriptome against the nrEVEs identified in the reference genome. Knowledge of the presence and expression of nrEVEs in An. darligi contributes to elucidating the dynamics of the Anopheles virome and its endogenization in the genome. Future studies may explore possible antiviral mechanisms associated with the nrEVEs identified.

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ANALYSIS OF THE GENETIC VARIATION OF THE FRUITLESS GENE WITHIN THE ANOPHELES GAMBIAE (DIPTERA: CULICIDAE) COMPLEX POPULATIONS IN AFRICA

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One promising strategy for genetic control is to reduce the reproductive potential of disease vectors or pests by targeting genes involved in sexual determinism. However, targeting these genes requires a better understanding of their polymorphism in natural populations to ensure good stability and persistence of the transgene in nature. The genomic data of Anopheles gambiae s.l. used in our study were sequenced by the An. gambiae 1000 Genomes (Ag1000G) project in which the Institut de Recherche en Sciences de la Santé is partner. We used Jupyter notebooks to analyze the genetic variation and conservation score of the fruitless gene

in 18 populations across Africa. A total of 34339 SNPs were identified including 3.11% [1071 SNPs] of non-synonymous polymorphic sites. The overall nucleotide diversity of the gene was low (0.0036) and the Tajima neutrality test (-2.52) was negative indicating an excess of low frequency SNPs. Allelic frequencies of non-synonymous mutations were low except for SNPs at position X: 1309218 (C>G) and X: 1300290 (C>G) that were identified at high frequencies (0.8 - 1) in all populations. The conservation score was variable throughout the fruitless gene with maximum values in the exonic regions compared to the intronic regions. These results would be a good indicator for the spread and persistence of a transgene targeting the fruitless gene in wild populations of An. gambiae s.l.

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UNRAVELLING THE GENOMIC AND PHENOTYPIC DIVERGENCE WITHIN SUB-POPULATIONS OF TWO MAJOR MALARIA VECTORS: ANOPHELES GAMBIAE AND AN. COLUZZII

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Although a significant reduction in malaria incidence over the decades, this mosquito-borne disease remains a major public health concern. The use of insecticides is a cornerstone in malaria vector control, but widespread insecticide resistance coupled to increasing drug resistance and high costs of implementation, is jeopardizing the efficacy of this strategy making malaria resurgence a grim reality. New strategies with novel tools that complement LLINs and IRS to target the major vectors could prevent the resurgence of disease and hasten malaria elimination. Despite the central role of oviposition preference in selecting suitable environments in blood-feeding insects, its contribution to ecological specialization and local adaptation remains elusive. Population studies at early stages or ecological/genetic divergence provide an excellent opportunity to assess the role of oviposition preference in local adaptation of mosquitoes. Combining laboratory dual choice experiments and whole genome sequencing, we conducted the first assessment of phenotypic variation among some of the subpopulations of two major malaria vectors that are emerging along gradients of anthropogenic disturbance in sub-Saharan Africa. When offered choice, Anopheles gambiae gravid females released individually in cages under standard conditions, lay eggs almost exclusively in water collected from their locality of origin while An. coluzzii mosquitoes did not show any preference. This extreme source-specialization prevails in populations belonging to the same ecological biome and displaying very low levels of genome-wide divergence. Interestingly, An. gambiae females maintained in laboratory conditions for several generations using regular water retained water discrimination and were able to choose between source water and exogenous water. We conclude that favourable aquatic oviposition sites though highly heterogeneous in form, space and time are strong enough to drive ecological specialization in the presence of extensive gene flow in mosquitoes and act as signature cues at early stages of divergence in gravid Anopheles mosquitoes seeking to lay.

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IDENTIFICATION OF SEX-SPECIFIC PATTERN OF THE DOUBLESEX GENE IN THE MOSQUITO CULEX PIPIENS

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Gaining insight into the molecular mechanisms behind sex differentiation in the mosquito species Culex pipiens might lead to the identification of genes that could be used to achieve selective male sterility in transgenic lines or to regulate the expression of deadly genes. In many insects, sexual dimorphism is controlled by doublesex (dsx), a double-switch gene located at the end of the somatic sex-determination cascade. Here, we report the isolation and characterization of sex-specific transcripts and isoforms for the Cx. pipiens dsx homologue. The CpdsxF and CpdxM transcripts in females and males. The exon/intron structure of Cpdsx shows that it employs a mechanism for sex-specific splicing distinct from that of Drosophila melanogaster dsx. Insect transgenic technology may be used to alter Cx. pipiens sex ratios, and these results will be useful for sterile insect-based vector control initiatives.

5963

CHIP-SEQ STUDY IDENTIFIES TARGETS OF THE CLOCK GENE, PAR DOMAIN PROTEIN 1 (PDP1), THAT REGULATE DIAPAUSE IN CULEX PIPIENS

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Multivoltine insects use diapause to endure adverse seasons. Insects employ environmental cues like short day length in late summer and early fall to enter diapause, but how they measure day length is unknown. The circadian clock is necessary for photoperiodism in many insects, including the northern house mosquito, Culex pipiens, which enters diapause, stops egg follicle development, and gains fat. We employed ChIP sequencing to identify PDP1's downstream targets that contribute to diapause's features and how circadian clock genes regulate diapause. We identified the nearest genes in a 10-kb region of the anticipated binding sites, listed prospective targets, and searched for PDP1-specific binding sites. We then examined the genes for functional significance to diapause-specific behaviors and alterations such as metabolic pathways, lifespan extension, cell cycle regulation, and stress tolerance. We validated PDP1 targets from those candidate genes using ChIP-qPCR. In addition, qRT-PCR demonstrated increased expression in diapausing females compared to non-diapausing counterparts. Our investigation uncovers PDP1-controlled diapause-specific genes.

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ASSESSING THE FEASIBILITY OF TWO 'MULTIPLEXED' STRATEGIES IN ANOPHELES STEPHENSI MOSQUITOES

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Anopheles stephensi is a major malaria vector mainly present in southern Asia and the Arabian Peninsula. Since 2012 it has invaded several countries of eastern Africa, requiring urgent efforts to develop more efficient strategies for vector control such as CRISPR/Cas9-based homing gene drives. One of their challenges is to ensure efficient recognition of the target site by the gRNA. Unfortunately, when a double-stranded break is repaired by NHEJ, it can lead to the creation of mutations. These can destroy the target site, making it difficult for the gRNA to recognize the homologous chromosome. Recent studies have explored the use of multiple gRNAs to solve the issue of target site resistance. In theory, 'multiplexing' would require the individual to become simultaneously resistant to all gRNA target sites for it to be completely resistant to the drive. A potential downside to this strategy is that homing efficiency may depend on perfect homology near the cut site. Thus, the optimal distance between gRNA target sites must be considered. We performed different set of crosses to assess the homing and cutting efficiency of two different 'multiplexing' strategies targeting the cardinal locus: the classic multiplexing and the additive strategies. To assess the feasibility of the first strategy, we generated a gRNA-expressing line with 4 gRNAs separated by a maximum distance of 142bp, which was crossed to a Cas9-expressing line. No significant difference was observed in homing in comparison to a single gRNA-expressing line targeting the same locus. Furthermore, a mutation altering one of the gRNA target sites was introduced to observe changes in the drive's performance. For the additive strategy, we tested the homing efficiency of two independent

gRNA-expressing drives by crossing them to a Cas9-expressing line. Then, we repeated these crosses while adding a mutation in the other gRNA-expressing drive target site found in a 481bp distance to see if homing was affected. We don't expect to see any significant reduction in homing efficiency for any of the performed crosses, showing that these are feasible strategies to tackle target site resistance in An. stephensi.

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GEOGRAPHICAL DISTRIBUTION AND GENETIC POPULATION STRUCTURE OF AEDES ALBOPICTUS IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Aedes albopictus, a major vector of dengue, zika, and chikungunya viruses, has recently been introduced to central Africa, including the Democratic Republic of the Congo (DRC). Although it is well-known that the establishment of this mosquito poses a serious public health threat in the invaded area, ecological and genetic data for the invading populations in DRC are still scarce. Therefore, our study aimed to reveal the nation-wide geographical distribution of Ae. albopictus and differences in genetic structure among populations. We conducted two entomological surveys at 308 sites within 104 cities from May 2017 to September 2019 and from March to August 2022. We sequenced and analyzed the mitochondrial cytochrome c oxidase subunit 1 gene (COI) (1,434bp) of 498 samples from 16 populations. Neutrality tests and genetic distance analyses were performed on the populations which were classified into three distinct geographical groups. Aedes albopictus was found at 193 (62.6%) sites within 82 (78.8%) cities, mainly in the western and northern DRC, as well as in the western part of the central DRC. This species has become the preponderant Aedes species in these areas, but was not found in the southeastern DRC. Nine COI haplotypes were detected, with one being widely distributed and the most frequent (49%). Aedes albopictus exhibited moderate haplotype diversity (Hd = 0.69 ± 0.02) but low nucleotide diversity (Pi=0.00174 ± 0.00004). Neutrality test revealed Tajima's D (2.14; $p<0.05$) and Fs values (Fs = 3.078; p=0.044) indicating an excess of intermediate-frequency alleles, which can be due to either positive selection or a recent population expansion. Low to moderate genetic differentiation (Fst = 0.016, 0.067 and 0.1328) and high level of gene flow (Gamma St, Nm = 3.75, 7.1 and 24.15) were observed among the groups. Phylogenetic analyses showed that all the nine haplotypes clustered with the populations from Vietnam. The results suggest that Ae. albopictus has established in the western and the northern DRC and was recently introduced to DRC from Southeast Asia.

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GENETIC VARIATION AND TRANSCRIPTIONAL ENHANCER ACTIVITY IN THE MALARIA VECTOR, ANOPHELES COLUZZII

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Enhancers are an important class of non-coding regulatory elements, and genetic variation in enhancers can underlie phenotypic variation. A genome-wide map of transcriptional enhancers for the malaria vector Anopheles coluzzii was filtered to highlight 16 candidates with potential influence over differential malaria susceptibility. The effect of candidate enhancer alleles from malaria susceptible and resistant mosquitoes was assessed by site-directed mutagenesis and Dual-Glo luciferase assays, with 7 enhancers displaying significant differences between resistant and susceptible mosquitoes. Computational prediction of transcription factor binding sites (TFBS) in the enhancers identified 82 enriched motifs that represent i) TFBS conserved with Drosophila melanogaster and ii) predicted mosquito-specific TFBS. DNA-protein pulldowns were implemented to confirm TFBS identification and distinguish enhancer allele-specific differences in TFBS binding that could be associated with differential transcription regulation.

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IDENTIFICATION OF H3K27ME2 SITES THAT CAUSE VARIOUS DIAPAUSE PHENOTYPES IN THE MOSQUITO CULEX PIPIENS

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To survive winter, the mosquito Culex pipiens enters diapause, a state that enables adult females to accumulate fat, cope with stress, and survive longer. Epigenetic controls, specifically histone changes, have been linked to several diapause phenotypes. In our recent Western blot investigation, we observed significantly fewer H3K27me2 marks in the fat bodies of diapausing females, suggesting that H3K27me2 may regulate diapause, although the regulatory mechanisms remain unclear. Using ChIP-sequencing, we identified H3K27me2's direct targets in the mosquitoes' fat bodies and proposed that epigenetic modification of these histone methylation marks may activate diapause-programmed genes. We selected and evaluated diapause-related genes and prioritized the top 300 candidate genes with the highest fold enrichment for functional annotation based on their proximity to the peaks within 1 kb of the promoter's transcription start site. We then verified a collection of candidate genes of H3K27me2 ChIP-seq using ChIP-qPCR and qRT-PCR.

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GENETIC AND NEURAL BASIS OF ATTRACTION OF GRAVID AEDES AEGYPTI TO AFRICAN BERMUDA HAY INFUSIONS

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The yellow fever mosquito Aedes aegypti is a prolific disease vector with explosive population dynamics. Its ability to thrive in urban environments lies in the ability of female Ae. aegypti to seek out standing pools of water to lay their desiccation-resistant eggs. Of note, females are highly attracted to the scent of decomposing botanical matter in water. Currently, hay infusion preparations made from African Bermuda Grass are widely used to bait the CDC autocidal gravid ovitrap for mosquito surveillance and control in the field. However, the molecular and cellular basis of how mosquito attraction to this potent oviposition attractant is unknown. To gain insight into olfactory preferences of female Ae. aegypti for oviposition stimuli, we established a two-choice behavioral assay that quantifies attraction to odors emitted by fermenting African Bermuda hay. Mated and blood fed females of different Ae. aegypti strains were more attracted to hay infusion odor than water alone. In addition, the preference for hay infusion is state-specific as it was not observed in unmated blood-fed, nor mated unblood-fed females. To understand the molecular and neural basis of this attraction, we first tested mutants for olfactory co-receptors to understand which are necessary for female olfactory choice. Next, we generated a mosquito line with an inward rectifying potassium channel (Kir2.1) downstream of the QUAS binary expression sequence. In concert with olfactory co-receptor QF2 driver lines, we are testing the role of different subsets of olfactory co-receptor-expressing cells in hay infusion attraction. This research will fundamentally improve our understanding of biological basis of oviposition site search behavior and catalyze development of novel approaches that target this important aspect of female mosquito reproductive biology. Furthermore,

the generation of a line for neural silencing in Ae. aegypti can be used more generally to investigate the neural basis of mosquito behaviors that underly its population dynamics and capacity to transmit arboviral diseases.

5969

LEVERAGING FIELD DNA SEQUENCING TO MEASURE SPATIOTEMPORAL VARIATION IN MOSQUITO COMMUNITY COMPOSITION AND FEEDING BEHAVIOR IN RURAL MADAGASCAR

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Understanding how climatic variables impact mosquito distribution in tropical highlands is particularly paramount, as human populations in regions with historically low mosquito-borne disease burdens are potentially immunologically naive relative to nearby lowland groups and may lack genetic or behavioral adaptations to pathogens such as Plasmodium. Despite this pressing public health need, baseline data from mosquitoes in tropical highlands are scarce due to the historically low vector-borne disease burden of these regions. Critically, this gap in information hampers fine-scale modeling of disease likelihood in areas where the predicted risk of climate-linked disease increase is highest. Here, we report longitudinal sampling of mosquitoes along altitudinal gradients in the montane tropical rainforest of southeastern Madagascar to understand the ecological drivers of malaria disease dynamics. We measured mosquito community composition and distribution in six villages surrounding Ranomafana National Park in southeastern Madagascar that vary in altitude and intensity of land use change. We additionally applied new portable sequencing technology to sequence individual mosquitoes in-country for assessment of population connectivity and vertebrate host species selection. Such data across seasons and altitudes will allow us to understand the human health impacts of the predicted shift for higher elevation areas to the vector dynamics of the lowlands.

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CHARACTERIZATION OF THE VIROME IN AEDES AEGYPTI VECTOR OF CONDORCANQUI PROVINCE, AMAZONAS REGION, THROUGH SHOTGUN METAGENOMIC SEQUENCING

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The total virome in mosquitoes has yet to be explored in the population of Aedes vector in Condorcanqui province, Amazonas region, Peru. Since the last few years, dengue cases have been considerably increasing in this tropical area, mainly through A. aegypti bites. There is an urgency in scrutinizing A. aeypti viral ecology and interrelations due to its public health relevance. Here, we characterized for the first time, through untargeted shotgun metagenomic sequencing, the virome of Aedes mosquitoes collected in the Rio Santiago district of Condorcanqui. A total of 137 individuals morphologically identified as A. aegypti were collected using mouth aspirators. These were grouped into twelve pools of ten to fifteen individuals. A protocol based on RNA extraction, reverse transcription, metagenomic library preparation, and sequencing, using the Illumina NextSeq 500 system, was performed. Bioinformatic analysis for screening shotgun metagenomic data was used. This included filtering out low-quality reads, assembling reads into contigs and viral classification using the ViralRefSeq Protein NCBI database. The results indicated a complex diversity of viral family members in A. aegypti, mainly Phenuidiridae, Flaviviridae and Totiviridae; also, Rhabdoviridae, Chuviridae, Baculoviridae, Mimiviridae and other viral families were found. Phenuidiridae, Flaviviridae and Totiviridae viruses were consistently found in the pools, suggesting these might be members of the core virome of A. aegypti in Amazonas. Some viruses detected have been identified as pathogenic for plants, ruminants and insects; a few might be used as biopesticides for biological control of insects due to their high pathogenicity and host specificity. Anopheline-specific viruses were also found, suggesting that there might be an exchange of viruses during their blood feeding. Additionally, targeted methods are needed for a more sensitive and precise search of human pathogenic viruses in vectors of these endemic areas.

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EXAMINING WEST NILE VIRUS INFECTION OF CULEX TARSALIS MIDGUTS AT SINGLE-CELL RESOLUTION

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In mosquito vectors, the midgut functions as a critical interface between pathogen and vector. Several studies have demonstrated that the mosquito midgut plays an important role in systemic infection, host immune response, intrahost virus population dynamics, and vector competence. Recent work examining mosquito hemocytes and midgut epithelium at the single-cell level has uncovered distinct functions within immune cell populations and identified key markers in the midguts of Aedes aegypti that overlap with major cell types found in Drosophila midguts. However, studies characterizing cell populations and their functions in the mosquito midgut are scarce and, in Culex tarsalis mosquitoes, nonexistent. Cx. tarsalis is a main enzootic vector of West Nile virus (WNV) and one of the most important arthropod-borne virus (arbovirus) vectors in North America. The Cx. tarsalis midgut is a stringent escape barrier that impacts the diversity of WNV populations that escape the midgut, infect the salivary glands, and escape into the saliva where transmission occurs. To gain a better understanding of how Cx. tarsalis midgut tissue functions as the interface between the vector and WNV, we performed single-cell RNA sequencing (scRNA-seq) on dissociated midgut cells from both WNV infected and mock-infected Cx. tarsalis mosquitoes. Examining WNV infection of the midgut at single-cell resolution will allow us to identify distinct cell populations and differentially expressed genes associated with WNV infection. Further, by using an approach to scRNA-seq that is flavivirus inclusive, we hope to identify cell types that serve as either sites of virus replication or cellular bottlenecks. Identification of midgut cell populations and genes impacted by WNV infection, will provide key insight into the physiology of WNV infection within a critical vector, and further characterize mechanisms that influence intrahost evolution of WNV.

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EVOLUTIONARY HISTORY OF SYLVATIC POPULATIONS OF ANOPHELES GAMBIAE AND IMPLICATIONS FOR MALARIA TRANSMISSION

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Apart from the increasingly reported adaptation to urban environments, the adaptation of malaria vectors to sylvatic, non-anthropogenic environments remains poorly studied. Recent observations on the existence of stable populations of Anopheles coluzzii in the Lopé National Park, Gabon, led us to investigate the evolutionary history of this population and their potential involvement in pathogens transmission. We analyzed the genome of 96 individuals of An. coluzzii from 3 different biotopes: urban, rural and sylvatic. We revealed the existence of structure between the populations of Libreville and those found in La Lopé (rural and sylvatic). However, despite the existence of important gene flow between the sylvatic and rural populations, we highlighted the existence of selection signals that suggest local adaptations of these different populations of An. coluzzii. In addition, the carrying of human and non-human Plasmodium by mosquitoes found in the

park, revealed by an extensive field collection, could be a threat to malaria control. The park could then be a reservoir of vectors and vector-borne pathogens. Further analyses are underway to better characterize these different populations from a genetic and phenotypic perspective.

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TEMPORAL AND COEVOLUTIONARY ANALYSES REVEAL THE EVENTS DRIVING THE EMERGENCE AND CIRCULATION OF HUMAN MAMASTROVIRUSES

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Characterized by high genetic diversity, broad host range, and resistance to adverse conditions, coupled with recent reports of neurotropic astroviruses circulating in humans, mamastroviruses pose a threat to public health. The current astrovirus classification system based on host source prevents determining whether strains with distinct tropism or virulence are emerging. By using integrated phylogeny, we propose a standardized demarcation of species and genotypes, with reproducible cut-off values that reconcile the pairwise sequence distribution, genetic distances between lineages, and the topological reconstruction of the Mamastrovirus genus. We further define the various links established by co-speciation and resolve the dynamics of transmission chains to identify the sources from which different mamastrovirus species circulating in humans have emerged. The well-known 'human' astrovirus, defined here as mamastrovirus species 7, has co-speciated with humans, while there have been two additional host-jumps into humans from distinct hosts. Newly defined species 6 genotype 2, linked to severe gastroenteritis in children, resulted from a marmot to human jump taking place ~200 years ago while species 6 genotype 7 (MastV-Sp6Gt7), linked to neurological disease in immunocompromised patients, jumped from a bovine source only ~50 years ago. Through demographic reconstruction, we determined that the latter reached coalescent viral population growth only 20 years ago and is evolving at a much higher evolutionary rate than other genotypes infecting humans. This study constitutes mounting evidence of MastV-Sp6Gt7 active circulation and highlights the need for diagnostics capable of detecting it.

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A COMPARATIVE ANALYSIS OF COMMERCIAL ANTI-DENGUE VIRUS IGG TESTS TO AID DENGUE IMMUNIZATION PROGRAMS

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The Advisory Committee on Immunization Practices (ACIP) recommends screening with anti-dengue virus (DENV) IgG tests to confirm prior DENV infection in children aged 9-16 years living in dengue-endemic areas of the United States before vaccination with Dengvaxia®. The minimum recommended test performance is ≥75% sensitivity and ≥98% specificity. To ensure safe implementation of Dengvaxia®, it is necessary to evaluate commercial anti-DENV IgG tests to assess which meet these criteria. We evaluated the performance of seven tests using serum panels from early convalescent specimens paired with acute specimens characterized by DENV and Zika virus (ZIKV) RT-PCR. The five best performing tests along with two additional tests specifically designed for pre-vaccination screening were evaluated with a panel of 44 specimens collected from healthy 9-16-year-old children in Puerto Rico. Four of these tests had promising discriminatory capacity for past DENV infections and were further evaluated using 400 specimens from the same population. Specimens from this population were classified as DENV exposed, ZIKV exposed, DENV and ZIKV exposed or unexposed using DENV and ZIKV virus Focus Reduction Neutralization Tests in combination with an in-house DENV IgG ELISA. No single test met the recommended performance to identify children eligible for Dengvaxia®, but the Euroimmun anti-DENV NS1 Type 1-4 ELISA combined with the CTK OnSite Dengue IgG rapid test R0065C with a visual test read yielded 80.3% sensitivity and 100% specificity. Manufacturers of these two tests modified their tests to meet the recommended performance standards with a single test. Using the automated ALTA rapid test reader, the modified CTK OnSite Dengue IgG rapid test R0065C yielded 76.2% sensitivity and 98.1% specificity. The preliminary performance for the modified Euroimmun anti-DENV NS1 Type 1-4 ELISA was 76.6% sensitivity and 99.1% specificity. These modified tests allow the benefit of vaccination while reducing the risk of vaccinating individuals without prior DENV infection and provide additional options for dengue pre-vaccination screening.

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CHALLENGES TOWARDS CLINICAL ALPHAVIRUS ENCEPHALITIS DIAGNOSTICS IN A DENGUE ENDEMIC COUNTRY

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Febrile undifferentiated diseases are often treated empirically in arboviral endemic regions due to the lack of available commercial diagnostics for highly diverse and sometimes unknown pathogens. Therapeutic decisions rely on clinical symptoms and sympatric circulation of multiple etiologic agents underscore the need to generate strategies for accurate diagnostics. Madariaga (MADV) and Venezuelan equine encephalitis virus (VEEV) have been associated with severe and sometimes fatal disease. We explored potential symptoms as predictors of alphavirus encephalitis infection. A total of 78 MADV and VEEV cases that occurred between 2010-2019 were compared to 1152 Dengue (DENV) controls. Case-patients and controls were compared based on reported symptoms registered using epidemiological forms. A total of 40 symptoms were collected from alphavirus encephalitis patients. The most common symptoms were fever, myalgias and petechiae. We found no major differences in symptoms between cases and controls. Vomiting (OR 2.9; p=≤0.001, 95% CI 1.7-4.8) and diarrhea (OR 11.9; p=≤0.001, 95%: CI 3.3-40.2) were the only non-specific early symptoms that increase in cases compared with controls. Symptoms associated with advanced clinical progression such as seizures (OR 70.3; p= ≤0.001, 95%: CI 25.8-218.8) and altered mental status (OR 5.2; p=≤0.001, 95% CI 1.43-15.5) were associated with alphavirus encephalitis, while respiratory symptoms (OR 7.8; p=≤0.001, 95%: CI 2.0-25.8), an uncommon symptom were found increased with alphavirus infection. Taken together, our results suggest that alphaviral encephalitis infections remain a diagnostic clinical challenge in dengue-prone regions, because of similarities in acute symptoms and the difficulty of predicting severe outcomes such as encephalitis, which can have significant morbidity and mortality. This underscores the necessity for building diagnostic capacity and lab surveillance in such areas.

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POST-DISCHARGE DEATHS AMONG SEVERE ACUTE RESPIRATORY INFECTION PATIENTS WITH SARS-COV-2 IN BANGLADESH DURING 2020-2022

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To understand the real burden of SARS-CoV-2-associated deaths among patients with severe acute respiratory infection (SARI), it is crucial to consider post-discharge deaths along with in-hospital deaths. We aimed to describe the characteristics of SARS-CoV-2-infected SARI patients who died at post-discharge in Bangladesh excluding accidental deaths. From March 2020-December 2022, we conducted COVID-19 surveillance among WHO-defined SARI patients at nine tertiary-care hospitals. We tested nasopharyngeal and oropharyngeal swabs for SARS-CoV-2 by rRT-PCR. We collected information on demographics, clinical characteristics and outcome at discharge and 30 days post-discharge. We used Chi-square test to compare post-discharge decedents and survivors. We identified 10,886 SARI patients with a median age: 16 years (IQR:1-50), 63% were male and 12% (1,319) were laboratory-confirmed SARS-CoV-2. Among patients with SARS-CoV-2, 10% (132) died during their hospital stay and 9.5% (112) died within 30 days of post-discharge. Of 112 post-discharge deaths, 4% (5) were discharged as fully recovered, 72% (80) as partially recovered, and 24% (27) were referred to specialized hospitals for further treatment. Adults aged ≥60 years were more likely to die at post-discharge compared to those aged <60 years [22% (74/330) vs. 4% (38/853); p<0.001]. Males were more likely to die at post-discharge compared to females [11% (79/698) vs. 7% (33/485); p=0.009]. Compared to the SARS-CoV-2 infected survivors, a higher proportion of SARS-CoV-2 infected post-discharge death cases had difficulty breathing on admission (94% vs. 77%, p<0.001), received in-hospital oxygen (92% vs. 64% p<0.001) and had at least one co-morbid condition (50% vs. 38%, p=0.017). One in five SARS-CoV-2-associated SARI patients died; of these, half occurred within 30-days post-discharge commonly among males, elderly, and patients with comorbid condition. Thus, post-discharge deaths might be unrecognized contributor to the true SARS-CoV-2 mortality in Bangladesh. Limiting premature discharge among high-risk groups should be considered to reduce these post-discharge deaths.

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RATS' FEEDING BEHAVIOR AT FRUIT TREES IN BANGLADESH AND IMPLICATIONS FOR PATHOGEN SPILLOVER

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Rats are the reservoir of important zoonotic pathogens like hantavirus, lymphocytic choriomeningitis virus, Salmonella, and agents of rat-bite fever. Food contaminated with rat saliva, feces or urine is a transmission route for these pathogens. Raw date palm sap and fruits dropped on the ground are consumed by humans and animals in Bangladesh, and sap consumption is a known route of Nipah transmission from bats to humans. Here, we describe rats' feeding behavior in date palms and fruit trees (jujube, banana, star fruit, sapodilla, olive, tamarind, fig, guava) in home gardens in Bangladesh captured using motion sensor-activated infrared cameras in two different studies. One study was conducted during the winter of 2011 and 2012, in 137 villages across Bangladesh, and the second in a village in the northern part of Bangladesh, from March 2013 to February 2016. We investigated how rats may contaminate date palm sap and fruits that may be consumed by humans. We recorded a total of 1002 rat visits with 150 nights at date palm trees and 118 nights at fruit trees during the winter season. We used descriptive statistics and a generalized linear model to identify conditions associated with rat visits. Among the 1002 rat visits observed, 831 (84%) were detected at date palm trees, 67 (7%) at jujube trees, 48 (5%) at banana plants, and 35 (4%) at start fruit tree. Camera images showed that rats were licking date palm sap either alone or in pairs or in some cases alongside bats. Rats ate larger fruits in the tree, like star fruit, and took away smaller fruits, like jujube. The longest duration of contact/night was recorded at date palm trees (78 sec) followed by olive trees (37 sec), star fruit trees (23 sec), and jujube trees (17 sec). Our study has some limitations as the cameras recorded the events only in the focused area and we do not have any evidence of rats urinating or defecating either in the sap or on the fruits or dropping fruits on the ground. However, the opportunities for pathogen transmission through shared food deserve additional follow-up to identify if rat-borne pathogens are infecting humans through shared food sources.

5978

PREVALENCE AND PREDICTORS OF PERSISTENT SYMPTOMS POST-ACUTE COVID-19 INFECTION AMONG A COHORT OF FRONTLINE HEALTHCARE WORKERS IN BANGLADESH

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Despite evidence of a wide range of persistent symptoms among COVID-19 survivors, commonly known as long COVID, their frequency, clinical spectrum and risk factors are not well characterized. We assessed the prevalence and predictors of long COVID among healthcare workers (HCWs) in Bangladesh. Between July 2021-March 2023, we enrolled a cohort of HCWs from purposively selected hospitals of four divisions across Bangladesh to prospectively record COVID-19 illness. At enrolment, we captured data on HCWs' demographics, co-morbid conditions and COVID-19 illness. The study physician followed the participants biweekly to record any new and persistent symptoms following acute illness. We used the WHO case definition for long COVID (symptoms occurring 3 months from the acute COVID-19 infection and persisting for at least 2 months). We performed a multivariable logistic regression to identify the predictors of long COVID. The analysis included 875 HCWs with lab-confirmed SARS-CoV-2 infection: 30% (261) doctors, 53% (468) nurses, and 17% (146) support staff. The median age of the HCWs was 35 (IQR, 29-44), and 69% (601) were female. Of the 875 HCWs, 462 (53%) reported persistent symptoms, with fatigue being the most common (83%), followed by brain fog (14%), cough (5%), breathing difficulties (4%), and joint pain (4%). HCWs with co-morbidities (aOR 3.39, 95% CI 2.32-4.95; p=0.0001), breathing difficulty during the acute phase (aOR 2.84, 95% CI 1.77-4.55; p=0.0001), and those who required hospitalization during acute infection (aOR 2.25, 95% CI 1.53-3.04; p=0.0001) were more likely to develop persistent symptoms than HCWs without a history of co-morbidities, respiratory symptoms, or hospitalization. Nurses (aOR 1.36, 95% CI 1.01-1.85; p=0.04) were more likely to develop persistent symptoms than doctors. More than half of the HCWs in our cohort experienced long-term symptoms of COVID-19, with a greater risk observed among nurses and those with the co-morbid condition. These findings underscore the pressing need for long-term care and rehabilitation strategies with a standardized guideline to enhance the post-acute recovery of COVID-19 patients.

5979

PSYCHIATRIC SEQUELAE AND PSYCHOSOCIAL IMPACT OF LASSA FEVER IN SURVIVORS IN EDO STATE, NIGERIA

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Lassa fever (LF) is a viral haemorrhagic fever with high mortality rates endemic to West Africa. Psychiatric sequelae in survivors of other high consequence infectious diseases have been reported before; in particular, high rates of post-traumatic stress disorder (PTSD) were found in survivors of Ebola virus disease. Yet, there is a paucity of data on the psychological impact of LF. This comparative cross-sectional study aimed to determine the occurrence of psychiatric diagnosis and psychosocial aspects of LF in survivors in Edo State, Nigeria. From May 2022 to date, 123 cases and 51 age- and sex- matched controls were enrolled. The mean age was 33.2 ± 11.4 years, 46% were female. Validated and established psychiatric screening tools were administered to screen for PTSD, depression and anxiety. In case participants scored above cut-offs, further psychiatric evaluation using the Mini Neuropsychiatric Interview (MINI) was conducted to confirm diagnosis. To investigate the psychosocial impact of LF, survivors completed a 15-item Likert scale questionnaire on perceptions related to the infection. There was no statistically significant difference in the frequency of anxiety and depression between survivors and controls. However, a higher rate of PTSD (7%) was found among survivors. All confirmed PTSD cases received counselling, yet most required pharmacotherapy. In the Likert scale, a majority of survivors stated that they were scared of the severity of LF and feared for their life when on the ward. Most respondents reported that they were anxious to infect others and that admission was stressful for both themselves and their families. In addition, 76% of survivors found being admitted with LF to be a financial burden. Our findings suggest that LF causes considerable psychosocial stress, in some cases even leading to clinical diagnosis of PTSD. This is the first study to show the perceptions of LF survivors regarding the impact of the disease on their life. These results indicate the importance of integrating mental health services into the care of LF patients. Moreover, knowledge of the perception of LF will greatly aid in public health interventions.

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SECONDARY ATTACK RATES AND DETERMINANTS OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2) HOUSEHOLD TRANSMISSION IN PAKISTAN: A CASE-ASCERTAINED PROSPECTIVE, LONGITUDINAL STUDY

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Households are considered ideal settings for studying the transmission dynamics of an infectious disease. A prospective study was conducted, based on the World Health Organization FFX protocol from October 2020 to January 2021. Household contacts of laboratory-confirmed index cases of SARS CoV-2 were followed up for their symptomatic history, nasal swabs for RT-PCR and blood samples for anti-SARS CoV-2 antibodies were collected at enrollment and days 7, 14, and 28. We estimated the secondary attack rate (SAR), effective reproduction number (Re), and determinants of secondary infection among susceptible household contacts using multivariable logistic regression. We enrolled 77 index cases and their 543 contacts. Out of these, 252 contacts were susceptible at the time of enrollment. There were 77 household clusters, out of which, transmission took place in 20 (25.9%) giving rise to 34 cases. The acquired secondary attack rate (SAR) was rate 14.0% (95% CI 9.0-18.0). The average effective reproduction number (Re) was 0.44 (95% CI 0.33-0.60). Reported symptoms of nausea and vomiting (OR, 7.9; 95% CI, 1.4-45.5) and fatigue (OR, 9.3; 95% CI, 3.8-22.7) were associated with SARS-CoV-2 transmission. We observed low SARS-CoV-2 transmission in the backdrop of high seroprevalence among households in Karachi, Pakistan. Symptomatic history influences infection transmission.

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COMPARISON OF THE PERFORMANCE OF RNA EXTRACTION KITS USED IN THE DIAGNOSIS OF COVID-19 AGAINST THE INHOUSE TRIZOL RNA EXTRACTION METHOD

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The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiologic agent of the COVID-19 pandemic which has since spread across the globe, placing a burden on society. Measures taken to reduce its spread depend on timely and accurate diagnosis done using various RNA extraction techniques and RT-PCR. Many commercial RNA extraction kits have been manufactured and released globally on the market however, due to growing demand, a shortage in kit supplies could be experienced in several labs. For these reasons, the use of different commercial or in-house protocols for RNA extraction may provide a basis for various labs to choose reliable extraction kits from the available pool and pave the way for seeking alternative procedures to replace commercial kits using common reagents found in a basic molecular biology laboratory. This study aimed to compare the analytical performance of different SARS-CoV-2 RNA extraction kits used in the diagnosis of SARS-CoV-2 in Uganda against the conventional TRIzol extraction method to address the existing knowledge gap. This work retrieved SARS-CoV-2 positive nasopharyngeal swabs from -80°C storage at biobank and Makerere University. SARS-CoV-2 RNA was then extracted from the samples using four commercial kits and the TRIzol method. The study demonstrated variations in the performance of the different kits/methodologies; The TRIzol extraction method generated the highest concentration of RNA; however, its purity was significantly lower than that of the commercial kits. When comparing the CT values, there was no statistically significant difference between TRIzol and the commercial kits except one. This research concludes therefore that although the TRIzol method recovered RNA with relatively lower purity, its performance in diagnosing SARS-CoV-2 using RT-PCR did not differ significantly from the tested commercial kits.

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CHANGING PATTERN OF DENGUE SEROTYPE IN THE SINDH REGION OF PAKISTAN, 2006-2022

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Dengue virus infection is a major threat to public health in Pakistan (PK). over the past few decades, the risk of infections with severe disease outcomes is increasing with the changing environmental and climatic conditions making PK a hotspot for mosquito breeding the disease has become hyper-endemic, with different serotypes causing epidemic outbreaks with severe clinical presentation. we analyzed the DENV serotypes circulating in the Sindh region of PK between 2006 -2022. Archived serum samples of two Filed surveillance studies conducted in 2006-2011 and 2014-2017 for patients with acute febrile illness along with prospective random selected clinical laboratory samples collection (2020-

2022) of DENV positive samples were used to assess the changing trends. All samples were tested by rapid NS1- antigen and PCR using serotype-specific primers, a significant changing trend of the predominant DENV serotypes in the three cohorts studied. From 2006-11 samples (n=200), DENV-3 was the predominant serotype tested in 60% (n= 57) of the total 94 DENV PCR positive samples followed by DENV-2, 38.3% (n=36) and DENV-4 1.1% (n= 1) we did not find DENV-1. The 2015-17 samples (n=168),34.52% wereDENV-2 followed by DENV-1 5.9%, DENV-3 8.92%, and DENV-4 3.57%. The results of 2020-22 showed changing trend with a progressive predominance of DENV-1 over other serotypes, accounting for 74% of all DENV positive (n=50) samples. Our study confirms that PK is hyperendemic for DENV as all four serotypes are found to be circulating and the temporal trend suggests the fluctuation in the predominant type circulating during the epidemic season. These findings are significant as changing pattern makes the population vulnerable to secondary infections with severe clinical outcomes warrant large-scale genomic surveillance of the DENV to better understand the role of factors responsible for varying trends such as human migration, climatic changes, and virus evolution. such surveillance is also required to better predict and prepare for the outbreaks outcomes as an entry of new serotype in the community after a gap of few years creates a risk for severe secondary infections.

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SEVERE MORBIDITY AND MORTALITY FROM RIFT VALLEY FEVER DISEASE BETWEEN NOVEMBER 2017 AND MARCH 2020 AMONG HUMANS IN UGANDA

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Rift Valley fever (RVF) is a zoonotic viral disease affecting animals and humans. Over the last two decades the disease has occurred with increased intensity in humans. In Uganda, cases reported prior to 2016 were either mild or under-reported. Here, we report on the morbidity and mortality of human cases identified in Uganda between November 2017 and March 2020. Human cases reported to the Uganda Virus Research Institute (UVRI) were identified and confirmed by polymerase chain reaction (PCR). Ethical and regulatory approvals were obtained to enrol survivors into a one-year follow-up study. Data were collected on patient socio-demographics, medical history, laboratory tests, and potential risk factors, and analysed using Stata software. Forty (40) cases were confirmed in four outbreak clusters that occurred over 29 months in 20 districts. Nearly all confirmed cases were male (39/40; 97.5%), median age 32 (range 11-63). Over three-quarters (31/40; 77.5%) of patients presented to the health care system with fever and bleeding. Twenty-eight (70%) cases were hospitalised, and more than half (21/40; 52.5%) of all confirmed cases died. Mortality was highest among admissions in regional referral (11/16; 68.7%) and district (4/5; 80%) hospitals, patients with bleeding at case detection (17/31; 54.8%), and older than 44 years (9/9; 100%). Survivors presented with mild disease manifesting commonly as gastro-intestinal syndrome with nausea (83.3%), anorexia (75%), vomiting (75%), abdominal pain (50%), and diarrhoea (41.7%). Symptom duration varied between two to 120 days. In conclusion, RVF causes high mortality and prolonged morbidity among humans that present to the health care system and are confirmed positive for RVF by PCR. Interventions should be developed to prevent infections, promptly detect disease outbreaks, and improve patient outcomes. 1

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KNOWLEDGE, AND PERCEPTIONS OF COVID-19 INFECTION AMONG PEOPLE REPORTING FOR COVID-19 VACCINATION IN HEALTH FACILITIES IN MALAWI

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Knowledge and perceptions of COVID-19 play a significant role in the uptake of preventive measures within communities. Understanding the knowledge and perception of COVID-19 infection among subjects willing to be vaccinated allows planning additional health education campaigns to be included in the routine COVID-19 vaccination. These subjects may act as role models, motivating other community members to take up vaccine and other prevention measures. An ongoing cross-sectional study interviewed 138 adults at the time they received first dose of the COVID-19 vaccine in a peri-urban and urban health facility in Blantyre, Malawi. A score summarized information on four domains of knowledge on COVID-19: symptoms, prevention, transmission and people at risk. This score was dichotomized into low vs. moderate/advanced knowledge. Through logistic regressions, determinants of low vs. moderate/ advanced knowledge were investigated including age, gender, educational level, and employment. We also investigated the source of the subject's information about COVID-19. Only 71 (52%) and 52(37%) had moderate/advanced knowledge on symptoms and prevention of COVID-19, respectively, whilst 125 (91%) had moderate/advanced knowledge on transmission. A total of 52 (37%) understood the highest risk groups. Females were more likely to have moderate/advanced knowledge on prevention than males (odds ratio ([OR] 2.1; P=0.04); subjects > 40 years had higher moderate/advanced knowledge at identifying highest risk groups (OR 3.8; P=0.01). Being a farmer was associated with low knowledge on at risk groups compared to office work/manual unskilled workers (OR 0.4; p value = 0.05). However, poor knowledge and understanding of symptoms and transmission of COVID-19 were uniformly spread in the population. Radio stations were the major sources of COVID-19 information (80% subjects). Our results suggest that after three years of the start of pandemic, information about COVID-19 has not been widely disseminated in Malawi. This may be negatively impacting uptake of preventive measures. There is a need to integrate COVID-19 health education in routine vaccination.

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A SIMULATION-BASED METHOD TO INFORM SEROSURVEY DESIGN TO ESTIMATE DENGUE FORCE OF INFECTION USING EXISTING BLOOD SAMPLES

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Limited knowledge exists on the extent of dengue virus circulation in Africa. Cross-sectional serological surveys provide the ideal data to investigate historical dengue transmission, to reconstruct the age-dependent immunity profile of a population, and to estimate transmission intensity, as measured by the force of infection (FOI), the per-capita risk of infection for

susceptible subjects. However, owing to limitations in capacity for arboviral disease surveillance, according to the published literature, only 17 dengue serosurveys have been conducted in the African region so far. A convenient strategy to overcome this limitation is to retarget existing blood biobanks, e.g., from previous serosurveys, for dengue surveillance by secondary testing for anti-dengue antibodies. Here we present a new simulation-based method developed to identify both the optimal number and age-distribution of samples required to obtain informative FOI estimates through secondary testing of existing blood samples. We discuss its application to the sample sizes previously collected during a SARS-CoV-2 serological survey conducted in Ghana, and show that the method is effective in reducing sample sizes required for testing without affecting the accuracy of the FOI estimates.This study highlights how existing blood samples from cross-sectional serosurveys can be leveraged for dengue surveillance and provides a framework for generating new immunological data to understand dengue historical circulation while optimising resources. The methods developed in this study can be adopted to investigate multiple viruses and diseases in different transmission settings around the world.

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LASSA FEVER OUTBREAK IN GHANAIAN COMMUNITIES, FEBRUARY 2023

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Lassa fever (LF) is an acute viral haemorrhagic illness, endemic in rodent populations in parts of West Africa such as Benin, Ghana, Guinea, Liberia, Mali, Sierra Leone, Togo, and Nigeria with case fatality of 15% among patients hospitalized with severe clinical manifestations. Infection can occur by exposure to food or household objects contaminated with the urine or faeces of infected Mastomys rats; person-to-person infections and laboratory transmission can also occur. On February 24th, 2023, the Noguchi Memorial Institute for Medical Research (NMIMR) confirmed two cases of LF and alerted the Ghana Health Service. As of February 28th, 2023, there were 14 confirmed cases, with one fatality. The other cases were contacts of the index cases, and Ghana had previously reported an epidemic in 2011. Korle-Bu Teaching Hospital submitted two probable viral haemorrhagic fever (VHF) patients, 33- and 40-year-old women with symptoms indicative of LF, including fever, vomiting, diarrhoea, abdominal pains, difficulty in breathing and bleeding from the eyes and nose.
The samples were submitted to viral RNA extraction, purification, and amplification using molecular testing methods for recognized endemic VHFs such as LF, Ebola, Yellow Fever, Dengue, and Marburg virus. The molecular testing methods employed yielded presumptive positive findings for LF. The initial close relationships in 12 other cases were confirmed as well as 156 contacts were observed for the stipulated period of 21 days. The number of confirmed patients for this epidemic is 26 with one fatality as of March 20th, 2023, with 512 samples received. All 25 patients are alive and well and were treated and subsequently discharged in authorized health institutions. In conclusion, there is a need to continuously strengthen public health systems to ensure effective and timely responses to outbreak situations or future emerging pathogens. The VHF testing capacity established by NMIMR as well as the GHS public health disease control unit has proven to be active and sensitive to detecting emerging pathogens for public health response.

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CLINICAL EVIDENCE ON DISEASE BURDEN OF THE MOSQUITO-BORNE CHIKUNGUNYA VIRUS (CHIKV) : A SYSTEMATIC LITERATURE REVIEW

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Chikungunya virus (CHIKV) is a re-emerging arbovirus that causes an infection characterized by an acute phase frequently including severe polyarthralgia, myalgia, and fever, which can progress to chronic sequelae and consequently result in productivity losses and a significant decline in health-related quality-of-life (HRQoL). To investigate the available clinical evidence on the disease burden associated with CHIKV, we conducted a systematic literature review (SLR). The SLR of clinical evidence was performed in Medline and Embase databases (no date restriction) and congress abstract repositories (2019-2021). The search adhered to Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Acute and chronic polyarthralgia and myalgia, two of the most prevalent CHIKV infection symptoms, have been identified as severely impairing the physical capacity of the patients and further affecting their daily functioning and HRQoL. Since the patients experience severe pain symptoms, their mental health is also significantly impacted, which often results in several psychological disorders. A chronic CHIKV infection may lead to long-term disability due to multiple long-term sequelae associated with a reduction in HRQoL. The low number of identified interventional studies (i.e., 17) displays the shortage of available interventions for the treatment of CHIKV infection. CHIKV is a serious threat to global public health and causes considerable disease burden worldwide. The rapid geographic expansion of CHIKV outbreaks and distribution is a result of a combination of travel, CHIKV mutations, global warming, and the spread of the mosquito vector. Currently, no antiviral treatment exists for chikungunya, and vector control is suboptimal and challenging. Due to the increase in the global spread of CHIKV and the paucity of treatment options for chikungunya, an effective preventive measure such as a vaccine is urgently needed.

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MONKEYPOX VIRUS OUTBREAK IN GHANA

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Monkeypox viral infection is a zoonotic disease caused by the Monkeypox virus from the family Poxviridae. It is usually a self-limiting disease with its clinical presentation like that of the smallpox virus. Reservoirs for the Monkeypox virus is unknown however, some animals that are susceptible to this virus include tree squirrels, and non-human primates. Since 1970 when the first human Monkeypox virus was detected, 11 African countries have reported cases of the virus with Nigeria recording the largest outbreak of 200 confirmed cases in 2017.The 2022-2023 Mpox outbreak in Ghana is a part of the larger outbreak of human Mpox caused by the West African clade of the MPXV. Ghana, as compared to its neighbors including Nigeria, had hitherto no endemic presence or active search and diagnosis for Mpox, until the 2022 outbreak. The first 5 cases of Mpox in Ghana were detected on 8th June 2022 and as of 20th March 2023, 569 suspected cases have been investigated. Here we sought to establish the molecular evidence and elucidate on the characterized circulating strains of MPXV of the cases investigated. Viral DNA was processed from lesion exudate or crust on a swab and/or serum specimens of patients identified by clinicians to have met the case definition of an initial febrile prodrome accompanied by headache, and fatigue prior to rash development. Polymerase chain reaction was then performed at the NMIMR to amplify the viral DNA. As of 2March 2023 a total of 569 suspected MPXV cases have been received from health facilities across the country and tested. Of the total, 65 (11.4%) have been confirmed to be MPXV cases whilst 87 (15.3%) were other orthopoxviruses. Nearly 60% of all confirmed cases were children under 15 years old and 3 fatalities have been recorded. Sequenced and characterized MPXV positives were found to belong to the West African clade. This work documents molecular evidence of monkeypox virus circulation in Ghana. It is worth to consider vaccinating affected areas with vaccinia (smallpox vaccine), and to intensify education on good personal hygiene as well as heightened surveillance for monkeypox and other orthopoxviruses in the country.

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NEUTRALIZING ANTIBODY TITER AFTER COMPLETE SARS-COV-2 VACCINATION

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Vaccination against SARS-CoV-2 is a priority and fundamental strategy to prevent the spread of this disease and avoid the collapse of the health system. The recommended vaccination schedule for this vaccine is 2 doses with an interval of at least 21 days between them. Neutralizing antibodies are considered a good marker for measuring humoral responses. To evaluate the humoral response following COVID-19 vaccination by measuring the antibody titer against the receptor binding domain (RBD) of the spike (S) protein. We conducted an observational study in volunteer health care personnel who had received two doses of vaccines. We detected binding antibodies against SARS-CoV-2 by chemiluminescence immunoassay test (CLIA) for quantitative determination of specific IgG antibodies against the trimeric spike protein. We log-transformed the amount of SARS-CoV-2 IgG. We performed ANOVA tests to evaluate by months of follow-up (every 30 days) and linear regression between elapsed days with antibody titers. We considered a p-value less than 0.05 as significant. RESULTS: A total of 224 persons who completed the vaccination schedule (2 doses) were evaluated. Every 10 days that elapsed since the first vaccine dose, the coefficient of difference of the Log difference of the IgG titer of binding antibody decreased on average 0.25 log(IgG) (p-value<0.001). Patients started with an average SARS-CoV-2 binding antibody titer at 9.33(±1.5) log(IgG SARS-CoV-2) during the first 30 days, and at the end of follow-up (days 150-180) on average had 5.12(±1.1) log(IgG SARS-CoV-2). A history of COVID-19 resulted in increased antibody titers during the 61-180 day post-vaccination period relative to those without a history of COVID-19 (p<0.001). There was no difference in mean log(IgG SARS-CoV-2) according to sex (p=0.0.274). In conclusion, antibody production against SARS-CoV-2 virus has shown to have good humoral response the first 30 days, but has been decreasing up to 54% in the sixth month post-vaccination. The COVID-19 background sustained SARS-CoV-2 IgG antibody levels above those who had not been infected.

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LOW SEROPREVALENCE OF EBOLA VIRUS IN HEALTH CARE PROVIDERS IN AN ENDEMIC REGION (TSHUAPA PROVINCE) OF THE DEMOCRATIC REPUBLIC OF THE CONGO

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A serosurvey among health care providers (HCPs) and frontliners of an area previously affected by Ebola virus disease (EVD) in Boende, Democratic Republic of the Congo (DRC) was conducted to assess the seroreactivity to Ebola virus antigens. Serum samples were collected in a cohort of HCPs and frontliners (n=698) participating in the EBL2007 Ebola vaccine trial (December 2019 to October 2022). Specimens seroreactive for EBOV were confirmed using either the Filovirus Animal Nonclinical Group (FANG) ELISA or a Luminex multiplex assay. The seroreactivity to at least two EBOV-Mayinga (m) antigens was found in 10 (1.4%: 95% CI, 0.7-2.6) samples for GP-EBOV-m + VP40-EBOV-m, and 2 (0.3%: 95% CI, 0.0 - 1.0) samples for VP40-EBOV-m + NP-EBOV-m using the Luminex assay. Seroreactivity to GP-EBOV-Kikwit (k) was observed in 59 (8.5%: 95%CI, 6.5-10.9) samples using FANG ELISA. In contrast to previous serosurveys, a low seroprevalence was found in these HCPs and frontline population. The use of various tests, of different seroprevalence cut-offs, and of distinct geographical populations with different risk of exposure to EBOV, would contribute to this difference. This underscores the high need for standardized antibody assays and cutoffs in EBOV serosurveys to circumvent the wide variability in reported EBOV seroprevalence rates in EBOV endemic areas. Furthermore, it is unclear whether based on lessons learned from previous EVD outbreaks, the majority of HCPs and frontliners participants in the EBL2007 Ebola vaccine trial would have adequately adopted the EVD prevention key messages or were practicing good EVD prevention. This would have kept them safe, free of EBOV exposure and then explain the low seroprevalence. Similarly, other filovirus infections that can generate cross-reacting antibodies not investigated in this serosurvey may account for this low seroprevalence.

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MOLECULAR CHARACTERIZATION OF SARS-COV-2 IN HEALTHCARE PERSONNEL WITH THIRD GENERATION SEQUENCING IN LIMA, PERU, 2021-2022

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Genomic surveillance of SARS-CoV-2 variants has enabled the study of the emergence of new viral mutations during this pandemic. It is thought that mutations are emerging from infected persons with more than 14 days of viral shedding. We did a molecular characterization of SARS-CoV-2 virus detected in workers of a health facility that had a nasopharyngeal or nasal sample taken weekly until it became RT-PCR negative. RT-PCR positive samples obtained from 2021 and 2022, stored at -80°C, were sequenced in the MinION Mk1C device from Oxford Nanopore Technologies. Extracted viral RNA was processed following the PCR tiling of SARS-CoV-2 virus with rapid barcoding and Midnight RT-PCR Expansion (SQK-RBK110.96 and EXP-MRT001) protocol. 78 samples from 50 workers were processed for sequencing. Samples from 44 workers (88%) were able to be sequenced. All samples from 2021 were Lambda 21G (C.37) SARS-CoV-2 variant. In 2022, all SARS-CoV-2 belonged to the Omicron variant from different sub-lineages, mainly BA.2 (20%), BA.1.1 (17%), BA.1 (15%), BA.5 (13%) and BA.5.1 (10%). Samples from 10 workers with SARS-CoV-2 positivity over 1 week were processed; however, we only were able to sequence the first samples during the first week of episode from 8 workers and samples from both the first and second week of only 2 workers. All others with samples up to 7 weeks positive for SARS-CoV-2, were unable to be sequenced. Bioinformatic analysis of the 2 workers with sequenced samples for week 1 and 2 showed identical variants. These results suggest that prolonged RT-PCR positivity for SARS-CoV-2 may not represent viable viruses. We concluded that the identified SARS-CoV-2 variants detected in 2021 and 2022 were similar to those detected elsewhere, and that in this small series of cases in healthy individuals, prolonged positivity by RT-PCR may not represent viable viruses with potential to generate new variants. These results require confirmation in larger studies.

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ENTERIC VIRAL PATHOGENS AND CHILD GROWTH: INSIGHTS FROM SOUTH ASIA AND SUB-SAHARAN AFRICA

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Enteric viral pathogens such as rotavirus, norovirus, adenovirus, astrovirus, and sapovirus are associated with a significant burden of childhood morbidity and mortality. We investigated the relationship between viral

pathogens and child anthropometric outcomes among under-5 children in South Asia and sub-Saharan Africa. We analyzed data from 5,572 children enrolled in the Global Enteric Multicenter Study (GEMS) across seven study sites between December 2007 and March 2011. Viral pathogens: rotavirus and adenovirus were detected using stool immunoassays (ELISA) and norovirus, astrovirus, and sapovirus by RT-PCR. Multiple linear regression was used to examine the association between the viral pathogens and length/height-for-age (HAZ), weight-for-age (WAZ), and weight-for-length/height (WHZ) z-scores, stratified by diarrheal symptoms and adjusted for potential covariates. Rotavirus (18.51%) and norovirus (7.33%) were the most prevalent pathogens among symptomatic and asymptomatic under 5 children, respectively. Among asymptomatic children, viral pathogens were associated with lower WAZ: rotavirus (β=-0.09; 95% CI: -0.17, -0.01), norovirus (β=-0.12; 95% CI: -0.18, -0.06), adenovirus (β=-0.28; 95% CI: -0.47, -0.10), and sapovirus (β=-0.14; 95% CI: -0.23, -0.06). Among the symptomatic children rotavirus (HAZ:β=0.12; 95%CI:0.07,0.17 and WAZ:β=0.05; 95% CI:0,0.11), norovirus (HAZ:β=0.08; 95% CI: 0.01,0.15 and WAZ:β=0.14; 95% CI: 0.06,0.21), and sapovirus (WAZ:β=0.13; 95% CI:0.02,0.24) were associated with higher HAZ and WAZ, but astrovirus was associated with lower HAZ (β=-0.16; 95% CI: -0.28, -0.04). While previous studies hypothesized that several viral pathogens had a controversial role in child growth, our findings indicate that enteric viral pathogens are associated with growth shortfalls among asymptomatic children. This highlights the need for preventive strategies targeting enteric viral pathogens among asymptomatic young children, which could potentially reduce the burden of childhood growth faltering.

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PILOT SURVEILLANCE EVALUATION USING LEFTOVER MEASLES/RUBELLA NEGATIVE SURVEILLANCE SPECIMENS TO DETECT ARBOVIRUS INFECTIONS

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Dengue, chikungunya, and Zika virus infections remain a threat in areas where the Aedes (Stegomyia) mosquito vectors are established. Limited arbovirus surveillance results in underestimates of disease burden and delayed recognition of transmission activity. WHO recommends an integrated public health approach to Aedes-borne arboviruses. A proposed strategy for case detection in some regions is arbovirus testing of suspect measles and rubella cases, as patients present with clinically similar febrile rash illness and blood specimens are routinely collected. We describe the evaluation of a pilot sentinel surveillance strategy using this approach for infection detection and feasibility of implementation. Between 2019 and 2022, the national public health laboratories of Burkina Faso, Indonesia, Myanmar, and the Philippines tested stored specimens for measles and rubella testing from the preceding 1-12 years for evidence of acute dengue, chikungunya, and Zika infections using a validated RT-PCR molecular assay and IgM-capture enzyme-linked immunosorbent assays. Where feasible, IgM-positive specimens were transferred to the Uganda Virus Research Institute and the National Environment Agency Singapore, respectively, for further testing by repeat IgM and plaque reduction neutralization tests. In total, 8,648 leftover measles/rubella surveillance specimens were tested. Molecular testing detected either chikungunya or dengue RNA in 330 (4%) of all specimens and in three of four countries. All countries detected IgM antibodies to all three viruses, with overall seropositivity of 13% to at least one virus. Confirmatory testing demonstrated the continued challenges of flavivirus serologic cross-reactivity in endemic countries. Arbovirus testing of measles-rubella surveillance specimens leverages a widespread, robust collection of samples from patients with clinically compatible illness. However, the resources required to yield accurate results suggest that this approach should be targeted to specific objectives and sentinel locations for optimal utility.

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ESTIMATING THE INCIDENCE OF DENGUE IN INTERNATIONAL TRAVELERS FROM NON-ENDEMIC COUNTRIES

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We estimated the risk of dengue infection among travelers from non-endemic countries to inform public health preparedness, especially in non-endemic countries with suitable vectors where infected travelers can spark outbreaks. We used data from 2010-19 on ~30,000 traveler cases that were reported to national authorities in 21 non-endemic countries, hazards of infection in 102 endemic countries based on local seroprevalence studies, and the numbers of flights and trip durations between countries. From these, we estimated the total numbers of infections in travelers (i.e. regardless of symptoms) and the fractions of infections reported in travelers' home countries. We tested two simplifying assumptions: assuming time-constant country-specific reporting rates, and assuming the reporting rate was determined by endemic and non-endemic terms only (i.e. no interaction). We analyzed data using Bayesian Markov Chain Monte Carlo and used the leave-one-out information criteria to compare models. From 2010-19, nearly 30,000 traveler cases with known country of infection were reported in the 21 non-endemic countries. Australia, USA, and Germany reported the highest case numbers. Indonesia, Thailand, and the Philippines were the destinations giving rise to the most cases. The model assuming time-varying reporting and no interaction performed best. Estimated reporting rates varied across country pairs (median 1.7%, range 0.07% to 38.2%). We estimated that an average of 170,800 annual dengue infections occurred among travelers from these 21 countries, with most occurring among travelers from the USA (85,100), Japan (20,400), and South Korea (16,300). Thailand (18,700), Brazil (15,300), and India (14,300) were the destinations with the highest numbers of traveler infections. In conclusion, this study shows that reported dengue cases among travelers represent a small fraction of infections in this group and that this fraction varies greatly across countries. These estimates can guide public health preparedness, including quantifying the benefit of dengue vaccination in travelers.

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ARBOVIRUS DISEASE SURVEILLANCE AMONG FEBRILE PATIENTS IN KILIMANJARO, TANZANIA, 2016-2019

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Arthropod-borne flaviviruses and alphaviruses are emerging infectious diseases and causes of febrile illness in East Africa. A prospective cohort study enrolled febrile patients admitted to 2 referral hospitals in Moshi, Tanzania, September 2016 through May 2019. Acute serum was obtained at enrollment, and convalescent serum 28-42 days later.

Convalescent serum underwent antibody screening by ELISA for the following arboviruses: dengue (DENV), Zika (ZIKV), West Nile (WNV), yellow fever (YFV), Sindbis, o'nyong-nyong (ONNV), and chikungunya (CHIKV). Those with positive, uninterpretable, or equivocal screens underwent plaque reduction neutralization testing (PRNT) on acute and convalescent sera. PRNT results were expressed as the reciprocal of the serum dilution yielding >80% reduction in the number of plaques (PRNT80). Acute arboviral disease (ABD) was defined as having ≥4-fold increase from acute to convalescent PRNT80 titer with an end-titer PRNT80 >40 and ≥4-fold greater than other viruses in the same genus. Prior infection or vaccination (against arboviruses with available vaccines) was defined as PRNT80 titer >10 without a ≥4-fold rise in convalescent titer. Both for acute and prior infections, if there was not an end titer 4-fold higher for one species compared to others within the same genus, this was designated at the genus level (e.g., flavivirus disease). Of 1,132 patients enrolled, 430 (38.0%) were screened for ABD by convalescent ELISA and 110 reflexed to PRNT80. Eleven (2.6%) participants had ABD: 1 CHIKV, 4 DENV, 2 ZIKV, and 4 flavivirus. Twenty-five (5.8%) participants had evidence of prior infection or vaccination: 1 alphavirus, 7 flavivirus, 3 DENV, 2 ONNV, 7 WNV, 1 ZIKV, and 4 YFV. DENV was the most frequent acute ABD and WNV the most frequent prior infection. YFV seropositivity likely reflected prior vaccine exposure. While we found acute ABD to be a relatively uncommon cause of febrile illness, these serologic case detections suggest circulation or arrival of flaviviruses and alphaviruses of public health significance in northern Tanzania.

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ACCEPTANCE AND HESITANCY TOWARDS COVID-19 VACCINE AMONG HEALTHCARE WORKERS IN BUKAVU, EASTERN DEMOCRATIC REPUBLIC OF CONGO

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The Democratic Republic of Congo (DRC) is falling behind the global COVID-19 vaccination effort in achieving herd immunity against SARS-CoV-2 infection due to vaccine hesitancy, which poses a threat to global health and hinders the implementation of a successful vaccination program. Healthcare workers in the DRC were highly hesitant towards the COVID-19 vaccine even before its deployment, further complicating efforts to prevent and contain the pandemic. This study aimed to identify the factors associated with COVID-19 vaccine hesitancy among DRC's healthcare workers one year after the availability of the vaccine. From March 1st to March 31st, 2022, we conducted face-to-face interviews and web-based surveys using the WHO's modified Behavioral and Social Drivers of Vaccination instrument among healthcare workers in Bukavu, eastern DRC. Logistic regression models were built to identify predictors of vaccine hesitancy, defined as uncertainty or intention to refuse an available COVID-19 vaccine. Of the 380 participants, with a mean age of 35.0 (28.0-48.0) years and 198 (52.1%) males, 266 (70%) were hesitant to accept the COVID-19 vaccine, while only 29 (7.6%) were willing to accept it. A majority of participants (63.9%) believed that COVID-19 vaccines were not safe, and 77.9% and 81.6% distrusted central and local government authorities, respectively, in their ability to deliver a safer vaccine. While 42.4% trusted in the science behind the vaccine development, distrust in the central government (aOR=3.543, IC1.351-9.289), distrust in the science that proposed the COVID-19 vaccine (aOR=4.360, IC 1.351-9.289), perceiving that COVID-19 vaccines available are not safe (aOR=4.330 IC 1.854-10.111), and lack of knowledge of COVID-19 vaccination locations (aOR= 10,87, IC 3.785-31.246) were the main factors associated with vaccine hesitancy in an adjusted model. The study found a high and persistent prevalence of COVID-19 vaccine hesitancy among Congolese healthcare workers. Strategies to increase vaccine uptake need to include interventions that address trust in vaccine safety and public authorities.

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SOURCES OF INCONSISTENCIES BETWEEN DENGUE INFECTION INTENSITIES ESTIMATED FROM SEROLOGICAL AND PASSIVE CASE SURVEILLANCE STUDIES

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Force of Infection (FOI) is an important metric when designing and implementing interventions. Ideally, FOI would be calculated using serologic data from highly powered prospective cohort studies, directly measuring rates at which naive individuals seroconvert to the pathogen of interest. However, because this approach is resource intensive, FOI is typically inferred from mathematical models applied to cross-sectional seroprevalence or passive surveillance case datasets. Consistency of FOI estimates from these different approaches remains poorly understood. Here, we use data from a series of cohort studies in Kamphaeng Phet, Thailand (1998-2016: total 10159 individuals, 59801 bleeds with hemagglutination inhibition antibody measurements to all four dengue serotypes) and case data from the provincial hospital (1994-2019, n=12222). Considering the cohorts as both longitudinal measures (multiple samples per individual) and cross-sectional data (single sample per individual), we estimated the annual FOI between 1998 and 2018 using standard models for each data type. We found strong incongruence between the estimates with seroincidence-derived FOI being systematically higher than estimates from case data, and seroprevalence-derived FOI being systematically lower. To uncover sources of these inconsistencies, we performed simulations to study effects of commonly violated model assumptions on the inferred FOI. We found that noise in the assay alone leads to extreme inflation of FOI inferred from seroincidence data and dampened FOI inferred from seroprevalence data. While waning of monotypic antibody titers alone does not affect seroincidence-derived FOI, it can further exacerbate the inflation of FOI in noisy assays. Non-independence between observations and non-uniform infection risk in age affects the FOI estimates from each data type differently in non-trivial ways. Finally, we developed methods to correct for these biases and describe the extent at which these corrections can be done in empirical settings to guide future inferences and interpretations of empirical data.

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CIRCULATING NON-DENGUE FLAVIVIRUSES IMPACT DENGUE VIRUS DIAGNOSTIC TESTING AND DISEASE RISK IN CAMBODIA

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Mosquito-borne viruses are a growing global public health threat. Some areas have co-circulating flaviviruses that induce cross-reactive antibodies, which can increase risk of disease caused by dengue virus (DENV) but could also provide partial cross-protection. Cambodia is highly endemic for dengue virus (DENV), and there is serological evidence of West Nile virus (WNV) and Japanese encephalitis virus (JEV) in birds. Pre-existing immunity to JEV, WNV, and Zika virus (ZIKV) may impact DENV testing results and disease risk. Healthy children (n=771) aged 2-9 years living in Chbar Mon, Kampong Speu, Cambodia were enrolled in a prospective cohort study between July and August 2018 and followed for three years. DENV antibodies were measured bi-annually and with each febrile illness by an indirect dengue IgG ELISA (PanBio; Brisbane, QLD, Australia) and focus reduction neutralization test (FRNTs) to detect neutralizing antibodies (nAbs). The ELISA had a high false positive rate (13%) and specificity of 82%, which was lower than the 90-100% reported by others, including the manufacturer. Of 100 children ("discordants") with high DENV ELISA titer (>1.1) and low DENV nAbs (FRNT≤40), half had DENV nAbs levels below 10. After adjusting for age and sex, discordants had a higher odds of going on to experience a DENV infection compared to naïve (ELISA≤1.1 and FRNT≤40) children (OR 1.96, 95% CI 1.24-3.11). Interestingly, their infections were more likely to be inapparent (OR 3.95 [1.39-11.32]). To evaluate the high DENV ELISA false positive rate, we tested for nAbs against other flaviviruses in DENV naïves and discordants. ZIKV nAbs were present in 10% discordants vs 4% naïves (p = ns). JEV nAbs were also identified in discordants and these, along with WNV nAbs, will be compared with the naïve group. We found that immunity to other circulating flaviviruses altered the specificity of dengue testing and disease risk in Cambodian children. Investigators and clinicians in dengue endemic areas should consider co-circulating flaviviruses when testing children.

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FORECASTING DENGUE INCIDENCE: REVIEW OF METHODOLOGY AND COVARIATES

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Globally, there is an increase in dengue morbidity and mortality, resulting in a significant burden on health systems. Having accurate predictions for future dengue incidence is important to inform public health response and guide interventions. This study summarizes methodologies and covariates used to forecast dengue cases over time. Embase, Global Health, Medline, and Web of Science databases were reviewed using keywords related to dengue and forecasting. Only peer-reviewed articles in English, which predicted any aspect of human dengue transmission including case counts and incidence, used any methodology and conducted out-of-sample validation such that time-series nature of data was preserved were included. No geographical or time limitations were imposed. Following de-deduplication, 5,412 records were identified. Two reviewers reviewed each title and abstract and screened full text of articles, identifying 206 studies for inclusion. A further 17 studies were identified through search of references of previous reviews related to this topic. Data was extracted on study setting, data source, spatial and temporal scale of prediction, forecasting models, variables tested and variables included in final models, and evaluation methodology. Models identified were machine learning and statistical models, followed by mathematical models. Most common covariates identified included temperature and humidity. Review of this literature will inform current and future forecasting efforts and ensures public health responses incorporate latest methodological advances appropriate for context.

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COMPARISON OF REPORTED PRIOR DENGUE INFECTION WITH LABORATORY-CONFIRMATION OF SEROSTATUS AMONG 9 TO 14-YEAR-OLD CHILDREN IN CEBU, PHILIPPINES

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Dengue is an acute febrile illness that is an important public health problem in tropical Asia and Latin America. There are four dengue virus serotypes (DENV-1 to 4); infection produces durable homotypic immunity against the same serotype but waning cross-protection against the other serotypes resulting in repeat dengue infections. We aimed to assess the association between laboratory-confirmed presence of dengue antibodies with the reported history of prior dengue infection. In 2017, we enrolled 2,996 children who were 9- to 14-years of age and eligible to participate in a government dengue vaccination program in Cebu, Philippines. We collected a baseline blood sample from each participant, which was assessed for dengue antibodies by indirect ELISA and focus reduction neutralization test (FRNT). 1790/2996 children received a dose of CYD-TDV during the mass vaccination in July 2017. After an additional safety concern of CYD-TDV was announced, the dengue vaccination program in the Philippines was discontinued. We actively monitored the children in the cohort for febrile illness from November 2017 to October 2022. Data on past history of dengue illness was collected using a brief questionnaire when a child in the cohort had a febrile illness. 674/2996 (22.5%) children had at least one febrile episode detected during the five-year period. Of the 674 children, 458 (68%) received a single dose of CYD-TDV. The majority (593/674 or 88.7%) were dengue seropositive at baseline: 512/593 or 76% with a multitypic profile and 81/593 or 12% with a monotypic response. Of the 593 children who were seropositive at baseline, 520 (87.7%) did not recall previous dengue illness. In 2018, the World Health Organization has recommended a pre-vaccination screening strategy for the dengue vaccine, CYD-TDV, whereby the vaccine should only be given to those who are dengue seropositive. We found that recall of previous dengue illness is unreliable in establishing dengue serostatus in our setting.

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DETECTION OF OTHER HUMAN CORONAVIRUSES (HCOVS) AND CROSS- REACTIVITY AGAINST SARS-COV-2 IN CLINICAL SAMPLES

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The emergence of SARS-CoV-2 ignited a pandemic with reported 633 million cases and over 6.6 million deaths. There is evidence of disparity between reported SARS-CoV-2 infections and the actual infections in African populations. These have been attributed to many factors such as lack of accurate data on the rates of infections and death. As compared to other populations however, lower morbidity and mortality rates have been reported in Africa. Some studies have attributed it to possible immune protection conferred by viral and parasitic infections in the Ghanaian population. This study set out to determine cross-reactivity of SARS-CoV-2 in clinical samples collected before and during the COVID-19 pandemic and investigate the presence of other human coronaviruses (HCoVs) circulating within the Ghanaian population. Naso-pharyngeal swabs were collected from 999 consenting individuals aged ≥5 years for the detection of SARS-

CoV-2 and the other human coronaviruses (HKU1, OC43, NL63, 229E and SARS) infections by RT-qPCR. Preliminary results show that overall positivity for SARS-CoV-2 was 20% (200/999) and other HCoVs was 23.8% (238/999). SARS accounted for 60% (143/238) of the HCoV positives while, OC43 made up 9% (23/238) of positives. One sample (0.42%;1/238) was positive for four HCoVs and another (0.42%;1/238) was positive for all 5 HCoVs. Males were observed to be 1.47 times more likely to be positive for SARS-CoV-2 [95% CI: 0.98 – 2.20, p-value=0.06] as compared to females. Living in an urban area gives a higher risk of being positive for all HCoVs and SARS-CoV-2 [aOR: 1.67, 95% CI: 0.97 – 2.66, p-value=0.07] [aOR: 2.49, 95% CI: 1.49 – 4.14, p-value<0.001] respectively. Positive HCoV participants were approximately 4 times more positive for SARS-CoV-2 [95% CI: 2.51 - 5.68, p-value<0.001]. The co-presence of HCoV and SARS-CoV-2 may be a possible indicator of cross immune protection. This may play a role in the high numbers of asymptomatic SARS-CoV-2 infections during the peak of the pandemic in Ghana.

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PREVENTION AND CONTROL OF VIRAL HEMORRHAGIC FEVER IN LEARNING INSTITUTIONS IN UGANDA

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Uganda is located in East Africa. On the 22nd September, 2022 an outbreak of Ebola Virus Disease was confirmed in Mubende District located in the Central region of the country West of the capital city Kampala. Uganda has approximately 15 million learners concentrated in close to 50,688 education institutions with an average of about 1,000 learners or more in a learning institution. Many schools are high volume congregate settings and are mixed Day and Boarding posing an increased risk of infection transmission. To control spread interventions in learning institutions were jointly carried with the key line ministries and partners. The multi sectoral committee supported the different pillars with the National School Health Task force as a sub -pillar for the coordination of the activities including development of guiding documents. Ebola Virus Disease surveillance was built on the existing COVID-19 school-based surveillance system. Risk Communication team played a key role in the development of Information Education and Communication materials for the general public and school settings. Confirmed cases were evacuated to the Ebola Treatment Unit. Arrangements were made for continuity of learning by the school. Contact listing of the close playmates and classmates were isolated from home or a designated place with daily monitoring of symptoms for a period of 21 days. Infection prevention measures at the school together with daily fever screening. By 14 October 2022, 58 cases had been confirmed among which was a Primary school pupil from Mubende Municipal Council. By 23 October2022, a total of 28 cumulative cases of EVD were registered amongst persons aged 0-19 years, of these 19 were attending school in the three districts of Kampala, Mubende and Kassanda that had been greatly affected. Of these seven died resulting in a case fatality rate of 37%. A total of about 10 learning institutions were affected during the outbreak. The prevention and control of EVD was made possible through strict compliance to the standard operating procedure, political commitment, continuous monitoring and support supervision by the different administrative levels.

6003

A COHORT STUDY IN GHANA REVEALS HIGH SEROPREVALENCE OF MONKEYPOX IN GHANA

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Monkeypox virus (MPXV), an orthopox virus endemic to West and western Central Africa, is the etiological agent of Monkeypox (Mpox) disease. While the recent global outbreak has been fuelled primarily through human-to-human contact, primary transmission in endemic areas is most likely through contact with reservoir host species with secondary transmission to caregivers and close relatives. Prior to the year 2022, Ghana had not reported any human cases of Mpox, however, the 2003 Mpox outbreak in the US was initiated by rodents that were exported from Ghana. This preliminary study was done to determine the seroprevalence of Mpox after about 40 years of global eradication and discontinuation of smallpox vaccination in Ghana. Direct ELISA was conducted on a total of 1507 archived sera collected prior to 2022 from the 16 regions of Ghana and 281 samples collected from clinical patients and their contacts to detect the presence of anti-monkeypox IgG antibodies. The overall seroprevalence of the mpox virus estimated by the study was 29% (526/1788). People living in rural communities were also found to be 0.62 times [95% CI:0.47 – 0.81, p=0.001] more likely to be exposed to the virus which explains the seroprevalence of participants from the Upper East region having a 71% (12/17). Participants younger than 35 years accounted for 66% (1185/1788) of the samples tested and were considered to be unvaccinated with the smallpox vaccine. The likely odds of monkeypox exposure in participants aged >19years, between 20-29 years and 30-39 years were higher compared to other age groups (aOR 1.89: 95% CI 1.23 – 2.91, p=0.004), (aOR 2.04: 95% CI 1.30 – 3.21, p=0.002) and (aOR 1.89: 95% CI 1.19 – 3.01, p=0.007) respectively. The study results indicate a fairly high seroprevalence suggesting existing MPXV circulation, especially among unvaccinated people living in the rural part of Ghana.

6004

SHIFTS IN THE SEASONALITY OF DENGUE ASSOCIATED WITH THE TRANSITION TO ENDEMICITY

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The incidence of many pathogens in humans is affected by seasonality due to climate factors. However, the timing of peak incidence of emerging pathogens often differs from post-emergence seasonal patterns. This study examines the seasonality of dengue in Brazil over a 16-year period to determine if the timing of the dengue season has changed as immunity to dengue in the population accumulates. The hypothesis is that there is a shift in the seasonal timing of dengue due to the accumulation of immunity to dengue over time and a shift towards endemic transmission after the re-emergence of dengue in Brazil in 1986. Alternatively, the seasonality of dengue may be changing due to climatic change. The study analyzed monthly time series from 1999 to 2014 of reported cases of dengue from Brazil surveillance data and associated changes in the timing of the dengue season with climate factors such as temperature, precipitation, and humidity. The age-specific rates of immunity over time were reconstructed using infectious disease transmission models and the potential impact of accumulation of immunity on the timing of seasonal peaks was simulated. The study found that 25 of 27 provinces across Brazil experienced a delay in the timing of seasonal peaks in dengue incidence with an average

delay across all provinces of 2.5 days per year. Temperatures increased throughout Brazil, but only subtle changes in the timing of season have occurred. Mechanistic models incorporating changes in immunity show shifts in the timing of the dengue season consistent with observed data whereas increases in temperature shift the season earlier. The study concludes that the shift in dengue seasonality towards later times of year is consistent with the slow accumulation of immunity in the Brazilian population over the last thirty years. The findings may help to understand changes in seasonality for other emerging pathogens such as Zika, influenza, and SARS-CoV-2.

6005

FACTORS ASSOCIATED WITH CHIKUNGUNYA INFECTION AMONG PREGNANT WOMEN IN GRENADA, WEST INDIES

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Neonates are vulnerable to vector-borne diseases given the potential for mother-to-child congenital transmission of arboviruses and associated complications of neonatal infection. To determine factors associated with chikungunya virus (CHIKV) infection among pregnant women in Grenada, West Indies, a retrospective cohort study enrolled women who were pregnant during the 2014 CHIKV epidemic. 520/688 women (75.5%) were positive for CHIKV IgG. Low incomes, use of pit latrines, lack of home window screens, and subjective reporting of frequent mosquito bites were associated with an increased risk of CHIKV infection in bivariate analyses. In the multivariate modified Poisson regression model, low income (aRR 1.05 [95%CI 1.01-1.10]) and frequent mosquito bites (aRR 1.05 [95%CI 1.01-1.10]) were linked to increased risk of infection. In Grenada, markers of low socio-economic status are associated with CHIKV infection among pregnant women. Given that Grenada will continue to face vector-borne outbreaks in the future, interventions dedicated to improving the housing and living conditions of the most disadvantaged will help to reduce the incidence of a range of arboviral infections and positively impact the health of the population.

6006

FILOVIRUS VIRUS GLYCOPROTEIN - EPITOPE MAPPING, PSEUDOTYPING, AND INFECTIVITY TARGETING

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Recent disease outbreaks highlight the need to characterize the immune response to filoviruses to develop vaccines and therapies. We have used extensive GP mutation libraries to map the epitopes for >200 monoclonal antibodies (MAbs) targeting the EBOV surface glycoprotein, GP. We have extended these studies to Marburg virus (MARV) by generating an Ala-scan library of MARV Δmucin GP (Uganda strain). Initial maps of anti-MARV MAbs include those of two non-neutralizing MAbs MR228 and MR235, targeting the wing region of MARV GP, that showed therapeutic protection in animal models (MR228) or that increased binding (MR235) by neutralizing MAbs. The variety of EBOV MAbs mapped, many from survivors of ebolavirus infection, include cross-neutralizing MAbs targeting the GP membrane-proximal external region (MPER); a broadly cross-reactive MAb that blocks GP interaction with its endosomal receptor Niemann-Pick C1; and MAbs who synergistically transform a non-neutralizing MAb into a potent neutralizer. The epitope maps have expanded our understanding of how the immune system recognizes EBOV GP, and allow correlation of epitopes with MAb neutralizing capabilities, to develop anti-EBOV therapeutics and vaccines. Mapping also identified mutations that increase the exposure of neutralizing epitopes, impacting future anti-ebolavirus vaccine strategies. To provide critical reagents for analyses of antibody or serum immune responses to ebolaviruses, we have developed a pseudotyped lentiviral reporter virus (RVP) system for EBOV and MARV, expressing the appropriate viral GP. These replication-incompetent RVPs perform one round of infectivity and enable safe (BSL-2) and reproducible virus neutralization assays with luminescent or fluorescent readout. Using our knowledge of EBOV GP we have also retargeted pseudotyped lentivirus to multiple cell surface receptors using antibodies inserted into GP1. In mixed primary cell populations, pseudotyped engineered GPs containing B- or T-cell-specific antibodies showed specificity for the targeted cell lineages. Such targeted EBOV GPs enable transduction of specific PBMC cell types.

6007

TRANSMISSION DYNAMICS OF DENGUE VIRUS IN LARGE AND SMALL POPULATION CENTERS IN NORTHERN ECUADOR USING A PHYLOGENETIC ANALYSIS

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Although dengue is considered an "urban" disease, rural communities are also at high risk. To further our understanding of dengue virus (DENV) transmission in settings with characteristics generally considered rural (e.g., lower population density and remote), we conducted a phylogenetic analysis in 6 communities in the northwestern province of Ecuador that have distinct landscape, ecological and social variables that we identify as contributors to transmission risk. During household-based active fever surveillance, we collected 488 serum samples with suspected dengue from participants between 2019 and 2021. One hundred and twenty one had detectable DENV RNA by PCR. Twenty seven samples with CT under 30 were selected for whole genome sequencing (MinION nanopore technology) and phylogenetic analysis that included available DENV sequences from Ecuador and South America. Our data confirmed that DENV-1 circulated from May 2019 to March 2020 and DENV-2 from December 2020 to July 2021. Combining locality and isolation dates, we found strong evidence that DENV entered Ecuador into the northern province of Esmeraldas from neighboring country Colombia, and that viral isolates were related to Colombian and Venezuelan DENV. Phylogenetic patterns suggest that within this province communities with larger populations and commercial centers were more often the source of DENV but that smaller remote communities also play an important role in the regional transmission dynamics acting as sources or sinks of DENV.

6008

DETECTING AND MONITORING THE RE-EMERGENCE OF DENGUE VIRUSES IN PUERTO RICO WITH GENOMIC SURVEILLANCE

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The Americas experienced the highest numbers of dengue cases in 2019 and 2022. The four dengue virus serotypes have recently been reported throughout the Americas, and the emergence of the DENV-2 Cosmopolitan genotype and recent emergence of DENV-3 underscore the importance

of maintaining genomic surveillance. After a period of absence, DENV-1 re-emerged in Puerto Rico in 2019, followed by DENV-2 and DENV-3 in 2022 and we have continued to detect transmission in the island. To characterize the genomic diversity circulating in Puerto Rico, we conducted next-generation sequencing (NGS) of representative samples (N>350) collected through entomological and human surveillance between 2019 and 2023 across Puerto Rico. Complete genomes were obtained directly from clinical samples and mosquito collections using a PCR-targeted NGS method developed by the CDC Dengue Branch. Phylogenetic diversity and the evolutionary dynamics of the circulating DENV-1, -2, and -3 were inferred using maximum likelihood and Bayesian methods. Phylogenetic trees were reconstructed with the addition of genomes from viruses of contemporary circulation in the region for context. Our analyses determined that the emergent DENV-1 variant is phylogenetically related to viruses circulating in the Caribbean but distinct from the lineages previously on the island. Wide-spread transmission of this new variant was confirmed in humans and mosquitoes. Similarly, the emergent DENV-2 is closely related to variants recently detected in Brazil and the emergent DENV-3 is closely related to a variant of Asian origin that caused a recent epidemic in Cuba. We also infer that the three serotypes circulated in the island before detection by laboratory surveillance, suggesting cryptic transmission. Despite detection of new variant introductions, new genotypes have not yet been detected in the island. Our genomic surveillance findings revealed that the re-emergence of dengue viruses in Puerto Rico was caused by the introduction of variants new to the island. We continue to monitor the evolution and spread of these variants to understand the impact to dengue epidemiology in the island.

6009

LOCATION AND TIME ARE DRIVERS OF VIRAL DIVERGENCE DURING ACUTE PHASE ZIKA VIRUS INFECTION

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The high error rate of the RNA-dependent RNA polymerase drives variation in the genome of RNA viruses as they replicate, generating a swarm of viral variants closely related to the original inoculum. A viral swarm is shaped by host and environmental factors which can modify the diversity of the population, and ultimately shape evolution. In the current study we evaluate the impact of T cells, as well as physical barriers, sites of replication and time on the population genetics of Zika virus during acute infection using a mouse model. We ultimately found that time and location of viral replication within the mammalian host are critical factors driving viral swarm divergence, with minimal detected effects of CD4+ and CD8+ T cells over eight days. Using different inoculation routes, we demonstrate that entry of the virus within the CNS acts as a bottleneck, restricting viral variants upon entry. However, once entry into the CNS, novel single nucleotide variant replication was driven by viral replication within the CNS (as opposed to peripheral tissues). Ultimately, this study highlights time and location of replication as important factors in driving divergence of viral populations from the original parent sequence.

6010

NEAR-COMPLETE GENOME SEQUENCES OF DENGUE VIRUS 3 ISOLATES ASSOCIATED WITH OUTBREAKS FROM DIFFERENT REGIONS OF KENYA IN 2011 AND 2019

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Dengue viruses (DENVs) are mosquito-borne viruses which can cause disease ranging from mild fever to severe dengue infection. These viruses are endemic in several tropical and subtropical regions. It is the most prevalent arbovirus in terms of human public health importance globally. Since 2011, Kenya has experienced increased number of outbreaks in mainly the north eastern and coastal regions. Despite the increased number of outbreaks, there is limited information on the genomic epidemiology of DENV in Kenya. In this study, we performed whole genome sequencing (WGS) on Dengue serotype 3 that was isolated from patients in Mandera and Mombasa counties of Kenya, to understand the genetic diversity of Dengue serotype 3 across time in the country and compare with other contemporaneous sequences across the globe. Twenty nine outbreak samples were received at the Arbovirus/VHF laboratory in KEMRI between 2011 and 2019 Ribonucleic acid (RNA) was extracted using QIAmp RNA kit (Qiagen, AG, Hombrech-tikon, Switzerland). Eighteen samples that tested positive and had cycle-threshold (Ct) values below 30 were selected for WGS. The RNA was reverse transcribed using Lunascript were then sequenced by next-generation sequencing using GridION Genome Sequencer (ONT, UK). We obtained 13 near complete genomes (78-97%). Genotyping showed that the Dengue 3 isolates sequenced fall within genotype III. The phylogenetic analysis indicates a variation in the clustering pattern of 2011 and 2019 outbreak isolates. This suggests the outbreak experienced in 2019 was as a result of a new introduction. The 2019 sequences clustered with an isolate from China, while the 2011 sequences clustered in a unique clade, which also shares a common ancestor with other African strains. The findings in the study reveals the existence of two different strains of Dengue 3 genotype III in Kenya. One of this was associated with the outbreak in 2011 and the other caused dengue outbreak in 2019. There is need to sequence more samples to help understand dengue virus trends in the country and in the region at large.

6011

DEVELOPMENT AND CHARACTERIZATION OF BARCODED POWASSAN VIRUS TO ANALYZE BOTTLENECK EVENTS DURING TICK TRANSMISSION

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Powassan virus (POWV) is an emerging tick-borne virus that can cause severe neurologic disease including encephalitis and meningitis. POWV is classified into genetically defined lineages: Powassan virus (POWV, lineage I) and deer tick virus (DTV, lineage II). DTV poses a significant threat to human health because it is transmitted by black-legged ticks (Ixodes scapularis), which display human-biting behavior in highly trafficked wooded areas of the northeastern and north central US. The evolutionary forces exerted on POWV during transmission and pathogenesis are poorly understood. To assess virus population structure during tick transmission, we developed a barcoded virus to quantitatively measure population bottlenecks in cell culture, arthropods, and vertebrates. Barcoded viruses are engineered to contain synonymous nucleotide substitutions that facilitate efficient and cost-effective measurements of the stochastic reductions in virus populations that occur during virus transmission by arthropods. Barcoded POWV (bcPOWV) was created by changing the third nucleotide of 11 consecutive codons in the NS2a coding sequence, resulting in 411 (~4.2

million) possible unique barcodes. DNA containing the synthesized barcode region was inserted into a DTV infectious clone and virus was successfully rescued and propagated in baby hamster kidney (BHK-21) cells to high titers (105 PFU/mL). To confirm the barcode sequence in bcPOWV, we sequenced the barcoded region and observed 11 degenerate nucleotides in sequence chromatograms as expected. In addition, we are performing deep sequencing to quantify barcode diversity. Using bcPOWV, we will assess POWV population dynamics during transstadial and vertical tick transmission, where we will perform deep sequencing to quantify the extent of bottlenecks during the tick life cycle. We expect to see very few changes in genetic diversity from larval to nymphal life stages and major reductions in diversity from adult females to their eggs. Overall, barcoded viruses are a powerful genetic tool, which we will use to assess POWV population dynamics during various transmission modalities.

6012

GENOMIC SURVEILLANCE OF SARS-COV-2 VARIANTS DURING DIFFERENT WAVES OF COVID-19 IN MALI

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Genomic epidemiology of SARS-CoV-2 has been important in the control of COVID-19 pandemic. SARS-CoV-2 genome sequencing has made it possible to detect new variants and inform the COVID-19 control strategies. However, in Mali there are very few genomic data available on SARS-CoV-2. Therefore, we sought to generate more genomic data to contribute the monitoring of SARS-CoV-2 variants circulating in Mali during different waves of the pandemic. A retro-prospective study was conducted on samples collected between March 2020 and September 2022 in Mali representing samples from the first four waves. RNA was extracted using the Qiagen kit. Libraries were prepared using either an Illumina or Nanopore kit and subsequently sequenced on an Illumina MiSeq and MinION respectively at the MRTC. Sequence data was analyzed on a local server. We successfully sequenced 89 viral genomes. In addition, we downloaded 21 Malian sequences from the GISAID repository. We detected ten (10) variants: A, A.1, A.21, A.27, B, B.1, B.1.525 (Eta), B.39, Delta, Omicron (BA.2, BA.5). The most recent increase of cases corresponded to the occurrence of BA.5 Omicron sublineage. Except the A.21 variant, which might have emerged locally, the other variants detected were all cases introduced into Mali. Our results highlight the importance of sequencing SARS-CoV-2 locally and provide information on variants circulating during the first waves of the COVID-19 pandemic. We are monitoring the evolution of variants and updated data will be presented.

6013

SPATIOTEMPORAL DYNAMICS OF CIRCULATING DENV-1 IN LA VIRGINIA, RISARALDA BETWEEN 2019 AND 2021

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Dengue virus (DENV) in Colombia has an endemo-epidemic transmission pattern characterized by circulation of multiple serotypes and lineages with a heterogeneous spatiotemporal distribution. It is not clear how inter-epidemic transmission is sustained, and the triggers for epidemic seasons in the country. This work aims to understand how a recent dengue serotype 1 outbreak is related to transmission dynamics between near and distant endemic regions of Colombia. We performed sequencing and assembly of complete genomes of dengue virus circulating in La Virginia, Risaralda (2019-2021) and Santiago de Cali, Valle del Cauca (2021). Genomes were aligned with sequences from other cities that were available in GenBank. We performed a Maximum-likelihood and Bayesian phylogenetic analyses and identified the best-fit molecular clock and population growth model. Subsequently, we reconstructed the spatial dispersal of the virus using a discrete diffusion phylogeographic model with Markov chains.The lineage of DENV1 that circulated in La Virginia between 2019-2021 is related to the lineages that circulated in the department of Antioquia and share ancestry with viruses introduced in the 1990's from Venezuela. By contrast, the lineage detected in Cali in 2021 is more closely related to a lineage that circulated in the department of Santander in 2008. The reconstructed dispersal routes show that distinct DENV1 lineages from two nearby locations experiencing recent DENV1 transmission (La Virginia and Cali) likely derive from different sources. We hypothesize that introduction and re-introduction of new lineages can be related with sustained transmission and epidemics in our setting. Our results provide insights about the heterogenous dispersal of DENV1 in Colombia, and its potential impact on transmission dynamics.

6014

INTRODUCTION OF A NEW CLADE OF ECSA GENOTYPE DURING THE LARGEST OUTBREAK OF CHIKUNGUNYA VIRUS IN PARAGUAY

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Chikungunya virus (CHIKV) is an arthropod-borne virus (arbovirus) of epidemic concern. CHIKV was introduced to Paraguay in 2015 and caused minor outbreaks in some regions of the country. However, in late 2022 a major outbreak started. Between October 2022 and mid-March 2023, more than 27.700 cases were reported, also cases of meningoencephalitis and deaths caused by CHIKV infection were registered. In this study, we sequenced 30 serum samples collected in Asunción and Central Department in January, 2023. Nanopore technology was used to generate CHIKV near-complete genomes (average coverage nt: 94,06% - CDS: 98,87%). Consensus sequences were assigned as East/Central/South African (ECSA) lineage by Genome Detective tool. Maximum Likelihood phylogeny showed that the current Paraguayan strains grouped separately from the Paraguayan ECSA strains detected in 2018, but within the same clade of Rio de Janeiro ECSA strains from 2019, indicating the introduction of a new clade to Paraguay. Interestingly, CHIKV detected in Paraguay in 2023 formed a monophyletic cluster with a larger branch within the clade. All Paraguayan strains presented new amino acid substitutions: Q368L and S405P at the N-terminal domain of nsp2; A366V at the hyper variable domain of nsp3; L129 and Q175K at RdRp domain of nsp4. Even though E2:V264A was detected at low frequency in sequences from Brazil in 2019, this substitution was present in all the sequences analyzed in this study. Altogether, this data suggest that this ECSA clade of CHIKV this clade may have circulated undetected since 2019 (or the data is not publicly available at the moment). Further studies are needed to address whether the mutations observed in non-structural proteins may have functional consequences for CHIKV replication and/or infectivity, evasion from the immune system or pathogenesis. This study reinforces that continued genomic surveillance strategies are needed to support the monitoring of CHIKV epidemics in order to better understand changes in the incidence, severity of the disease and to shed light onto the highest outbreak caused by CHIKV in Paraguay.

6015

PURIFYING SELECTION DECREASES THE POTENTIAL FOR BANGUI ORTHOBUNYAVIRUS OUTBREAKS IN HUMANS

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Pathogens carried by insects, such as Bunyaviruses, are frequently transmitted into human populations and cause disease. Knowing which spillover events represent a public health threat remains a challenge. Metagenomic next-generation sequencing (mNGS) can support infectious disease diagnostics by enabling detection of any pathogen from clinical specimens. mNGS was performed on blood samples to identify potential viral co-infections in HIV+ individuals from Kinshasa, Democratic Republic of Congo (DRC) participating in an HIV diversity cohort study. Time-resolved phylogenetics and molecular assay development assisted in viral characterization. The nearly complete genome of a novel orthobunyavirus related to Nyangole virus, a virus previously identified in neighboring Uganda, was assembled from an HBV+ patient. A quantitative PCR assay was designed and used to screen over 2,500 plasma samples from Cameroon, DRC, and Uganda, failing to identify any additional cases. Recent sequencing of a US CDC Arbovirus Reference collection revealed that this same virus, now named Bangui virus, was first isolated in 1970 from an individual in the Central African Republic. Time-scaled phylogenetic analyses of Bangui with the related Anopheles and Tanga serogroup complexes indicate that this virus emerged nearly 10,000 years ago. Pervasive and episodic models further suggest this virus is under purifying selection and that only distant common ancestors were subject to positive selection events. This study represents only the second identification of a Bangui virus infection in over 50 years. The presumed rarity of Bangui virus infections in humans can be explained by its constraint to an avian host and insect vector, precluding efficient transmission into the human population. Our results demonstrate that molecular phylogenetic analyses can provide insights into the threat posed by novel or re-emergent viruses identified by mNGS.

6016

PROFILING OF DENGUE SEROTYPE -2 SPECIFIC MICRORNA EXPRESSION IN THE SERUM SAMPLES OF DENGUE PATIENTS IN SABAH, MALAYSIA

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Dengue is an Aedes mosquito-transmitted human arboviral disease which remains endemic in Asia Pacific countries including Malaysia The Dengue virus is a single-stranded, positive-sense RNA virus with four antigenically distinct serotypes namely DENV-1, DENV-2, DENV-3 and DENV-4. MicroRNAs (miRNAs) are a class of small non-coding RNA molecules. There has been substantial prior report which showed the association of MicroRNA (miRNAs) in many viral infections. However, data on circulating microRNA expression patterns in dengue patients are scanty. This study aims to identify the circulating DENV serotype-specific microRNAs in patient's serum. Here we investigate the microRNA expression profiles in the serum samples of DENV-2 serotype patients from Sabah, Malaysia. We have subjected to high-throughput small RNA (sRNA) sequencing. Total RNA was isolated and small RNA sequencing was performed using Illumina MiSeq high-throughput next generation sequencing collected clinical samples from a total of 30 patients with DENV-2 serotype infection and 30 apparently healthy individuals as controls. The serum RNAs was isolated from these subjects and platform to identify deferentially expressed miRNAs. After quality control of the sequence reads, we identified 19 miRNAs that were expressed in DENV-2 serotypes. Of these, 13 were upregulated (hsa-miR-122-5p, hsa-miR-92a-3p, hsa-miR-451a, hsa-let7b-5p, hsa-miR-619-5p, hsa-miR-652-3p, hsa-miR-16-5p, hsa-miR-191-5p, hsa-miR-22-3p, hsa-miR-26a-5p, hsa-miR-320a-3p, hsa-miR-423-3p and has-miR-486-5p) and 6 were down regulated (hsa-miR-197-3p, hsa-miR-27a-3p, hsa-miR-449a, hsa-miR-342-3p, hsa-miR-574-3p and hsa-miR-204-5p). Our preliminary findings seem to suggested significant alterations in the miRNA levels in patients with dengue infection. In conclusion, the differential expression of DENV-2 serotype specific miRNA may provide a better understanding the disease and can be used as a potential biomarker candidate for monitoring dengue viral infection.

6017

METAGENOMICS ANALYSES REVEALS PRESENCE OF THE MERIDA-LIKE VIRUS IN GEORGIA (COUNTRY)

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Emerging arbovirus infections can rapidly expand and adapt in new geographic and environmental conditions. For this reason, mosquito surveillance serves as a tool to detect, monitor, and prevent pathogens which present a potential threat of human infection. In this study, we evaluated the presence and abundance of viral pathogens in mosquitoes of the Culex pipiens specie. Supporting this effort, a total of 467 mosquitoes, were collected from the country of Georgia between 2018 and 2019. We used an unbiased total RNA-seq approach and conducted a Heat Map analysis to explore the mosquito virome. The viral reads from this analysis were mostly aligned to insect-specific viruses from two main families, the Iflaviridae; a positive-stranded RNA virus and the Rhabdoviridae; a single-stranded, negative RNA virus. It was intriguing to find in our heat map analysis viral reads aligning to the Merida-like virus Turkey (MERDLVT) strain. The Merida like-virus is a single-stranded RNA that's known to have high levels of amino acid identity. A Blast sequence analysis of our positive samples aligned to the MERDLVT strain showed an 96-100% sequence identity and an 99.7-100% of sequence coverage. We proceeded to use a phylogenetic tree to further evaluate the evolutionary relationship among these positive pooled specimens with the (MERDLVT) strain and other Merida-like virus strains. As expected, the Merida like- virus found in Georgia mosquitoes clustered with two strains from Turkey; the Merida-like virus KE-2017a isolate 139-1-21 and the Merida-like virus Turkey isolate P431. Collectively, these results imply presence of the MERDLVT strain in Georgia.

6018

CO-INFECTION OF DENGUE AND CHIKUNGUNYA IN BENGALURU CITY, SOUTHERN INDIA - A MOLECULAR SURVEILLANCE APPROACH

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Dengue virus (DENV) and Chikungunya virus (CHIKV) are RNA viruses belonging to families Flaviviridae and Togaviridae transmitted by Aedes sp. Mosquitoes. Globally, the monoinfections and coinfections result in fatalities in the tropical and subtropical regions. Detection of DENV and CHIKV primarily relies on Enzyme Linked immunosorbent assay (ELISA) and rapid antigen tests, which are nonconfirmatory detection methods. Our molecular surveillance study across Bangalore, with local municipal

corporation, aims to understand the prevalence of infections from DENV, CHIKV and coinfections with both arboviruses in ELISA tested patient samples. We screened 892 serum samples from July 2022 to November 2022 collected across the Urban Primary Health Centres, Referral hospitals and Maternity homes. Samples were initially screened for DENV and CHIKV using ELISA. Subsequently, RNA extractions were conducted followed by TaqMan Probe based RTPCRs for serotype-specific detection of DENV and CHIKV. We found 304/892 (34.08%) samples tested positive for DENV and 167/ 892 (18.72%) for CHIKV whereas 77/892 (8.63%) showed presence of coinfection with DENV and CHIKV. Among DENV infections, DENV-serotype-2 showed 56% of infections followed by DENV-serotype 1 showed 46% and DENV-serotype -3 showed 23% of infections. We found 3% of samples infected with multiple serotypes. Total prevalence from DENV and CHIKV exhibited a significant decreasing trend from July to November (Wald's $\chi 2$= 239.66, df =4; P &lt 0.001). This trend was also reflected in infection from DENV (Wald's $\chi 2$= 171.2, df =2; P &lt 0.001) and CHIKV (Wald's $\chi 2$=175.33, df=4 P &lt 0.001) across months. There was no significant variation in viral prevalence by gender. Comparatively, the total prevalence of DENV and CHIKV using ELISA and RTPCRs based detections was found to be 28.14% and 64.70% respectively. Our study represents real-time disease detection using two methods which helps in strengthening the existing the public health surveillance system and contributes towards developing cost-effective protocols in low-resource settings.

6019

SEROLOGICAL EVIDENCE OF PRIOR EXPOSURE TO EMERGING PATHOGENS IN RURAL LIBERIA, WEST AFRICA

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West Africa is a source of emerging pathogens, largely zoonotic, that can cause intra- and extra-regional outbreaks. The extent to which emerging pathogens are transmitted to and by humans undetected is unclear. We assessed serological status to several emerging viruses using serum collected at baseline from a purposefully sampled (age and gender distribution) cohort of individuals >2 years of age living in rural Liberia participating in the observational Coalition for Epidemic Preparedness Innovations (CEPI) ENABLE Study. Samples were analyzed in duplicate using the AFRICOM bead panel for detection of IgG on a Luminex MAGPIX. Viruses included were Ebola Virus (EBOV), Crimean-Congo Hemorrhagic Fever Virus (CCHFV), Lassa Virus (LASV), Marburg Virus (MARV), Rift Valley Fever Virus (RVFV), and Panflavivirus (Panflavi) and Panalphavirus (Panalpha) panels. Median ratios of signal to noise (S:N) and the proportion above selected thresholds were calculated for each virus. Two S:N thresholds were considered including an empirically selected S:N of 10 and a threshold of 40, which in a separate West African cohort was associated with viral neutralization. Serum from 461 participants (age: median = 18; range 2-97. 54% female) were analyzed. The median S:N for individual viruses ranged from 3.6 for MARV to 55.9 for LASV. The proportion of participants exhibiting S:N >10 ranged from 16.7% for MARV to 72.2% for LASV; using a threshold of S:N ratio >40 the proportion ranged from 3.9% for MARV to 55.5% for LASV. Approximately a third of participants exhibited seropositivity for Panflavi or Panalpha antibodies at the >40 S:N threshold. Correlation of seropositivity across the pathogens was observed but while significant, was moderate. Overall, serological evidence of prior infection with emerging pathogens was not uncommon among residents of rural Liberia and, although Lassa fever is endemic, the rate of LASV seropositivity was greater than expected. The detection of seropositivity to the other emerging pathogens tested suggest unrecognized spillover events and the need for enhanced diagnostic capacity to identify these infections in real time.

6020

MAYARO VIRUS EXPOSURE IN FREE-RANGING BATS OF ANIMAL-HUMAN INTERFACE AREAS, MIDWEST BRAZIL

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Arboviruses as Dengue (DENV), Zika (ZIKV) and Chikungunya (CHIKV) are maintained in epidemic cycles of transmission among humans and Aedes aegypti mosquitoes in Brazil, and are of great importance to public health. Other arboviruses such as Yellow Fever (YFV), Mayaro (MAYV) and Oropouche (OROV), that are maintained in enzootic cycles of transmission involving wild vertebrate and diptera species, have also great medical importance in the country. The circulation of these arboviruses in wild vertebrate species at the human-animal interface in Brazil remains poorly investigated. Bats are among the synanthropic vertebrates found in large populations in these areas and their exposure to these arboviruses is still obscure. Here, we aimed to search for the circulation of the main epidemic and enzootic arboviruses in Brazil in specimens of bats collected in forested areas of the metropolitan regions of the Midwest region of Brazil between 2017 and 2018. RT-qPCR assays were used for the investigation of active DENV, ZIKV, CHIKV, YFV, MAYV and OROV infections in liver, kidney and brain tissues of euthanized bats (n=168). Carollia perspicillata, Artibeus lituratus and Artibeus planirostris were the most common species collected. Previous exposure to MAYV and OROV was also evaluated by the investigation of specific neutralizing antibodies by plaque reduction neutralization test (PRNT) in 79 bats from several species. No active infections were identified and none of the bats showed neutralizing antibodies for OROV. On the other hand, 2.6% (2/76) of the bats were seropositive for MAYV, one Noctilio albiventris (PRNT50 titer 40) and one Molossus rufus (PRNT50 titer 80). The role of bats in arbovirus cycles of transmission remains unclear worldwide, and the exposure of bats to MAYV in Midwest Brazil merits further investigation.

6021

EVIDENCE OF CORONAVIRUS TRANSMISSION AMONG PTEROPUS MEDIUS IN BANGLADESH, 2019-2021

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Pteropus bat species are the known reservoirs for henipaviruses; humans are infected with the Nipah virus by P. medius in Bangladesh through the consumption of contaminated date palm sap. The ecological drivers and transmission dynamics of these viruses within the reservoir hosts remain poorly understood. The objective of this study was to investigate coronavirus transmission among P. medius in Bangladesh, which could pose a risk for spillover. Serum samples from 3,023 P. medius in eight colonies across seven districts in Bangladesh were collected between 2019 and 2021 and screened by multiplex immunoassay (MIA) for antibodies reactive to the viral spike glycoprotein (S) from the Severe acute respiratory syndrome coronavirus (SARS-1), Severe acute respiratory syndrome coronavirus-2 (SARS-2), Middle East respiratory syndrome coronavirus (MERS), Bat SARS-like coronavirus isolate Rs4874 (Rs4874), Bat coronavirus isolate PREDICT/PDF-2180 (PDF2180), and Rousettus bat coronavirus HKU9 (HKU9). In addition, pooled oral and fecal swabs from 307 of these bats were screened for coronaviruses using conventional PCR. Two percent (62/3023) of bats tested had coronavirus IgG antibodies from four of the seven districts. Adult seroprevalence (3%, 51/1943) exceeded juvenile (1%, 10/1021) and pup (2%, 1/60). Among the 62 IgG

positive samples, 60 samples (97%) indicated reactivity to Bat-CoV Rs4874 suggesting prior exposure to Bat-CoV Rs4874 or an antigenically similar virus. Bat seroprevalence was highest (4%, 39/876) from Cox,s Bazar, in southeastern Bangladesh. The PCR results revealed that 1% (3/307) of the samples were positive for betacoronavirus, (nobecovirus), which were closely related to bat coronavirus previously identified in the South East Asian region and Bangladesh. These three bats were negative in the serology test for all coronaviruses. The seroreactivity and PCR results (active infection) indicate continuous exposure of the bats to different coronaviruses. The finding of this study added information to support the role of bats as natural reservoirs of coronaviruses.

6022

DETECTED ARBOVIRUSES IN EASTERN MEDITERRANEAN REGION AND SOUTH EAST ASIAN REGION MOSQUITO POPULATIONS: A SYSTEMATIC REVIEW

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The circulation of arboviruses in mosquitoes implicates many arboviruses as causes of undifferentiated fever that remain undiagnosed due to lack of available testing methods and short viremia in humans. We aim to determine what arboviruses have been discovered circulating in mosquito species in Eastearn Mediterranean Region and South East Asian Region. We used the PubMed database to identify 3100 related articles on surveillance of mosquitoes for arboviruses. Following data, among other datapoints, from included studies was extracted: country of surveillance, duration of collection, number of mosquitoes collected, number of different mosquito species identified, detection technique used, viruses screened for and viruses detected. 34 included studies were done in EMR and SEAR, including 3 from Pakistan. Culex are the most prevalent mosquito species. Dengue, West Nile, Japanese Encephalitis and Rift Valley Fever viruses have been detected; dengue and West Nile in Pakistan. The most common method of detection is pooled PCR of mosquitoes using virus-specific primers. Several viruses not currently implicated in human infection such as Tembusu virus, Bagaza virus, Barkedji virus, cell-fusing agent virus, Phlebotomus-associated flavivirus and Culex-specific flaviviruses have also been detected.

6023

FACTORS RESPONSIBLE FOR POST-DISCHARGE DEATH IN COVID PATIENTS

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The post-discharge all-cause mortality of COVID-19 disease is known, but predictors for the same are not much studied. The current research was a single-center unmatched case-control study conducted at a tertiary care center in northern India, between April and September 2022. The data were extracted retrospectively from the hospital's electronic medical records of patients with the assistance of trained physicians using a standardized data extraction sheet. A total of 184 patients were enrolled and were segregated into two groups cases and control with 92 in each. The mean age of patients was 49.3 ±17.53 years. The mortality group had a higher mean age (53.24 ± 18.53 yrs) as compared to the control group (45.37 ± 15.58 yrs, p - 0.002). Bivariate analysis revealed a significant difference in the two groups with respect to O2 saturation at the time of admission (Case - 91.12 ± 12.49 %, control - 95.46 ± 5.01 %, p - 0.003); Maximum O2 flow rate [L/min] (Case - 11.01 ± 22.2, Control - 6.41 ± 13.31, P - 0.04); ICU need (p - 0.005), Cancer (p - 0.001), O2 requirement at discharge (p - 0.001) and AKI (p - 0.007). On multiple regression analysis, Cancer (aOR- 2.469; 95% CI,1.183- 5.150, p-0.016), ICU admission (aOR- 2.446; 95% CI, 1.212-4.938, p- 0.013), Oxygen at discharge (aOR- 2.340; 95% CI, 0.971-5.640, p-0.0586) and Acute kidney injury (aOR- 5.6; 95% CI, 2.351-13.370, p-0.00) only found to be significant. Among the patients discharged from the hospital post-COVID-19 treatment, the following aspects oxygen requirement (2.3 times), Malignancy (2.4 times), ICU admission (2.4 times), and Acute Kidney Injury (5.6 times) are risk factors of mortality. The presence of these variables would warrant a close follow-up for these patients in order to decrease post-COVID mortality.

6024

ROLE OF TELEHEALTH AND COMMUNITY MOBILIZATION IN MANAGING COVID -19 WITHIN THE CONTEXT OF A DISTRICT HEALTH SYSTEM IN MALAWI

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The COVID-19 pandemic has impacted health systems globally. High demand for health services and staff absenteeism due to illness are some of the barriers that negatively affected healthcare delivery. To reduce pressure on healthcare services, academics from Blantyre implemented the "Strengthening COVID-19 Response in Blantyre District" (SCORE) project, which established a remote case management system (phone clinic) and community mobilization workforce in fighting COVID-19. A cross-sectional study was done to evaluate the pilot implementation of the project. Qualitative and quantitative methods were used to collect data from community leaders (n=27), volunteers (n=49), and members (n=201) from communities served by the project: Chileka, Limbe, Mpemba and Ndirande. Data was also collected from District Health Management Team (DHMT) (n=5) and Health Surveillance Assistants (HSAs) (n=6). Focus Group Discussions, in-depth interviews and structured questionnaires were used to collect data. Quantitative data was analyzed descriptively using SPSS 26. Qualitative data was transcribed and analysis was done using Nvivo 12. Phone calls data showed 58% of inquiries were for COVID-19 followed by general healthcare (25%). Of COVID-19 enquiries, 41% were for general information, 29% for preventive measures, and 14% for signs and symptoms. 99% of participants said the SCORE project helped spread COVID-19 preventive measures, 92% raised awareness of risk factors, and 90% encouraged vaccination. Qualitative data showed volunteers had a good working relationship with community leaders, HSAs, and members. Both interventions were recommended by communities and District Health Office staff for scale up and extension to other health conditions like HIV and Cholera. The project showed its potential to enhance remote case management, information sharing and community mobilization efforts related to COVID-19. In conclusion, the project has shown that effective remote case management and community mobilization can reduce pressure on healthcare systems and improve health outcomes, providing a model for future health crisis response efforts.

6025

DISTRIBUTION AND OUTCOMES OF ANIMAL BITES IN THE MBALE REGION OF EASTERN UGANDA

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Animal bites can lead to rabies, tetanus, and skin/soft tissue infection, and are a significant cause of global morbidity and mortality. Although an average of 16,414 animal bites are reported each year in Uganda, there is a paucity of data on animal bites in the country. In this cross-sectional study, we aimed to determine the distribution and outcomes of animal bites in the Mbale region of eastern Uganda. We collected data on demographic characteristics of those with animal bites in the Uganda District Health

Information Software 2 database maintained by the Uganda Ministry of Health. We included data that were reported from January-December 2022 from outpatient departments in the 16 districts of the Mbale region. We determined frequencies and proportions of each variable and used the QGIS to present the analyzed data. Animal bites were documented in 984 of 4,656,700 patient visits to health centers in the Mbale region. During the same period, a total of 15,261 rabies exposures were reported in the country with 833 (5%) reported from the Mbale region. Of those bitten by animals in the Mbale region, 540 (55%) were male and the median (interquartile range) age was 17.5 (7.5-25.5) years. The frequency of animal bites ranged from 10 to 20 per week. Bukwo, Tororo, and Busia districts had the highest prevalence rates of animal bites in the Mbale region with 1.74, 1.68, and 0.81 bites per 1000 population, respectively. Of those bitten, there were 7 deaths (case fatality ratio 0.71%), all of which were attributed to rabies. Animal bites and rabies exposure are common in the Mbale region. Our findings emphasize the need for the availability and administration of routine and post-exposure vaccination to prevent rabies and tetanus following animal bites in the high prevalence at-risk Mbale region of eastern Uganda.

6026

MOSQUITO IDENTIFICATION: NANOPORE SEQUENCING OUT OF A SUITCASE LAB AS AN EARLY WARNING SYSTEM FOR EMERGING INFECTIOUS DISEASES

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Mosquito-borne diseases are responsible for spillover to around 700 million people each year, including many neglected tropical diseases such as Dengue fever and Chikungunya virus disease. Case reports are rising over the last decades, as mosquito species flare-up as a result of climate change and globalization. Surveillance tools and early warning systems are essential to prevent disease spread to humans and animals. Next generation sequencing technologies offer great advantages for disease outbreak investigation. The aim of this study was to develop a rapid and field deployable sequencing platform to identify potential mosquito-borne pathogens, mosquito species and host in blood meals. First a rapid extraction reverse purification method was developed. Nucleic from mosquito specimens, including Culiseta longiareolata, Culex pipiens, Aedes albopictus, Ae. cretinus and Ae. aegypti were isolated using a rapid "all-in-one" extraction protocol based on lysis buffer, glass beads, magnetic beads, heating and vortexing. Nucleic acid from 30 mosquito samples were extracted using commercial purification kits as a control. Rapid barcoding 96 sequencing (Oxford Nanopore Technologies) was performed using a MinION Mk1c device. For RNA targets, a reverse transcription step was performed using random hexamers. All handling steps were carried out in the fully equipped suitcase lab. A specific offline BLAST database was created to semiautomatically identify mosquito species, host in blood meal and pathogens. In all samples, the species was correctly identified. Both animal and human DNA could be detected. Interestingly, only mosquito origin viruses could be detected in the pool. The nucleic acid extraction and detection protocol performed in the suitcase lab allows fast mosquito "footprint" analysis directly in the field. This could pave the way as an early warning tool for mosquito-borne diseases and on-site outbreak investigation. Ultimately, the point-of-need generated data can lead to more accurate and fast preventive measure implementation. We are testing the whole system in a highly endemic region in Bangladesh.

6027

SIMIAN ARTERIVIRUSES: A ZOONOTIC THREAT?

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Simian arteriviruses are endemic in African nonhuman primates yet remain largely unstudied and uncultured in vitro. These viruses can cause Ebola-like diseases that are fatal to Asian macaques but are not yet known to infect humans. To evaluate the risk for a spillover event, we tested the ability of a simian arterivirus, simian hemorrhagic fever virus (SHFV), to enter human cells and replicate within them. First, we substantiated CD163 as the cellular receptor for SHFV entry into host cells. Next, we showed that CD163 acts as an intracellular receptor, a rare mode of virion entry that is shared with other high-consequence viral pathogens (e.g., Ebola virus and Lassa virus). Alarmingly, we found that the human version of CD163 is a fully functional receptor for SHFV entry into cells. Further, SHFV can replicate robustly in human cells, showing full functionality of the orthologs of all host proteins required for the SHFV lifecycle. Our study raises concern about future possible spillovers of simian arteriviruses to humans and the potential public-health risk that such spillover events would pose. Indeed, it is possible that people in Africa are already being infected with simian arteriviruses but that these cases remain undetected in the way HIV-1 infections did for decades. For elucidation, development of serology tests for human surveillance should be a priority.

6028

CASE AND WASTEWATER SURVEILLANCE TO MONITOR COVID-19 AND OTHER INFECTIOUS DISEASES IN ATLANTA K-12 SCHOOLS

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For schools, timely responses to outbreaks of infectious diseases rely on information from disease surveillance systems. Epidemiological case surveillance information for schools can be extracted from public health databases at county/city level or collected from schools that use a self-reporting system. Wastewater surveillance has been recognized as a valuable tool to complement case surveillance. Wastewater samples are typically collected at wastewater treatment plants, but can also be collected at manholes adjacent to schools. This study compares information from wastewater surveillance at the city and school level to reported case data at the county and school level for 14 K-12 schools in Atlanta, GA. COVID-19 epidemic curves for Fulton County, the City of Atlanta, and specific school zones were generated using geocoded case information reported to the Georgia Department of Public Health. Self-reported case information was obtained for K-12 schools within Atlanta Public School district. Wastewater surveillance data from wastewater treatment facilities in Atlanta was also obtained. From 09-07-2021 to 03-14-2023, we collected and analyzed 489 Moore swab samples from manholes that only received wastewater from the study schools. All samples were tested for SARS-CoV-2 RNA, and after 11-29-2022, 88 samples were also tested for Influenza A and RSV, and 74 were tested for Influenza B by qPCR. 41% (201/489) of samples tested positive for SARS-CoV-2. Temporal and school variation were observed with high schools having the greatest proportion of wastewater samples

positive for SARS-CoV-2 and the lowest reported COVID-19 incidence. Very few samples were positive for Influenza A (5.7%), RSV (2.3%), and Influenza B (0%). We found increasing discordance between results from different case and wastewater surveillance systems which may reflect greater underreporting of cases, changing SARS-CoV-2 fecal shedding patterns, and decreasing sensitivity of assays for emerging variants. The results from this study provide insights for how K-12 schools can use information from different surveillance systems to guide public health measures.

6029

DETECTION OF HUMAN CORONAVIRUSES AMONG PATIENTS WITH RESPIRATORY TRACT INFECTIONS IN GHANA

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Acute Respiratory infections are caused by various microorganisms particularly viruses including influenza, human metapneumovirus, adenoviruses and coronaviruses; human coronaviruses (HCoVs). HCoVs account for up to 18.4% of ARIs burden globally and between 3.5-12.4% in Ghana. During the COVID-19 pandemic, individuals presented with febrile-like-illnesses exhibiting respiratory symptoms yet, tested negative for SARS-CoV-2 and influenza viruses. HCoVs and influenza viruses are known to exhibit symptoms similar to SARS-CoV-2 hence there is the plausibility that during the pandemic, the symptomatic but negative SARS-CoV-2 and influenza samples could have tested positive for these other HCoVs. To investigate the presence of other human coronaviruses from archived negative SARS-CoV-2 and Influenza samples. The study will adopt a retrospective cross-sectional study which will involve archived samples collected from influenza sentinel surveillance sites in Ghana. RNA will be extracted from samples and and amplified by RT-qPCR to detect the other human coronaviruses (OC43, NL63, HKU1 and 229E) and sequenced using MinIon sequencing to detect variations in the strains. Conclusions, this investigation will contribute to an understanding of the causes of ARI in Ghana and aid health authorities enact policies to improve quality health care delivery and patient management.

6030

USE OF LIGHTWEIGHT GPS DATA LOGGERS TO TRACK HORSESHOE BAT MOVEMENT PATTERNS IN EASTERN UGANDA

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Bats are reservoirs for pathogens with zoonotic potential; therefore, it is crucial to investigate aspects of bat ecology that may facilitate spillover events. Bats in the genus Rhinolophus, commonly called horseshoe bats, are known to harbor SARS-like coronaviruses. Geospatial investigations of horseshoe bat ecology are often hindered by the small size of these insectivorous bats. To evaluate seasonal movement and foraging patterns of horseshoe bats in Eastern Uganda, we fitted 36 bats with ultra-lightweight (<1.1g) GPS data loggers in January and May of 2022 as part of a larger viral surveillance program targeting bat caves in the region. We demonstrate the successful deployment and recapture (9/36) of data loggers collecting high-resolution short-term foraging data from cave roosting Rhinolophus spp. in Eastern Uganda, and share recommendations on their future use in other bat-related applications.

6031

IGG HYPORESPONSIVENESS AFTER DENGUE VIRUS INFECTION IN KENYAN CHILDREN

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An important serologic hallmark for dengue virus (DENV) infection is the development of DENV specific IgG. Previously, we observed IgG hyporesponsiveness after DENV infection in a cohort of febrile Kenyan children who had DENV viremia, documented by RT-PCR, who failed to seroconvert from negative to positive serum anti-DENV IgG after one month (median interval 31 days between febrile and follow up visits, interquartile range 28-36 days). We hypothesized that the serum IgG response to DENV infection may be transitory or delayed. To investigate our hypothesis, we designed a study to measure anti-DENV IgG in cases of DENV infected children at 6 different timepoints over the course of a year: at the febrile visit, 14 days, 30 days, 3 months, 6 months, and 12 months. We enrolled 1046 subjects and identified 12 cases of acute DENV infection (by RT-PCR), along with temporally and geographically matched controls without DENV infection. One case developed anti-DENV by 3 months post-infection. Another case did not develop anti-DENV until 3 to 6 months later. The remaining DENV cases and non-infected controls did not develop anti-DENV IgG at any time point throughout the 1 year follow up period. Ongoing characterization of the peripheral memory B cell population by mass cytometry may yield insights into the mechanisms that govern DENV IgG hyporesponsiveness. These examples of delayed development of anti-DENV IgG or complete anergy after infection imply that previous cross-sectional serologic surveys based on anti-DENV IgG prevalence may have grossly underestimated DENV exposure in our population. IgG hyporesponsiveness to DENV infection also may underlie the low incidence of severe dengue disease previously observed in our population. Finally, IgG hyporesponsiveness to DENV must factor into the design of future vaccine studies and/or immunization campaigns.

6032

CHIKUNGUNYA VIRUS SPECIFIC T CELLS PREDOMINANTLY RECOGNIZE VIRAL STRUCTURAL PROTEINS

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Chikungunya disease (CHIK) is a mosquito-borne re-emerging viral disease, that is defined by its capability to induce incapacitating chronic arthralgia and inflammation in patients' months to years following infection. Despite CHIKV outbreaks occurring worldwide and several vaccines currently in development, CHIKV immune response remains largely understudied. Chikungunya virus (CHIKV) the causative agent for CHIK, is an alphavirus, coded in five structural proteins (CP, E3, E2, 6K, E1) and four non-structural proteins (nsP1, nsP2, nsP3, nsP4).We have tested pools of overlapping peptides spanning each of these viral protein in peripheral blood mononuclear cells (PBMCs) collected from patients diagnosed with CHIKV during the 2014-2015 outbreak in Colombia. The majority of these patients still experienced diseases symptoms 7 years after infection, representing a chronic infection with CHIKV. To characterize the CHIKV specific T cell response we performed high resolution flow cytometry analysis utilizing the Activation Induced Marker (AIM) and Intracellular Cytokine Staining (ICS) assays, to evaluate CHIKV-specific T cell responses directly ex vivo,

without the need for intensive manipulation.Interestingly, we detected CHIKV specific CD4+ T cell responses in the majority of patients 7 years after CHIKV infection. Memory CD8+ T cell responses were also observed but at much lower frequencies. Overall, two thirds of antigen-specific CD4+ T cell responses were directed against structural protein while one third was directed against non-structural proteins. In conclusion, this study comprehensively characterizes the T cell response against CHIKV during the chronic phase and provides insights in the possible role of T cells in CHIK disease.

6033

INVESTIGATING THE IMMUNE PROFILES ELICITED BY CLINICALLY APPARENT AND CLINICALLY INAPPARENT DENGUE VIRUS INFECTIONS

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Dengue virus (DENV) is a flavivirus transmitted by Aedes mosquitoes that can cause symptoms ranging from febrile illness to hemorrhagic fever. There are an estimated 400 million cases of dengue every year, with the majority being clinically inapparent. While much is known about the immunological differences between mild and severe dengue infection, the immunological correlates of clinically inapparent and clinically apparent infections are currently unclear. To fill this knowledge gap, our team initiated a prospective, hybrid cohort-cluster study designed to characterize DENV transmission in multigenerational households in Kamphaeng Phet, Thailand. Enrollment requirements for this study include a household containing a pregnant female, an adult 50 years or older, and a child, with the newborn being enrolled in the study at birth. Annual blood draws from all study participants are obtained starting upon enrollment, supplemented with blood draws taken from each of the family member upon confirmation of a dengue illness in the household through active surveillance. Currently in its eighth year, this study design allows for the investigation of pre- and post-infection DENV-specific immunity, and the detection of inapparent DENV infections. Using virologic and serologic assays we have identified 148 acute infections through active surveillance. Of these, 43 out of 65 primary infections and 16 out of 83 secondary infections were inapparent. Preliminary data has shown a lower titer of IgG and IgM in inapparent samples from both primary and secondary infections when compared to total antibody titers of the same samples, suggesting that there may be more IgA present in the serum from clinically inapparent cases. Using a multiplex serology assay we are assessing the contribution of IgA to the antibody profile following apparent and inapparent DENV infections, as we propose that IgA may be a biomarker associated with less severe DENV infections. These findings would have implications for the identification of correlates of protection from dengue illness, urgently needed for the design and evaluation of DENV vaccines and potential therapeutics.

6034

MALARIA-EXPOSED UGANDANS EXHIBIT A DIFFERENTIAL SARS-COV-2-SPECIFIC T CELL RESPONSE

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While SARS-CoV-2 and its interaction with the immune response has been well-studied in resource-rich areas, there are still many unanswered questions about how it affects malaria-endemic areas in sub-Saharan Africa. Compared to other global regions, during the pandemic, hospitalization and death rates have been reported to be much lower in these areas. One possible explanation could be differential immune responses due to different infectious exposures such as malaria. Using samples collected from SARS-CoV-2 exposed Ugandan adults, and similarly aged adults from California, we investigated the SARS-CoV-2-specific T cell response by intracellular cytokine staining (ICS) and an activation-induced marker (AIM) assay. Overall, we found that COVID-19 seropositive Ugandans have a diminished SARS-CoV-2-specific T cell response compared to convalescent Californians. IFNg- and TNFα-producing T cells were predominant in the Californian cohort early on and months after initial infection. However, very low or no IFNg and TNFα production was found in the Ugandan cohort. Furthermore, Ugandans have a heightened IL-10-producing CD4+ regulatory response after polyclonal stimulation. Ongoing research will investigate whether and how other pathogenic exposures, specifically malaria, may influence the T cell response. We hypothesize that previous exposure to malaria mitigates infection with SARS-CoV-2 due to a more 'tolerized' immune response. Potential explanations for our findings include epitope cross-reactivity or down-modulation of an inflammatory response that is implicated in severe COVID-19. Identifying differences in immune responses across populations will be important for future therapeutic innovations and vaccine development.

6035

17DD-BASED YELLOW FEVER INACTIVATED VACCINE IN ASSOCIATION WITH THE NS3 HELICASE DOMAIN INDUCES T LYMPHOCYTE RESPONSES AND SEROCONVERSION TO YELLOW FEVER VIRUS IN A MURINE MODEL

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Yellow fever is a disease caused by the Yellow Fever virus (YFV), an arbovirus that belongs to family Flaviviridae, genus Flavivirus. Like other flaviviruses, YFV RNA genome encodes a polyprotein that is cleaved into 7 non-structural and 3 structural proteins that harbor the majority of epitopes involved with the cellular and humoral immune responses. Yellow Fever clinical manifestations range from a mild disease to a severe disease characterized several organ impairment. However, different from other arbovirus diseases, a live-attenuated virus vaccine (17D/17DD) is available to prevent against YFV infections but, in rare cases, the immunization with this vaccine can cause serious adverse effects, such as viscerotropic or neurological diseases. Furthermore, it is not recommended for immunosuppressed individuals. An inactivated YFV vaccine was manufactured using YFV-17DD virus, either in its pure preparation [inactivated (i17DD)] or in combination with a recombinant NS3 helicase peptide (i17DD+NS3Hel). The safety and immunological responses to these inactivated vaccines were evaluated in C57BL/6 mice. Our preliminary results showed that the combination of i17DD+NS3Hel promoted TCD4+ and TCD8+ lymphocyte expansion undistinguishable from the groups that received either inactivated or attenuated YFV-17DD virus. When investigating the response profile of TCD4+ cells, it was observed that this population is more associated with a Th1 profile, which grants cellular immunity to viruses, since no IL-4 expression was detected and IL-2 and IFN-gamma levels were similar to those observed with both YFV-17DD viruses. Regarding the antibody response, 100% of the mice that received the formulation i17DD+NS3Hel seroconverted to YFV. Neutralization and survival testing are ongoing to finalize the vaccine validation. Up to this moment, it was observed that, in mice, the i17DD+NS3Hel vaccine formulation elicits an immune response compared to that observed with

both YFV-17DD vaccines and might be an alternative to vaccination against Yellow fever in individuals in whom the attenuated vaccine is not recommended.

6036

ANTIBODY-DEPENDENT COMPLEMENT ACTIVATION AND DENV3 DISEASE SEVERITY

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Dengue Viruses (DENV), consists of a family with four serotypes. Dengue is a mosquito-borne agent responsible for causing Dengue Fever (DF), which in a small proportion of cases can further develop into a more severe disease, dengue hemorrhagic fever (DHF), characterized by blood plasma leakage, that can lead to cardiovascular shock and organ failure. Dengue disease overall is an inflammatory-driven pathology, with complement dysfunction having been implicated as playing a role in the progression to DHF. The extent to which antibody-dependent complement activation (ADCA) participates in this process is not fully known. To investigate the ability of dengue antibodies specific to DENV3 NS1 to perform ADCA using a novel bead-based complement assay. In this assay, DENV3 NS1 is bound to fluorescent beads to incubate with patient samples, allowing for the formation of immune complexes. The beads are then incubated with a complement source, allowing for immune complexes to perform ADCA. The beads are then stained with an anti-complement factor 3 (C3) fluorophore-conjugated antibody, and flow cytometry is used to quantify the deposition of C3 fragments. This assay was utilized to quantify ADCA in serial samples from acute and convalescent cases of primary and secondary DENV3 cases, from both DF and DHF. Additionally, antibody endpoint titers were measured by ELISA to determine correlation with ADCA. When comparing the ADCA capacity in the cohort, it is determined that secondary DENV3 infections have higher complement deposition than primary DENV3 infections and that secondary infections with DHF develop the most potent antibodies to activate complement. Antibody titer was shown to have a moderate correlation with C3 deposition and ADCA, as expected. Data utilizing the complement assay supports the hypothesis that secondary DENV3 infections show greater complement deposition, particularly in secondary DENV3 DHF cases during the onset of severe symptoms. Further work will be done with this assay to further explore the potential relationship between ADCA and severe outcomes of dengue.

6037

STRUCTURE-GUIDED DENGUE VIRUS TYPE 2 SUBUNIT VACCINE DESIGN TO FOCUS ANTIBODY RESPONSE TO POTENT, NEUTRALIZING EPITOPES ON VIRAL ENVELOPE PROTEIN

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The four dengue virus (DV) serotypes are mosquito-borne flaviviruses responsible for dengue fever and dengue hemorrhagic disease. Leading vaccine candidates based on tetravalent live-attenuated DV formulations have had variable efficacy and safety due to an imbalanced response to the DV serotypes in the vaccine and dengue serostatus pre-vaccination. DV subunit vaccines based on recombinant envelope (E) proteins from the four serotypes have also performed poorly, partly because at physiological temperature the secreted wild-type E protein (WT rE) is mainly present as a monomer that does not display quaternary structure epitopes on the native E dimer recognized by potent neutralizing human antibodies (Ab). Using the molecular modeling software, Rosetta, and experimental approaches, we have previously defined a small number of mutations that stabilize DV rE dimer (SD rE) under physiological conditions of vaccination. Here, we report on studies to test if the SD rE vaccine antigen redirects the functionally-neutralizing Ab response to E dimer-dependent quaternary structure epitopes on the infectious virus. Since fusion loop (FL) Ab can cause antibody-dependent enhancement which increases disease severity upon heterologous DV infection, we also tested SD rE with mutated FL. To compare Ab properties induced by different antigens, we immunized mice with DV2 WT rE or SD rE variants. We found that SD-vaccinated mice had significantly higher DV2 IgG binding titer and more than 20-fold greater neutralizing Ab titer compared to WT-vaccinated mice. Using Ab depletion techniques to remove sub-populations of DV-specific Ab and recombinant E protein domain transplant viruses, we mapped the specificity of binding and neutralizing Ab induced by WT and SD rE. Studies are ongoing to compare levels of DV enhancing Ab by different vaccine constructs. Preliminary results indicate that neutralizing Ab from WT-vaccinated mice bind to simple epitopes on rE monomers, while those from SD-vaccinated mice are mostly dimer-specific. Our results demonstrate the promise of structure-guided design to preserve epitopes of interest on dengue subunit vaccines.

6038

MOLECULAR ANALYSIS OF THE ANTIBODY REPERTOIRE ELICITED AFTER YELLOW FEVER VACCINATION

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Flavivirus co-circulation and outbreaks have been reported in the Americas during the last decade. Evidence indicates that pre-existing immunity to one virus can influence the disease course of a heterologous virus infection; however, little is understood about the molecular dynamics and prevalence of the cross-reactive antibodies in the repertoire of an endemic population vaccinated against yellow fever virus (YFV). Therefore, here we seek to determine the serological response among YFV, Dengue and Zika viruses following the YFV vaccination of healthy Brazilian donors. We performed YFV, DENV and ZIKV virus neutralization tests (PRNT) and indirect IgG ELISA in longitudinal samples obtained 0, 7, 14, 28 and 180 days after vaccination. Furthermore, we assessed the diversity and clonal expansion of the B-cell repertoire at seven and fourteen days after vaccination. All donors had anti-YFV antibodies that peaked between 14 and 28 days post vaccination. Results from both neutralization and ELISA tests revealed cross-reactive antibodies to ZIKV and DENV viruses before and 28 days after YFV vaccination, with NAb to DENV slightly higher (approximately 3-fold higher) than NAb to ZIKV among all individuals. The DENV and ZIKV seroprevalence in this cohort ranged from 75% and 50% (IgG ELISA) to 100% (PRNT), respectively. Analysis of the B cell clonotypes identified 600 shared clones among the individuals (75%). Most of these clonotypes were found expanded and presented greatest diversity 7 days after the vaccination. Taken together, we observed a variable degree of serological cross-reactivity across three flaviviruses, which we speculate is related to donor YFV vaccination status, endemic co-circulation of ZIKV and DENV, or both. These observations may have implications for accurate diagnostic testing, for vaccination strategy and for the study of host-virus interactions.

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CONSERVED MONOCYTE RESPONSES TO ACUTE RNA VIRUS INFECTION

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The 21st century has seen five virus-driven pandemics. Despite emerging viruses constantly threatening global health, we remain largely unprepared for the next pandemic. Previous studies have shown that emergency myelopoiesis and monocyte dysregulation are associated with severe COVID-19. In this study, we aimed to identify conserved and

diverse features of antiviral immunity through single-cell proteomic and transcriptional profiling studies across acute RNA viral diseases. Our analysis revealed shifts in monocyte populations towards increased CD14+ monocytes across viral infections in humans and macaques caused by various viral species, including Lassa, Ebola, Marburg, influenza, Zika, and dengue. We integrated single-cell RNA sequencing (scRNA-seq) data from all publicly available datasets that profile non-COVID-19 viral diseases, including blood samples from 38 individuals infected with dengue, influenza, or RSV with an additional 49 samples from SARS-CoV-2-infected individuals. By using this integrated data, we found conserved shifts in monocyte phenotype that were correlated with disease severity and defined by genes that also mark myeloid-derived suppressor-like cells and bacterial sepsis-induced monocytes. This signature was observed across disease progression in Ebola-challenged rhesus macaques and could be detected across over 2000 bulk RNA-seq blood samples collected from virally-infected humans and macaques, allowing us to differentiate between infected and uninfected subjects. Our study demonstrates that integrative single-cell profiling can identify dysfunctional immune responses shared across different viral infections and yield detailed insights into the underlying monocyte-specific pathological processes that may be targeted in a broad-spectrum manner. We expect that our findings will contribute to the development of effective strategies for combating future viral pandemics.

6040

ANTIBODIES AGAINST THE SARS-COV-2 DELTA VARIANT SHOWED CROSS-REACTIVITY TO INFLUENZA VIRUSES

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According to sparse information from various countries, the seasonal influenza virus circulation has drastically decreased during the COVID-19 pandemic. The S protein of SARS-CoV-2 is heavily glycosylated, much like type I fusion proteins of influenza virus hemagglutinin. These glycosylation patterns can either result in immune evasion or viral neutralization by generating cross-reactive antibodies. Here, we show the cross-reactivity of anti-SARS-CoV-2 antibodies against influenza viruses. Serum samples were collected from 311 SARS-CoV-2 infected individuals. The samples were tested for antibody titers against SARS-CoV-2 by ELISA &seasonal influenza virus strains (influenza A/H1N1, A/H3N2, B/Yamagata, &B/Victoria) using a Hemagglutination Inhibition Assay (HAI). In addition, SARS-CoV-2 antibody-positive but Influenza antibody-negative samples (n=16) were investigated to determine the SARS-CoV-2 antibody-neutralizing potential against influenza viruses by microneutralization (MN) assay. The SARS-CoV-2 genomes were sequenced using Illumina next-generation sequencing, &an in-silico protein structural analysis was performed to identify epitope &antibody binding similarities between SARS-CoV-2 &influenza viruses. Among 16 samples that didn't contain antibodies against Influenza A strains (H1N1 &H3N2), five showed high (MN titer≥20), &six showed moderate (MN titer≥10) capability to neutralize Influenza A. Subsequent in-silico analysis revealed that most efficient binding (>8 Kcal/mole) was found between the antibodies of SARS-CoV-2 delta variant (ΔG) with influenza A/H1N1 HA (Hemagglutinin), A/H3N2 HA, A/H1N1 NA (Neuraminidase), &A/H3N2 NA glycoproteins with -12.4, -9.3, -10.1, &-11.7 Kcal/mole, respectively. This investigation revealed that neutralizing antibodies of the delta variant cross-reacted with the Influenza A virus, which might protect against influenza viruses &reduce &shift the seasonal influenza circulation during the COVID-19 pandemic. Our findings warrant further study to explain the probable mechanisms of this cross-reactivity.

6041

ROLE OF THE PLACENTA SPECIFIC CHROMOSOME 19 MICRORNA CLUSTER DURING ZIKA INFECTION

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The largest primate and placenta specific C19MC microRNA cluster has been implicated in the development and function of the placenta, and having an antiviral activity for specific viruses. The 2015 outbreak of the emergent flavivirus Zika in the Americas was associated with microcephalia and other congenital malformations. The risk of having congenital Zika was higher at the beginning of pregnancy, whereas the expression of C19MC miRNA cluster increases during pregnancy and is the highest at term. Thus, we hypothesized that, through its antiviral activity, C19MC miRNA could be implicated in the placenta protection of the foetus during pregnancy. The antiviral role of the C19MC miRNA cluster was demonstrated using a novel Knock-Out (KO) model. We generated an in vitro model from JAR human placental choriocarcinoma cell line using the CRISPR/Cas9 system. Through real time quantitative PCR, western blotting, flow cytometry, and immunofluorescence techniques to detect viral infected cells, we showed that C19MC KO cells infected with the Zika virus are more susceptible to viral infections than their wild-type counterparts. Additionally, the TCID50 assay and flow cytometry analysis showed a significantly higher viral infectivity of the supernatants containing virions released from infected KO cells than from WT cells. This antiviral effect of WT supernatants can be transferred to recipient cells (Vero cell line) by means of extracellular vesicles, suggesting a paracrine antiviral method of action. In conclusion, our study provides a novel KO-model to assess the complex role of C19MC miRNA cluster during viral congenital infections, and whether it can act, in part, via extracellular vesicles. Clear understanding of this cluster's antiviral role is key to the development of new and more reliable prognostic and therapeutic tools for viruses with a potential congenital effect.

6042

USE OF A STABILIZED CONFORMATIONAL DENGUE VIRUS SEROTYPE 2 ENVELOPE ANTIGEN TO ISOLATE MEMORY-DERIVED NEUTRALIZING MONOCLONAL ANTIBODIES FROM A CONVALESCENT PATIENT.

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Dengue is a mosquito-borne disease caused by four serotypes of dengue virus (DENV), each of which can elicit serotype-specific or cross-reactive antibodies that target the envelope (E) structural glycoprotein. Understanding how DENV-specific B cell responses drive antibody-mediated protection is important to vaccine design. To directly study this, we used a recently developed recombinant E protein stablized dimer (recED) derived from DENV serotype 2 to probe DENV-specific memory B cells from a patient recovered from dengue. Complementary approaches including direct sorting of recED-binding memory B cells followed by antibody gene sequencing or culture and characterization of secreted antibody from recED-sorted cells yielded 25 novel lineages of DENV-reactive monoclonal antibodies (mAbs), at least three of which exhibited neutralizing activity against multiple serotypes including DENV2. Unlike other DENV cross-reactive mAbs, some of which show neutralizing activity against Zika virus, the characterized recED-binding mAbs recognized, but did not neutralize Zika virus. These results indicate that recED can be used

to tag DENV2-reactive surface immunoglobulin-positive memory B cells and isolate DENV-neutralizing antibodies from patients. These data extend in vivo studies showing that immunization of animals with recED generates DENV2-neutralizing responses. We hypothesize that this antigen can be used to define the landscape of DENV-specific B cell responses in defined vaccination and viral challenge settings.

6043

TISSUE-SPECIFIC T-CELL RESPONSES AMONG 44 FATAL COVID-19 CASES

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T-cells play an essential role in recognizing and clearing viruses from infected tissues. The breadth and depth of circulating T-cell responses among patients with coronavirus disease 2019 (COVID-19) has in part been described. However, little is known about the distribution and evolution of T-cell responses within and across relevant tissues in patients with severe COVID-19. To fill this knowledge gap, we evaluated T cell clonality in lung, thoracic lymph node, and peripheral blood mononuclear cell (PBMC) samples collected from a cohort of 44 patients who died with or from COVID-19. We extracted DNA from formalin fixed paraffin embedded tissues collected at autopsy and from PBMCs collected perimortem. T-cell receptor beta sequencing was performed using the Adaptive ImmunoSeq platform. In preliminary analyses, significantly higher total unique T-cell rearrangements were observed in lymph node compared with lung tissues and PBMCs across all patients, indicative of highest T-cell diversity in lymph nodes. We observed evidence of clonal expansion (>1% of T-cell population) in 35 of 37 (95%) lung tissues, 14 of 37 (38%) lymph node tissues, and 35 of 41 (85%) PBMC samples. Additional analyses will characterize the impact of relevant metadata (e.g., demographic variables, viral load, interval from illness to death) on the breadth and depth of T-cell responses, including severe acute respiratory syndrome coronavirus-2 specific T-cell responses, within and across patients. This approach will provide unique insights into the evolution and specificity of T-cells responses among patients with severe and fatal COVID-19.

6044

SEROPREVALENCE OF SARSCOV2 ANTIBODIES IN THE GENERAL POPULATION OF BAMAKO, MALI

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The coronavirus disease 2019 (COVID-19) pandemic is not yet known with certainty in terms of its major epidemiologic, clinical, and serologic characteristics, including its ability to spread and its severity in the general population. This study assesses the seroprevalence of total antibodies and understand associated factors for SARS-CoV-2 infection in the general population of Bamako, the capital and epicenter of COVID-19 in Mali, with ultimate goal of drawing conclusions on the magnitude of the pandemic and contributing to the improvement of control strategies. A cross-sectional survey was done in September 2022 to collect socio-demographic and clinical data, and blood samples. Seroprevalence of SARS-CoV-2 of antibodies anti-Spike and anti-RBD were determined by ELISA. RedCap system was used for data recording and analyzed with RStudio. A total of 3601 participants were enrolled, Mean age of participants was 33.5± 15.9-year-old; the sex ratio was 3.6 for female. Age groups such as 20-29 and 30-39 years were most representative with 28.9% (n=1043) and 26.9% (n=967), respectively. Overall, COVID-19 vaccine coverage among participants was 36%, consisting of Covidshield AstraZeneca (AZ), Johnson & Johnson (J&J), Sinovac, and BioNTech Pfizer vaccines. Overall, seroprevalence of SARS-Cov-2 antibodies to S and RBD were markedly high in the general population, with 98% and 97% respectively. Factor such as male sex earlier age (1-9 year-old were associated with lower antibody responses to S and RBD, whereas having previous contact with COVID-19 patient and receiving COVID-19 vaccine increased odds for antibody responses. This study showed high seroprevalences of antibodies anti-Spike and anti-RBD in general population of Bamako and identified some factors that may influence antibody responses. Our findings lead to conclude that SARS-CoV-2 exposure in the general population is much higher than indicated by case-based surveillance, and that the magnitude of the pandemic is underestimated in Mali.

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IMPACT OF DENGUE VIRUS STRAIN AND MATURATION STATE ON DETECTION OF NEUTRALIZING ANTIBODIES INDUCED BY NATURAL INFECTION AND VACCINATION

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Dengue vaccine developers have relied on standard plaque or focus reduction neutralization tests (PRNT/FRNT) to assess immunogenicity of each of the 4 dengue virus (DENV) serotype components in tetravalent vaccines. However, leading vaccines have performed poorly in baseline dengue seronegative (SN) children despite stimulating neutralizing antibodies (NAbs) to DENV1-4 detected by standard PRNT/FRNT, which uses lab-adapted reference viruses. There are structural differences between DENVs produced in humans (predominantly mature) vs. cell lines (partially mature). The partially mature state of cell-culture produced virions may lead to neutralization in the standard assay by cross-reactive (CR) fusion loop (FL), potentially disease enhancing Abs. The goals of the current study were to compare the impacts of DENV strain (lab-adapted vs. low-passage) and maturation state on levels of NAbs to each serotype detected by the FRNT. We controlled for maturation state by growing virus stocks in regular Vero cells, producing partially mature virions, and Vero cells engineered to over-express furin (DENV processing protease), producing fully mature virions. We found that DENV CR human monoclonal Abs (MAbs) targeting the FL were maturation state sensitive, neutralizing partially mature virions better than fully mature virions. In contrast, neutralization by MAbs to serotype CR quaternary dimer dependent epitopes were maturation insensitive. Human sera from individuals recently exposed to a primary DENV infection also had higher titers of CR NAbs (vs. serotypes not responsible for primary infection) to partially mature lab strains compared to fully mature recent clinical isolates. Our results demonstrate that DENV NAbs detected using mature, low-passage clinical strains more accurately reflect the serotype responsible for infection compared to the current standard practice. We propose that using mature low passage clinical strains will also lead to more accurate determinations of the immunogenicity and protective potential of each serotype component in tetravalent DENV vaccines in comparison to the current standard.

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MOLECULAR SURVEILLANCE OF SULFADOXINE-PYRIMETHAMINE AND AMODIAQUINE RESISTANCE MARKERS IN KARAMOJA REGION, AN AREA IMPLEMENTING SEASONAL MALARIA CHEMOPREVENTION IN NORTHEASTERN UGANDA

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The effectiveness of seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine and amodiaquine (SPAQ) recommended for age groups at high risk of severe malaria, in areas where malaria transmission is highly seasonal, is threatened by widespread drug resistance in east and southern Africa. As part of a phased implementation study to evaluate the protective effectiveness of SMC with SPAQ in Karamoja region, we assessed the changes in the prevalence of resistance markers, over two annual rounds of SMC. Baseline and end-line health facility-based, cross-sectional surveys were conducted before and after SMC distribution for both rounds. In round one, 300 P. falciparum-infected dry blood spots were collected at each time point from symptomatic children aged 3 to 59 months from three districts while in round two, 750 samples using similar protocols were collected from five districts and analyzed for DNA purification using chelex method. Quintuple mutants (PfDHFR 59R, 51I, 108N, and PfDHPS 437G, 540E) that mediate moderate SP resistance are highly prevalent (range: 78-100%) and remained unchanged. The double mutants (PfDHFR 164L and PfDHPS 581G), the acquisition of which leads to significant pyrimethamine resistance, were rarely seen (prevalence range: <1%). This remains reassuring on the utility of pyrimethamine in SPAQ-SMC in Karamoja. The prevalence of PfCRT 76T, the principal mediator of 4-aminoquinoline (amodiaquine and chloroquine) resistance was low (~5-13%). Similarly, mutations in PfMDR1 (86Y and 1246Y) that moderate aminoquinoline resistance were low (<3%). 184F, a mutation with an unclear role in aminoquinoline resistance remains at a stable prevalence of up to 30%. While SP resistance is shown to be high, thus far SMC does not seem to impact the resistance profile across two annual rounds.

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MOLECULAR MARKERS ASSOCIATED WITH ANTIMALARIAL DRUG RESISTANCE AND DISTRIBUTION OF MSP1 AND MSP2 ALLELIC FAMILIES IN RURAL ENDEMIC SETTINGS, NORTHWESTERN BURKINA FASO

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Antimalarial drug resistance surveillance through the characterization of associated genes is crucial for malaria control in areas of high endemicity and transmission. The high diversity of Plasmodium genotypes characterizes the dynamic of malaria transmission and demonstrates the complexity of malaria vaccine development. The aim of the present study was to evaluate the effect of Plasmodium genetic polymorphism on the markers associated with antimalarial resistance in endemic settings. Blood-thick smears and dried blood samples on the paper filters were collected from populations living in Nouna and Kodougou, two localities of the Demographic and Health Surveillance System of the Nouna Health Research Centre. The blood smears were used for malaria microscopic examination. Filter papers from malaria-positive samples were used for DNA extraction by Qiagen and amplified by nested PCR for the search of genetic polymorphism alleles. The PCR-RFLP was used to characterize the molecular markers associated with antimalarial drug resistance. The Spearman's correlation test was used to compare allelic frequencies, MOI and mutant pfcrt, pfmdr, dhfr and dhps genes prevalence. Out of the 285 samples positive for Plasmodium falciparum, 279 were successfully genotyped for markers associated with antimalarial drug resistance. Significant positive correlations were found between msp1 allele frequencies, mean multiplicity of infection (mMOI), and pfcrt mutant prevalence. No significant correlations were found between msp1 and msp2 alleles, mean multiplicity of infection (MOI), and the prevalence of pfmdr, dhfr, and dhps mutants. Overall, this study showed a weak relationship between the different parasitic clones of Plasmodium falciparum and the expression of mutant pfmdr, dhfr and dhps genes. The correlation with the chloroquine resistance gene is certainly due to the adaptation of the malaria parasite to this molecule, probably linked to its long-standing use as an antimalarial.

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MOLECULAR MARKERS OF ANTIMALARIAL RESISTANCE, AN EXTENSION OF THERAPEUTIC EFFICACY MONITORING IN BURKINA FASO, 2021

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Data on molecular markers of resistance complement clinical data from therapeutic efficacy studies (TES). This study examined the prevalence of polymorphisms in genes associated with susceptibility to antimalarials used for treatment or chemoprevention using samples collected in a TES carried out in three sites in Burkina Faso: Niangoloko, Nanoro and Gourcy. Febrile children with uncomplicated P. falciparum monoinfection were recruited, treated with artemether-lumefantrine (AL), dihydroartemisinin-piperaquine or artesunate-pyronaridine, and followed for 28 or 42 days. Blood spots were collected on filter paper at Day 0 (D0) and follow up visits. All D0 samples and Day of Failure samples were included in molecular analyses, including 638 paired samples from treatment failures and 750 D0 samples from nonfailure patients combined into 152 pools for analysis. PCRs were performed to amplify full length pfk13, pfdhps, and pfmdr1 genes. Sequences were analyzed at loci representing the major reportable single nucleotide polymorphisms for each gene. There was no evidence of any pfk13 mutations associated with artemisinin resistance in the analyzed samples. The pfmdr1 Y184F mutation associated with reduced susceptibility to lumefantrine was found in the majority (59-64%) of samples. The pfdhps A437G mutation was present in all sites at rates ranging from 88-90%. The key K540E and A581G pfdhps mutations, defining the canonical "quintuple" and "sextuple" mutants associated with sulfadoxine-pyrimethamine (SP) resistance were present at low levels (<4%). The pfdhps haplotype VAGKGS, recently documented spreading westwards across the Sahel region of North Africa, was found in 7 (6%) samples from Nanoro, 2 (2%) samples from Gourcy, and 1 (1%) sample from Niangoloko. These results are consistent with continued high efficacy of artemisinin derivatives in Burkina Faso and provide insight to the suboptimal efficacy of AL. There is no indication of high-level SP resistance in any of the three sites. Continued monitoring, including molecular surveillance, is critical for decision-making on effective treatment and chemoprevention policy.

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ASSESSMENT OF PLASMODIUM FALCIPARUM CLONALITY AND DRUG RESISTANCE IN AN ARTEMETHER-LUMEFANTRINE DRUG EFFICACY TRIAL IN NORTHWEST ETHIOPIA

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Despite recent progress in malaria elimination, 68% of Ethiopia's population still lives in malarious areas. High-transmission areas theoretically increase the likelihood of the spread of resistant strains that may compromise the therapeutic effect of artemisinin combination therapies (ACTs). To evaluate this, a total of 162 Plasmodium falciparum isolates from 54 patients across three time points (day-0, day-3, and day-7 of treatment) were identified from an Artemether-Lumefantrine (Co-Artem) drug efficacy trial conducted in Northwest Ethiopia in 2018. The samples were analyzed to determine the complexity of infection (COI) and haplotype profiles using the genetic markers msp2, ama1-d2, and ama1-d3, the presence of kelch13 mutants, and gene copy number (GCN) of pfmdr1 and pfplasmepsin2 associated with antimalarial resistance. Infections were polyclonal at day-0 based on the msp2 (3.93±0.24), ama1-d2 (3.13±0.23), ama1-d3 (1.70±0.16) haplotype profiles. An overall decrease in the COI was observed across all the haplotype markers at subsequent trial time points. A prevalence of 21.95% (3.27 times higher than the previous surveillance in 2014) was observed for the R622I kelch13 candidate SNP rendering partial artemisinin resistance. In addition, we detected the M476I (2.94%), Y493H (2.43%), P574L (2.43%), and C580Y (33.3%) validated SNPs for partial artemisinin resistance. An elevated copy number of the pfmdr1 gene was observed at day-0 (95% C.I.=[1.07,1.33]) but not for the plasmepsin2 gene (95% C.I.=[0.93, 1.02]). When comparing day-0 and day-7, the COI ($p<0.0001$), prevalence of kelch13 mutants ($p<0.0001$) and GCN of pfmdr1 and pfplasmepsin2 ($p<0.0001$) decrease following Co-Artem treatment. Our study confirms that Co-Artem remains effective in this region of Ethiopia. However, genetic analysis reveals a high COI and multiple kelch13 mutants, which have the potential to confer greater artemisinin resistance with time.

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TEMPORAL GENOMIC ANALYSIS OF PLASMODIUM FALCIPARUM REVEALS INCREASED PREVALENCE OF PFAP2MU S160N AND PFMDR1 Y184F MUTATIONS ASSOCIATED WITH REDUCED PARASITE CLEARANCE OR SUSCEPTIBILITY TO LUMEFANTRINE IN CHOMA DISTRICT, SOUTHERN PROVINCE, ZAMBIA

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The emergence of anti-malarial drug resistance is a potential major impediment to achieving malaria control and elimination goals in Africa. The current intensive elimination activities, especially the use of antimalarial drugs such as artemisinin-based combination therapies (ACTs) in areas nearing pre-elimination like southern Zambia, is exerting significant selective pressure on malaria parasite populations that could facilitate the emergence of resistance strains. Analysis of temporal trends in drug resistance molecular markers can assist policy makers in choosing efficacious antimalarials and slow the emergence and spread of resistance. In a region of southern Zambia with low and seasonal transmission, we genotyped 441 Plasmodium falciparum samples collected from 2012 to 2018 from a cluster of 8 health centers using molecular inversion probes targeting 815 loci across 14 drug resistance genes. None of the isolates carried WHO-validated or candidate Kelch13 propeller mutations associated with artemisinin resistance, including recently reported mutations (R561H, A675V and C469Y) from Africa. In addition, none of the isolates carried known mutations associated with chloroquine (CQ) resistance at Pfcrt gene codons (72-76). However, 13% of isolates carried Pfap2mu S160N (a mutation associated with delayed ACT clearance in Africa), and 41% carried Pfmdr1 Y184F (a mutation associated with reduced susceptibility to lumefantrine), with increased prevalence between 2015-2018. More than 90% of sequenced samples carried N51I, C59R, and S108N (IRN triple mutants), and 81% carried A437G and K540E (GE double mutants) with less temporal variation. In conclusion, P. falciparum strains circulating in southern Zambia remain susceptible to ACTs and CQ, but the high prevalence of mutations associated with delayed ACT clearance or reduced susceptibility to lumefantrine warrants close monitoring of artemisinin and partner drug efficacy. Moreover, the high prevalence of mutations associated with SP suggests there may be a need to revise current treatment guidelines for intermittent preventive treatment of malaria in pregnancy.

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THE IMPACT OF SMC ON PLASMODIUM FALCIPARUM RESISTANCE TO SULFADOXINE PYRIMETHAMINE (SP) AND AMODIAQUINE (AQ) OVER A 2 YEAR PERIOD OF SMC IMPLEMENTATION IN NORTHERN MOZAMBIQUE

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Malaria is a significant public health problem in Mozambique, with high incidence rates and a high number of cases leading to many deaths, particularly in children under 5 years old. Seasonal malaria chemoprevention (SMC) is recommended by WHO to prevent malaria, with Sulfadoxina-Pirymethamine (SP) plus Amodiaquine (AQ) being the approved treatment. SMC can reduce malaria cases by 75% and has been recommended in areas with high malaria incidence in children since 2012. However, resistance to SP and AQ has been found in Mozambique, and this study aims to determine the prevalence of resistance markers to SP and AQ before and after the first annual round of SMC implementation. Between November 2020 and February 2021, a survey was conducted before (baseline) and after one complete round of SMC (end line) to measure resistance to SPAQ in symptomatic children under five years with a positive RDT in selected health facilities in intervention and control areas. Four first-level health facilities were selected in each district of the intervention and control areas. Blood samples were collected prior to SMC delivery onto filter papers. Key markers monitored included dhfr, dhps, pfcrt, and pfmdr1. 1198 blood spot samples (598 at baseline, 600 at endline) were analysed for molecular markers of resistance to SP and AQ. The pfdhps gene showed SNPs in 99% of samples with sufficient deoxyribonucleic acid (DNA) and all pfdhfr samples had mutations. More than half of samples showed SNP at codon Y184F in pfmdr1, no SNP was found for Pfcrt. No significant differences were observed between groups for SNPs or mutation combinations. Pfcrt mutations were absent, suggesting amodiaquine resistance is not mediated by Pfcrt. SNP combinations of relevant Pfdhps-dhfr mutants were notable among the analysed samples. Long term implications of these results will be much better understood once chemoprevention efficacy study data will be available. Continuous monitoring of SP and AQ resistant markers is crucial as the country scale up the implementation of SMC and introduce other quimioprevention strategies using this drug.

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ASSESSMENT OF QUANTITATIVE PCR FOR DETERMINATION OF DRUG RESPONSE OF PLASMODIUM FALCIPARUM IN THE ABSENCE OF DNA PURIFICATION

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Surveillance of antimalarial resistance in parasite populations is essential to identify and limit its spread in malaria-endemic communities. Genotyping of molecular markers, Therapeutic efficacy studies and in vitro/ex-vivo studies are commonly used to assess parasite sensitivity to drugs. However, in vivo efficacy studies are expensive and cumbersome, meanwhile, no single assay exists for both molecular genotyping and in vitro/ex vivo testing. Novel assays such as flow cytometry are accurate and fast, they require cumbersome downstream processing to obtain accurate results. Our goal is to develop a quantitative PCR-based molecular assay for determining growth, viability and drug resistance responses using validated molecular tools (qPCR). Parasite growth was assessed by deploying a direct PCR method targeting known parasite genomic regions (varATS & AMA-1). Laboratory-maintained Plasmodium falciparum strains were tested for 50% inhibitory concentrations of Chloroquine, Lumefantrine and dihydroartemisinin. These drugs were tested against laboratory-maintained P. falciparum strains 3D7(chloroquine-sensitive) and Dd2(chloroquine-resistant). Parasitemia was measured following post-drug exposure by flow cytometry and molecular assays. Differential growth relative to the drug-free assays was used to fit sigmoid curves of growth against drug concentration for IC50 determination in comparison to established methods. The IC50 values obtained from the direct PCR method correlated with results obtained from flow cytometry and fluorimetry with R2 values of 0.9996 and 0.9994 respectively. The bland-Altman analysis showed a better agreement between Direct PCR and Fluorimetry (Bias=3.676, Limit of agreement=4.09 - 11.40). Taken together, the direct PCR method allows for molecular detection of parasitaemia and parasite drug susceptibility in the absence of DNA purification. We conclude that upon further optimization this method can be successfully adapted into a handheld PCR-based assay that can be deployed in non-specialized settings for testing of field isolate sensitivity towards antimalarials.

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COX UNIVARIATE AND MULTIVARIATE ANALYSIS OF THE DETERMINANTS OF PARASITE RECURRENCE BY DAY 28 AFTER REPETITIVE TREATMENT OF UNCOMPLICATED MALARIA WITH ARTEMETHER-LUMEFANTRINE DURING TWO YEARS IN MALI

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In malaria endemic countries, treatment and control of the disease is hampered by the recurrence of parasite. Some people may experience more than ten episodes of malaria by year, necessitating repetitive treatment. The determinants of these recurrences by day 28 after treatment with artemether-lumefantrine are not well characterized. The objective of this work was to investigate the determinants of parasite recurrence after repetitive treatment of uncomplicated malaria case with AL during two years in Mali. This work was part of the WANECAM study. Participants, from 6 months were followed for two years and received AL at the standard dose for each new episode of uncomplicated malaria. Social, demographic, clinical, parasitological and lumefantrine concentration at day 7 variables were used as covariates. Cox univariate and multivariate analysis were used to determine variables associated with the parasite recurrence by day 28 of follow-up. In total 671 participants were treated with AL for 1732 episodes during two years of follow-up. The overall recurrence prevalence was 14.13%. The recrudescence level was less than 1%. The Cox proportional-hazards regression analysis showed that lumefantrine day 7 concentration, age, the high transmission season, the study site, the day 0 parasitemia significantly predicted parasite recurrence by day 28 of follow-up. Our results showed that by day 28 each increase of the natural log of the lumefantrine day 7 concentration had about 40% lower hazard rate to have recurrence (HR = 0.607, (95% CI; 0.499 – 0.739)). Each increase of the age had about 5% lower hazard rate (HR = 0.946, (95% CI; 0.914 – 0.979)). While we found a strong relationship between the high transmission season (June to November) and parasite recurrence There was no recurrence during the low transmission season. These results showed the relationship between different factors that influence parasite recurrence. Understanding these relationships is critical for the development of strategies in malaria control and elimination.

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HEALTH SEEKING BEHAVIORS AND BELIEFS SURROUNDING MALARIA IN THREE EAST AND SOUTHERN AFRICAN NEW GEOGRAPHIES PILOTING SEASONAL MALARIA CHEMOPREVENTION: A SECONDARY QUALITATIVE ANALYSIS

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Seasonal malaria chemoprevention (SMC) is a World Health Organization recommended intervention that consists of the intermittent administration of antimalarials to children in areas where transmission is highly seasonal. In 2021 and 2022, Malaria Consortium has been conducting hybrid SMC effectiveness-implementation studies to build the evidence base around new SMC in geographies in East and Southern Africa (ESA), and ensure that SMC is deployed safely, effectively, and sustainably in these settings; the approach used in the Sahel region may not be suited for ESA due to greater resistance profile, transmission, and immunity heterogeneities. Preliminary results from these studies show that SMC is an effective and highly acceptable strategy. However, one aspect that was not initially investigated in the qualitative component of these studies, but which provides insightful information on factors influencing interventions success, are the health seeking behaviours and beliefs surrounding malaria. To fill this research gap, an ongoing thematic analysis is being conducted on qualitative data collected between April and December 2022 in the Karamoja region of Uganda, Nampula province in Mozambique and Northern Bahr el Ghazal state in South Sudan. Qualitative methods employed included focus group discussions (FGDs) held with caregivers and community health workers in each setting, and semi-structured interviews held with key informants at various levels of the health systems in the three countries. A total of 41 FGDs and 51 interviews have been analysed. Perceptions, social practices, and religious beliefs surrounding malaria transmission, prevention, and health seeking behaviours have been described for each location and compared against each other, with a focus on identified similarities and differences. Results from this secondary qualitative analysis will contribute to the refinement of future SMC implementation campaigns with context-specific information for ESA geographies. Findings could be additionally used to generate hypothesis for further community-centred interventions.

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RARE PLASMODIUM FALCIPARUM CORONIN GENE MUTATIONS FOLLOWING ARTEMISININ (ART) TREATMENT OF MALARIA IN SOUTH WESTERN NIGERIA

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Non-Pfkelch13 parasite protein variants have been implicated in artemisinin (ART) resistance, but not in Africa. Genetic markers underlying in vivo reduced ART efficacy among African P. falciparum populations are currently unclear. We investigated SNPs in Plasmodium falciparum actin-binding protein (Pfcoronin) associated with in vivo ART tolerance in Nigeria. Seven isolates showing parasitaemia after Day 3 in a 28-day therapeutic efficacy study of artemether-lumefantrine among 51 volunteers in Lagos, Nigeria were investigated. Molecular diagnosis was done by conventional and real-time PCR amplification of Pf18S rRNA gene, var acidic terminal sequence, telomere-associated repetitive elements-2 and coupled conventional and real-time Pf18S rRNA PCR. Twelve neutral P. falciparum microsatellite loci genotyping were analyzed to confirm recrudescence in comparison with msp2 genotyping. We genotyped drug resistance targets (DHFR_51, DHFR_59, DHFR_108, DHFR_164, MDR1_86, MDR1_184, DHPS_581 and DHPS_613), and sequenced PfCoronin bi-directionally for presence and association of mutations with ART tolerance. Molecular techniques employed detected P. falciparum infections. One infecttion was recrudescent by microsatellites analysis out of the four identified as recrudescent infections by msp2 genotyping. Presence of the drug resistance-associated haplotypes, pfdhfr/pfdhps/pfmdr1 (108T/N/51I/164L/59R/581G/86Y/184F) was observed in two samples. He, allelic diversity, for each microsatellite locus from pre- and post-drug administration, revealed no significant difference in the mean He (P = 0.19, Mann-Whitney test). Significant LD (IAS = 0.2865, P=0.02, Monte Carlo simulation) around the neutral microsatellite loci was observed. Seven new Pfcoronin SNPs (V55L, V67E, I68G, K69G, L77I, D154Y and E200Q) were found. SNPs here reported may guide investigations on mechanisms of emerging African ART resistance.

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CHANGES IN SUSCEPTIBILITY OF PLASMODIUM FALCIPARUM TO LUMEFANTRINE IN EASTERN AND NORTHERN UGANDA OVER TIME

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Artemisinin-based combination therapies, the first line treatments for uncomplicated malaria, are threatened by emergence of artemisinin partial resistance in northern Uganda, where high prevalence of the PfK13 469Y and 675V mutations has been documented. Of additional concern, we recently reported decreased susceptibility to the key partner drug lumefantrine in northern, compared to eastern Uganda. To assess changes over time, we compared susceptibilities to 7 standard antimalarials of P. falciparum isolates collected from symptomatic patients in 2021 and 2022 in Patongo Health Centre in northern Uganda, and Tororo District Hospital and Busiu Health Centre, in eastern Uganda. We utilized 72-h growth inhibition assays with SYBR green detection and genotyped samples using targeted deep sequencing to identify linked genotypes of interest. With growth inhibition assays, median IC50s for lumefantrine were 14.7 (n=49) and 14.9 nM (n=94) in 2021 and 2022, respectively, in northern Uganda, compared to 3.0 (n=378), 5.1 (n=365), 6.2 (n=151) and 10.1 nM (n=144) in 2010-2013, 2016-2019, 2021, and 2022, respectively, in eastern Uganda. For 2021 and 2022 combined, median IC50s were significantly greater in northern vs. eastern Uganda (p =0.0001). Considering other standard components of artemisinin combination therapies (dihydroartemisinin, amodiaquine, piperaquine, pyronaridine, and mefloquine), IC50s were similar between northern and eastern Uganda. Preliminary molecular inversion probe sequencing of 70 genes of interest suggested that mutations in PfMDR1, PfK13, and falcipain cysteine proteases are associated with differences in lumefantrine susceptibility. The identified decreased susceptibility of P. falciparum to lumefantrine in northern Uganda is of great concern, as it suggests decreased antimalarial efficacy of artemether-lumefantrine, the first line antimalarial therapy in Uganda. Highlighting the need for continued surveillance of resistance patterns to inform on future trends, necessary for malaria control strategies.

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EX VIVO SUSCEPTIBILITY OF PLASMODIUM FALCIPARUM ISOLATES TO STANDARD ANTIMALARIALS IN BOBO-DIOULASSO, BURKINA FASO

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Malaria remains the leading cause of morbidity and mortality in Burkina Faso. The country utilizes artemether-lumefantrine, artesunate-amodiaquine, and recently dihydroartemisinin-piperaquine as first line therapies for uncomplicated malaria. Seasonal malaria chemoprevention (SMC) with amodiaquine plus sulfadoxine-pyrimethamine is implemented country-wide in children 5 years and under during the transmission season. With concerns regarding potential resistance to many classes of antimalarials, monitoring the efficacy of available antimalarial drugs is a high priority. We measured ex vivo IC50s for 11 compounds utilizing 158 isolates collected from patients aged 3-60 years old presenting with uncomplicated Plasmodium falciparum malaria in Bobo-Dioulasso, Burkina Faso from July to December, 2021 and 2022. Assays utilized a standard 72 h growth inhibition microplate assay with SYBR Green detection, with results compared to those with laboratory-adapted control parasite strains. Isolates (median IC50 [range], nM) were generally highly sensitive to: chloroquine (9.9 [0.87 - 262.8]), monodesethylamodiaquine (21.5 [0.6 - 205.6]), piperaquine (6.3 [1.2 - 211.5]), lumefantrine (7.4 [0.5 - 78.2]), mefloquine (7 [0.2 - 29.9]), atovaquone (0.2 [0.01 - 1.0]), dihydroartemisinin (3.7 [0.5 - 24.7]), pyronaridine (3.0 [0.1 -36.7]) and quinine (49.8 [1.5 - 637.7]). With a few exceptions, parasites were resistant to pyrimethamine (32,649 [33.2 - 191,190]) and cycloguanil (844[3.6 - 8265]). All median IC50 values were similar to those reported from our recent ex vivo studies in eastern Uganda, and suggested good antimalarial efficacy of tested drugs except for pyrimethamine and cycloguanil. However, it is noteworthy that the median IC50 for monodesethylamodiaquine was greater than that recently reported in Uganda (7.1 [1.1 - 202]; p <0.0001), possibly related to widespread use of amodiaquine as part of SMC in Burkina Faso. Genotyping of isolates to characterize key mutations associated with antimalarial drug resistance is underway.

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LACK OF CORRELATION BETWEEN IN VITRO POTENCY AND IN VIVO EFFICACY OF MADURAMICIN AGAINST PLASMODIUM LIVER STAGES

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Current strategies for anti-malarial drug development primarily focus on targeting the asexual and sexual stages of the parasite. Maduramicin, a polyether ionophore used as a coccidiostat in poultry has been shown to exhibit potent anti-plasmodial activity in vitro across Plasmodium species and stages with an IC50 of <14nM against both replicating (schizont) and dormant (hypnozoite) liver stages, and blood-stages of the parasite. In our efforts to further evaluate the efficacy and stage specific activity of maduramicin in vivo, wild type mice were infected with 2.5*104 P. berghei (Pb-GFP-luc) sporozoites and treated orally with maduramicin at timepoints corresponding to different stages of infection. Whole body in vivo imaging of mice was done at 24, 48 and 72 hours post infection, and thin blood smears stained with Giemsa were analyzed to determine blood parasitemia. While prophylactic administration of maduramicin prior to sporozoite infection fully blocked the formation of liver stages, delayed treatment after establishment of early or late liver-stages proved ineffective. Bioluminescence signal was detected in livers of the mice at 24 hours post treatment with an increase in signal at 48 hours, indicating a surprising lack of activity against liver-stages. Maduramicin was potent against blood-stages in vivo with animals being parasite free three days post drug administration with no recrudescence. Contrary to its high in vitro potency, a similar lack of activity against liver stages was observed in human liver-chimeric mice infected with P. cynomolgi, a strain that produces dormant hepatic hypnozoites. Parasite burden in treated livers could be quantified by qPCR with both schizonts and hypnozoites being detected by immunofluorescence assays four days post treatment, indicating the absence of liver-stage clearance. While further investigation is required to understand this disparity between in vitro and in vivo activity of maduramicin, our studies characterizing ionophores in murine malaria models highlight potential challenges in repurposing these molecules towards intervention strategies for malaria.

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MALARIA DRUG RESISTANCE MARKERS MOLECULAR SURVEILLANCE USING ANOPHELES MOSQUITOES IN BURKINA FASO

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Plasmodium resistance to antimalarials is hampering the fight against malaria in endemic countries. Here, we screen multiple antimalarial drug resistance genes (pfmdr), sulfadoxine pyrimethamine resistance markers (dhfr and dhps) within Anopheles populations to highlight the potential dissemination of these drug resistance makers. Anopheles mosquitoes were collected by using CDC light traps and manual collections in the health district of Nouna in Burkina Faso. The heads/thoraxes were used for the detection of Plasmodium falciparum infection. Positive samples were subjected to PCR-RFLP to assess their drug resistance polymorphisms. Plasmodium infection rate in Anopheles vectors was 5.5% during this study. For the pfmdr genes, the prevalence was 7.4%, 83.4% and 9.2% for mutants, wild type and hybrid. For the dhfr gene, the prevalence of mutant alleles was 4.02%, 8.16% and 12.5% for codons 51, 59, 108 respectively. Mutations on codons 437 and 540 of the dhps genes were also observed during this study with a prevalence of 14.3% and 2%. These mutations have been notified both in An. gambiae, the major vectors of malaria, and in An. nili another important vector in this region. This study highlights the level of antimalarial resistance genes in mosquitoes. The presence of mutant alleles shows the need for regular monitoring of these molecular markers.

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PFCORONIN MUTATIONS CONFER ARTEMISININ RESISTANCE IN PLASMODIUM FALCIPARUM BY ALTERING ACTIN HOMEOSTASIS: A POTENTIAL NEW PLAYER IN THE ENDOCYTIC AND VESICULAR TRANSPORT PATHWAY

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Pfcoronin mutations drive in vitro evolved artemisinin (ART) resistance in Senegalese P. falciparum isolates (coroninR100K/E107V). Coronin interacts with the cytoskeleton in other organisms, but its function in Plasmodium biology is not yet understood. To explore the role of Coronin, we immunoprecipitated (IP) Coronin and identified its interaction partners by mass spectrometry. In both CoroninWT and CoroninR100K/E107V parasites, Coronin's major interacting partner was actin, however, interactions with actin were substantially reduced in ring-stage CoroninR100K/E107V parasites. The second most enriched Coronin-interacting partner in CoroninWT rings was polyubiquitin (Ub), but like actin, Ub was significantly less enriched in CoroninR100K/E107V parasites. We hypothesized that ubiquitination might alter turnover or otherwise regulate actin behavior. Interestingly, western blot revealed that CoroninR100K/E107V rings contained 30% less actin than CoroninWT. To better understand which proteins might be ubiquitinated, we used IP with an anti-ubiquitin probe. Actin was highly enriched in CoroninWT line but not in the CoroninR100K/E107V parasites, consistent with the growing body of evidence that actin rearrangements involve regulation by ubiquitylation. We undertook ultrastructure expansion microscopy (UExM) to assess Coronin localization in rings. UExM revealed localization of Coronin at the parasite plasma/vacuolar membrane. Interestingly, we saw strong localization of Coronin at the food vacuole membrane and vesicular structures. To provide additional pharmacological evidence, treating CoroninR100K/E107V parasites with jasplakinolide, an actin depolymerization inhibitor, results in a reversal of the resistance phenotype, demonstrating the role of actin in coronin-mediated artemisinin resistance. These results demonstrate a role in endocytosis and vesicular transport—notably, actin is key to these processes. Altered vesicular transport has previously been implicated in kelch13-linked artemisinin resistance, and these results suggest that Coronin might work in the same pathway.

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KELCH 13 AND NON-KELCH 13 MEDIATED ARTEMISININ DRUG RESISTANCE

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The emergence of ART resistance in the Greater Mekong subregion earlier and recently in African subcontinent has marked a major setback for malaria elimination worldwide. Although Kelch 13 has been proposed as the primary marker and determinant of artemisinin resistance in Plasmodium falciparum, many other genes and proteins with variable degrees of influence on resistance phenotype have been identified. Based on genome wide association studies, in vitro generated ART resistance parasites and literature review we identify and validate additional markers of ART drug resistance. We are currently characterizing Kelch 13 muations either emerging in South East Asia or specific to African parasites, additionally we are also validating polymorphisms found in other potential markers of ART

resistance like Falcipain 2a, DNA mismatch repair protein PMS1, putative, regulator of initiation factor 2 (eIF2) and Phosphatidylinositol 4-kinase, putative. We have generated genetically modified parasites with single nucleotide polymorphism or haplotypes found in each of these proteins and are currently performing drug assays and parasite fitness assays to study their effect on drug susceptibility and parasite growth. The introduction of these polymorphisms in different genetic backgrounds would reveal any variability present in their artemisinin resistance profiles, food vacoule morphologies and parasite progression. This work would help us elucidate the role of these markers in artemisinin resistance.

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SUSCEPTIBILITY OF PLASMODIUM FALCIPARUM ISOLATES TO DIHYDROARTEMISININ IN NORTHERN AND EASTERN UGANDA IN 2021 AND 2022

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Artemisinin partial resistance, mediated primarily by mutations in the PfK13 propeller domain, was first reported in Southeast Asia, and has recently emerged in Africa, including Uganda and Rwanda, posing a great challenge to malaria control and elimination. We compared the prevalence of PfK13 mutations and ex vivo dihydroartemisinin (DHA) susceptibility of P. falciparum isolates collected in 2021 and 2022 from northern (N) Uganda, where resistance-associated PfK13 C469Y and A675V mutations have emerged, and eastern (E) Uganda, where such mutations have been rare. We collected whole blood samples from patients aged > 0.5 years with confirmed P. falciparum mono-infection attending Patongo Health Centre III in N. Uganda, and Tororo District Hospital and Busiu Health Centre IV in E. Uganda in May-August 2021 and March-July 2022. We evaluated 103 (N=65, E=38) and 160 (N = 110, E = 50) samples in 2021 and 2022, respectively. The pfK13 gene was sequenced using molecular inversion probe assays. Susceptibilities were determined with the ex vivo ring-stage survival assay (RSA; percentage survival, relative to controls, 66 h after a 6 h 700 nM pulse of DHA) and the standard 72 h microplate growth inhibition assay to estimate IC50 values. In N. Uganda, the prevalence of PfK13 mutations decreased (C469Y 34% to 10%, A675V 13% to 5%), RSA results were similar (median survival 3.5% to 3.1%) and IC50 values increased slightly (median IC50 2.3 nM to 3.5 nM) from 2021-22. In E. Uganda, the prevalence of PfK13 mutations was stable (C469Y 3% to 2%, A675V 3% to 4%), RSA survival increased (median survival 2.2% to 5.2%) and IC50 values increased (median IC50 1.5 nM to 2.5 nM) from 2021-22. The presence of C469Y or A675V mutations was associated with RSA values >5% in 2021, but not in 2022. Our results demonstrate persistent artemisinin partial resistance in northern and eastern Uganda, but with only a modest correlation between PfK13 mutation prevalence and drug susceptibility measures, highlighting the possible involvement of non-PfK13 mutations and the need for ongoing surveillance and monitoring of resistance patterns to inform malaria control strategies.

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DECREASED EX VIVO SUSCEPTIBILITY OF PLASMODIUM VIVAX TO CHLOROQUINE IN NORTHWEAST COLOMBIA

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Plasmodium vivax was responsible for 247 million cases of malaria worldwide in 2021, including severe cases and deaths. This is due to the difficulty in controlling this species. In Colombia, chloroquine has been used as the first-line treatment for P. vivax. However, in 2001 therapeutic failure was reported in 11% of the patients evaluated, therefore, there is a need for surveillance to determine the in vitro susceptibility of P. vivax to chloroquine (CQ). In this study, an ex vivo short culture was established from clinical P. vivax isolates with a duration of 48 hours to evaluate the in vitro susceptibility to CQ against isolates of P. vivax obtained in the municipality of Tierralta, Córdoba, Colombia. The schizonts maturation method (WHO microtest) was used and compared with SYBR Green method for IC50 determination. Seven serial concentrations in triplicate were evaluated. The inhibitory concentrations of 50% were 37.15 nM for chloroquine. However, 2/19 had IC50 values greater between 100nM-200nM and only one showed a IC50 more than 200nM, in two isolates it was not possible to determine the IC50 value. The SYBR Green and maturing methods give similar results. In conclusion, an in vitro short-term culture was established, the clinical isolates evaluated were susceptible to CQ (66.6%), although 33.3% of the isolates showed very low susceptibility.

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THE CONTINUED EXPANSION OF ARTEMISININ PARTIAL RESISTANCE MUTATION KELCH13 561H AND EMERGENCE OF 675V IN RUKARA IN 2021

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Plasmodium falciparum kelch13 (Pfk13) propeller-domain mutations that confer artemisinin partial resistance have emerged in Africa, with the first reported mutation being Pfk13-R561H in Rwanda. These mutations threaten control and elimination efforts and increase the likelihood of the emergence of partner drug resistance. Given this, it is vital to track their emergence and spread to inform modeling and public health efforts. In order to provide an update of the artemisinin resistance as well as potential RDT resistance we genotyped samples collected in 2021 from Rukara, Rwanda, the site where R561H was first detected in samples from 2014. Clinically validated artemisinin partial resistance mutations were found to be increasing in prevalence compared to previous reports from 2014. While the R561H mutation was observed at 23.5% (20/85 infections), A675V was seen at 8.5% (8/94). Additional nonsynonymous propeller mutations found were P574L at 2.4% (2/84), F699C at 1.1% (1/87), A575L at 1.1% (1/88), and P667R at 1.1% (1/94). In addition to these Pfkelch13 mutations, we also found that the Pfdhfr N164L mutation, associated with high grade Fansidar resistance, has increased in prevalence to 24.7% (19/77). We also investigated diagnostic resistance status and found 76.7% (102/133) contained intact HRP2/3. Overall, this investigation shows continued spread of artemisinin partial resistance within Rukara catchment area due to 561H, the concerning appearance of 675V previously found only at high prevalence in Uganda, and the emergence of dhfr 164L to a common level. Continued molecular surveillance in this region and surrounding areas is needed to monitor and understand these concerning antimalarial mutations which have significant potential impact on clinical and preventative therapy of malaria in east Africa.

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COMPARISON OF STRENGTH OF SELECTION FOR PLASMODIUM FALCIPARUM ARTEMISININ RESISTANCE-ASSOCIATED MUTATIONS BETWEEN SOUTHEAST ASIA AND UGANDA

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Partial artemisinin resistance, mediated by mutations in the kelch13 protein (PfK13), emerged in Southeast (SE) Asia and, more recently, in east Africa (Ethiopia, Eritrea, Rwanda, and Uganda). We investigated the rates of increase in mutation frequencies by comparing annual changes in PfK13 prevalence in Uganda with historical estimates from five countries in SE Asia. We fitted a Bayesian mixed effects model to the annual prevalence by district for each recently identified mutation in Uganda with a random slope and intercept to estimate selection coefficients, which define the percent change in relative frequency of the mutant genotype per parasite generation. In Uganda, we estimate preliminary selection coefficients per year from 2016-2021 across 7 districts for the 469Y, 469F, and 675V mutations to have been s=0.33 (range 0.26-0.44; 95% CrI: 0.13-0.51), s=0.16 (range 0.09-0.24; 95% CrI: -0.42-0.79), s=0.20 (range -0.04-0.32; 95% CrI: -0.03-0.40), i.e. prevalences are estimated to have increased by 33%, 16%, and 20% respectively each year. The selection coefficient estimated for all three mutations combined across all sampled districts in Uganda is s=0.36 (95% CrI: 0.19-0.46). To compare our estimates to the spread of PfK13 mutations in SE Asia, we employed the same model on data from the MalariaGen Pf7k database using samples from 2003-2018 in Cambodia (4 districts), Laos (2 districts), Myanmar (1 district), Thailand (2 districts), and Vietnam (2 districts). Selection coefficients for the 580Y mutation, the dominant mutation in much of SE Asia, and for all validated PfK13 propeller domain mutations were estimated to be s=0.38 (95% CrI: 0.20-0.57) and s=0.25 (95% CrI: 0.08-0.42), respectively. Together, these findings suggest that the strength of selection of partial artemisinin resistance in Africa has been similar to that in SE Asia, where partial artemisinin resistance is now widespread.

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INCREASED RATE OF ARTEMISININ-BASED COMBINATION TREATMENT FAILURE IN PATIENTS RETURNING FROM SUB-SAHARAN AFRICA WITH PLAMODIUM FALCIPARUM MALARIA; THE ROLE OF PFCORONIN GENE MUTATION

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Artemisinin-based combination therapies (ACTs) are recommended as first-line treatment against uncomplicated Plasmodium falciparum infection. However the emergence of mutations in the PfKelch13 propeller domain have resulted in resistance to artemisinin in Southeast-Asia. ACT treatment failures have been sporadically reported in Africa. Data of 15 Israeli travelers returning from Sub-Saharan Africa with P. falciparum malaria who showed ACT treatment failure were retrieved. Blood samples were tested for mutations in Pfkelch13 and Pfcoronin genes. Initial parasite load was evaluated through real-time PCR analysis of 18S rRNA and Pftubulin genes. Parameters were compared to well responders (n=55). During 2009-2020, 326 patients had P. falciparum malaria acquired in Africa. Of those, 15 (14 males, 24 to 69 years old) were clinically resistant to artemether-lumefantrine. Four had parasites in the blood after 3 days of treatment and 11 had recrudescence malaria 1-3 weeks later. No significant differences were found in average age and weight between the ACT-treatment failure and non-failure groups. Failure rate among ACT treated patients during 2009-2015 was 3% compared with 13% during 2015-2020. In all failures the Pfkelch13 propeller domain had wild type sequence. We did find the P76S mutation in the propeller domain of Pfcoronin in 4/15 (29%) of the treatment failure cases compared to only 3/55(5%) in the successfully treated patients (p=0.02). In conclusion, we observed an increasing rate of artemether-lumefantrine treatment failure in P. falciparum patients that could not be explained by patient characteristics, neither by a Pfkelch13 mutation. However, P76S mutation in the Pfcoronin gene was present more often in the treatment failure group and merits further investigation. The recent reports of increasing malaria incidence in Sub-Saharan-Africa partly attributed to COVID-19 related disturbances might also be a reflection of the wider spread of ACT resistance.

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DETECTION OF PLASMODIUM FALCIPARUM KELCH 13 GENE MUTATIONS IN CLINICAL SAMPLES FROM FOUR SITES ACROSS KENYA REVEALS INTENSE GENOMIC EVENTS THAT COULD PURIFY RESISTANCE

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The emergence and spread of Artemisinin based treatment-resistant strains call for ongoing surveillance. Therapeutic efficacy studies are the gold standard methods for testing drug efficacy. Recently, parasites with mutations that cause delayed clearance by artemisinin-based combination therapy have been identified in Africa, but these parasites are rare. Clinical samples obtained from five geographically varied areas in Kenya identified the polymorphism of the Plasmodium falciparum Kelch 13 (PfK13) gene and other markers of malaria treatment resistance. Blood samples were tested for in vitro susceptibility to selected antimalarial drugs using malaria SYBR green 1 assay. Sanger sequencing was used to detect polymorphisms in PfK13. PfK13 polymorphisms identified twelve mutations at 5.58% comprising three nonsynonymous mutations at codons: P553L, E612D, and F491L, four synonymous mutations at codons V637V, A504A, L488L, and C469C, for the last 2; three mixed wildtype and synonymous mutations at codons A626A, K455E, and G497G and one mixture of wild type and nonsynonymous mutation at codon S600F. One sample included two P553L and G497G mutations. The mixed genotypes, synonymous mutation A504A, nonsynonymous mutations at E612D, and F491L, and all of the nonsynonymous mutations have not been previously described. Also, we reported the synonymous mutation C469C in two samples compared to the WHO-validated marker C469Y which has been linked to slow clearance of parasites in Uganda. Whereas Ugandan reports of the mutation C469Y are non-synonymous, mutation C469C is synonymous. Previously, Congo saw the presence of the mutation C469C. The Pfk13 propeller gene has significant genomic activity, suggesting that once the fitness of the novel variant is established, the mutant state will progress. Continuous surveillance with sustained tools is needed to detect resistance and prevent transmission.

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IDENTIFICATION AND QUANTIFICATION OF PLASMODIUM FRAGILE IN AN IN VITRO CULTURE SYSTEM AND NON-HUMAN PRIMATE MODEL

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Zoonotic malaria infections are increasing in some areas of the world, posing a threat to malaria control efforts. Optimization of in vivo culturing of Plasmodium spp. that infect non-human hosts is critical for advancing our understanding of Plasmodium biology and identifying potential mechanisms that may underlie zoonotic infections. One such non-human primate (NHP) parasite is P. fragile, known to infect rhesus macaques (RMs) and induce clinical signs that mirror P. falciparum infection in humans. The aim of this work was to establish an in vitro culture system of P. fragile from the blood of an experimentally infected rhesus macaques (RM) and characterize P. fragile life stages during in vivo infection and in vitro culturing. An adult male RM (n=1) was intravenously inoculated with P. fragile (20x106 infected erythrocytes [iRBCs]). Peripheral parasitemia and parasite life stages were monitored throughout infection via Giemsa staining of thin and thick blood smears. Parasite life stages were counted in every 200 uninfected erythrocytes and reported as percentages. P. fragile cultures were started from 1mL of cryopreserved iRBCs, culture medium was changed daily, and fresh RM blood was added to restore 50% hematocrit. Cultures were monitored daily via Giemsa stain of thin smears, and life stages were quantified. Peripheral parasitemia was 15.8% at week 2 post-infection (p.i.) and 8.6% at necropsy (2.5 weeks p.i.). Giemsa staining of thin and thick blood smears collected throughout infection enabled identification of ring stages (5.9%) and trophozoites (6.6%), with no detection of schizonts or gametocytes. At necropsy, ring stage (1.1%), trophozoites (5.2%), schizonts (0.3%), and gametocytes (0.5%) were observed. P. fragile culture began at 2.9% parasitemia and reached 8.7% after 7 days of culturing. Establishing a continuous culture system of P. fragile is a critical step towards increasing understanding of the biology of P. fragile in vitro, providing needed tools for understand potential zoonotic malarias, and enabling translational research to facilitate therapeutic development.

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LOW FREQUENCY OF HISTIDINE-RICH PROTEIN 2/3 (HRP2/3) AND FLANKING GENE DELETIONS CORRELATES WITH THE HIGH DIAGNOSTIC PERFORMANCE OF HRP2-BASED MALARIA RAPID DIAGNOSTIC TESTS IN CAMEROON

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Histidine-rich protein 2 (HRP2)-based malaria rapid diagnostic tests (RDTs) are widely used for the detection of naturally occurring Plasmodium falciparum infections. Despite evidence of studies reporting false negative HRP2 RDT results due to Pfhrp2 and Pfhrp3 gene deletions in Africa, there exists a paucity of data on the deletions of these genes in Cameroon. Furthermore, genetic polymorphism of the hrp2/3 genes has been shown to impact the performance of PfHRP2- based rapid diagnostic tests (RDTs). This study investigated the presence of deletions of the Pfhrp2, Pfhrp3, and the respective flanking genes and characterized the polymorphism spectrum of the the hrp2 gene in P. falciparum parasite isolates from two localities (Gounougou and Elende) in Cameroon. A community-based cross-sectional survey was conducted in two communities - Gounougou and Elende in 2021. Malaria diagnosis was performed on 400 samples using microscopy and RDT and Whatman paper dry blood spots were collected for molecular typing of 18srRNA, msp2, hrp2/3, and neighboring genes. Furthermore, sequencing of the hrp2 gene was performed on 45 P. falciparum isolates to score polymorphisms diversity. Polyclonal infection depicted by msp2 typing alongside genotyping of the Pfhrp2 and Pfhrp3 genes revealed 1.3% and 2.1% overall prevalence with no significant difference between both communities. PCR confirmed 04 hrp2-deleted false negative RDTs. A frequency of 5.3%, 7%, 4.1%, and 5.5% was recorded in the MAL7P1.230, MAL7P1.228, MAL13P1.475, and MAL13P1.485 respectively. Sequencing of the Pfhrp2 exon2 from 45 isolates revealed a high level of genetic diversity, marked by the presence of variable repeat types in parasite isolates. The immuno-dominant AHHAHHAAD (81%) amino-acid Baker repeat epitope was characteristic of circulating P. falciparum isolates agreeing with significant RDT performance. In conclusion, despite the presence of low-frequency gene deletions in the HRP2/3 backbones, HRP2-based RDTs still maintain a high performance capacity for detecting malaria in the field.

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PRESENCE OF PFHRP2/3 DELETIONS INCLUDING POLYCLONAL INFECTIONS IN AN INTENSE MALARIA TRANSMISSION AREA OF SIAYA COUNTY, WESTERN KENYA

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Malaria remains endemic in western Kenya despite the various control interventions. Accurate diagnosis is key to the treatment and control of malaria. As such, the World Health Organization (WHO) recommends parasite-based confirmation of malaria prior to treatment. Plasmodium falciparum Histidine Rich Protein 2 (PfHRP2) based malaria rapid diagnostic tests (mRDTs) kits are commonly used throughout malaria endemic regions, including western Kenya, as an alternative to diagnosis with microscopy. However, the performance of the mRDT has been threatened by the emergence of the PfHRP2 deletion. In Siaya, western Kenya, an intense malaria transmission area, PfHRP2/3 deletions could be present but not detected due to polyclonal infections where the wild-type gene is predominant. As such, we investigated the presence of the PfHRP2/3 deletion using one-step multiplex qPCR in a pediatric cohort in Siaya (n=206). PfHRP2/3 deletions were detected in 12 parasite isolates (5.8%, 95% CI 1.9-8.7%). The PfHRP2 monoclonal deleted strains were present in 2 isolates (1%, 95% CI 0-2.4%), while no parasite isolates had PfHRP3 single deletion. Further, 9 isolates (4.4%, 95% CI 1.9-7.3%) had deletions for PfHRP2 and 1 isolate (0.5%, 95% CI 0.0-0.8%) had PfHRP3 deleted but were masked by polyclonal infection. The average relative abundance of PfHRP2 deleted parasites was 9.6%, (95% CI 4.8-14.5), while wildtype was 90.4% (95% CI 85.4-95.4) in polyclonal infections. Further analysis revealed that false negative mRDT results were associated with low parasite densities that were beyond the detection threshold (P≤0.001). The study provides evidence of PfHRP2-deleted strains, including polyclonal infections and their relative abundance in Siaya County. These results underscore the need for an active systematic surveillance program within the lake endemic

region. Moreover, our results are important in informing the Division of National Malaria Control Program (DNMCP) in establishing the profiles of PfHRP2/3 deletions and decisions making on the use of PfHRP2-based mRDTs in Kenya.

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PREVALENCE OF PFHRP2 AND PFHRP3 DELETIONS, AND PFKELCH13 MUTATIONS ASSOCIATED WITH PARTIAL RESISTANCE TO ARTEMISININ DERIVATIVES IN SOMALILAND

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Countries in the Horn of Africa Network for Monitoring Antimalarial Treatment (HANMAT) have reported high rates of Plasmodium falciparum (Pf) with hrp2 and hrp3 deletions, and sporadic pfhrp2/3 deletions have also been reported in Somaliland and in UK travellers returning from the region. In addition, pfkelch13 mutations associated with partial resistance to artemisinin derivatives have been reported in east Africa, further potentially threatening malaria control efforts in the region. The existence and extent of such Pf variants in Somaliland is unknown. We conducted systematic surveillance of pfhrp2/3 deletions and pfkelch13 mutations in five districts of Somaliland in 2021 and 2022. From suspected malaria cases, a total of 943 samples were collected, of which 231 were RDT positive and 238 microscopy positive, with a total of 33 discordant samples (HRP2-RDT negative/microscopy positive). We conducted molecular analysis on all the samples, and 195 were qPCR positive for Pf. Amongst these pfhrp2/3 deletions were confirmed in half of the districts with varying prevalence and in both mono and multiclonal infections. The detailed analysis and prevalence of the pfhrp2/3 deletions as well as the percentage of the deletions causing false-negative RDT results will be presented. We will also present analysis of pfkelch13 variants among those 195 qPCR-positive samples and the relationship with pfhrp2/3 deletion, and discuss implications of the findings for malaria control programme in Somaliland.

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ONE-STEP MULTIPLEX DIGITAL PCR FOR THE DETECTION OF PFHRP2 AND PFHRP3 DELETIONS IN POLYCLONAL INFECTIONS

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Early detection of malaria cases is critical for malaria control and elimination strategies. The majority of Rapid Diagnostic Tests (RDT) used for point-of-care diagnostics in malaria-endemic countries target the HRP proteins coded by Plasmodium falciparum histidine-rich proteins 2 and 3 genes (pfhrp2/3). Due to the global emergence of P. falciparum (Pf) parasites lacking pfHRP2/3 protein, the performance of HRP-based RDTs has been compromised. Lately, there has been an increase in pfhrp2 and pfhrp3 deletion reports in Africa, threatening malaria control efforts. Pfhrp2/3 deletion in polyclonal infections, common in high transmission settings have been shown to give false-negative RDT results, particularly at low parasitaemia (close to detection limit of RDTs). Therefore, there is an emerging demand to develop a rapid molecular tool capable of detecting those parasite clones with greater accuracy. In this study, we report the development of a one-step rapid digital PCR assay based on microfluidic nanoplate technology that measures the fluorescence released by each partition in a 3-target multiplex PCR. This assay is able to accurately detect pfhrp2 and pfhrp3 gene deletions and the ratio of parasites carrying deletions in an Pf infection. We optimized the assay using culture-adapted laboratory lines with different pfhrp2 and pfhrp3 status. Different mixtures and parasitaemia were tested to assess the limit of detection, improving the results from a previously published multiplex qPCR in our lab. Further validation was performed using field samples. This digital PCR assay has significantly improved the accuracy of detecting pfhrp2/3 deletions in multiclonal infections, common in high-malaria transmission settings. Moreover, the high sensitivity of this assay to capture the true clonal diversity of Pf infections can be applied to other malaria targets for other studies.

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CHANGES IN MALARIA TEST POSITIVITY RATE FOLLOWING SCALE UP OF LIFE-SAVING MALARIA CONTROL INTERVENTION IN EBONYI STATE, SOUTH EAST NIGERIA

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Nigeria accounts for 26.6% of global malaria cases according to the 2022 World Malaria Report. Surveillance is paramount to track malaria morbidity and guide decision-making for appropriate transmission-reducing responses. One tracking measure is the malaria test positivity rate (TPR) indicator which is used as an alternate indicator of malaria morbidity since it is based on parasitological confirmation. Over the years, TPR remained high regardless of season possibly due to poor quality of testing and documentation. This study investigates the correlation between the observed positive change in TPR and the interventions implemented to support the Ebonyi State Malaria Elimination Program (SMEP). These efforts include case and data management training, implementation of Behavior Economics (BE) prototypes to improve fever case management, supportive supervision and archiving of used rapid diagnostic test (RDT) cassettes to increase health provider adherence to national guidelines for fever management. This analysis consisted of a pre-post intervention comparison of TPR in similar periods over a 4-year period using secondary routine data from the National Health Management Information System across the 762 health facilities of the state. The data found that the pre-intervention TPR from January-March 2019 was 71% and remained high at 68% from January to March 2020. It is worth noting that COVID did not affect the TPR as only a total of 2,064 confirmed cases were reported in the state from 2020 to 2023. The intervention commenced in July 2020 and six -month post-intervention (January- March 2021), the TPR declined to 54% and further reduced to 50% from January to March 2022. While the reduction in TPR is promising, other factors such as bed net use can highly affect it. Nevertheless, it remains one measure of the effectiveness of the support to Ebonyi SMEP on the implementation of malaria program and suggests that training, supervision, archiving of RDT cassettes and BE prototypes implementation can influence the quality of malaria case management. These findings strongly present the opportunity to scale up our efforts in other states.

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IMPROVING QUALITY OF MALARIA MICROSCOPY THROUGH ONSITE COACHING AND MENTORSHIP TO HEALTH FACILITIES IN TANZANIA

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Quality malaria microscopy relies on the skills of technicians to prepare and examine blood films, high quality reagents, and efficient internal and external quality assurance. Capacity development is necessary to improve quality of diagnosis; however, scarce resources limit the number of technicians able to participate in training. From 2021 to 2022, the U.S. President's Malaria Initiative (PMI) Impact Malaria project, in collaboration with the National Malaria Control Program and health management teams, conducted Malaria Services and Data Quality Improvement (MSDQI) supportive supervision visits for microscopy at 55 health facilities in four project-supported regions. We categorized an average score <50% in key indicators as poor and unacceptable, 50-75% moderate and needs improvement, and >75% as good performance. In 2021, 16 (29%) facilities scored below 50% in preparation, staining, and examination of malaria slides. Nine mentors who had previously successfully completed advanced Malaria Diagnostics Refresher Training (MDRT) provided on-the-job training to staff at these 16 facility laboratories on sample collection, blood film preparation, and examination. A follow-up MSDQI visit conducted in 2022 to assess the quality of microscopy services found that these 16 facilities scored above 75% in specimen collection after receiving the mentorship. The proportion of facilities with poor performance (<50%) in fixing and staining of blood films decreased from 20% to 0%, and the proportion of facilities with moderate scores (50-75%) improved from 20% to 50%. The proportion of facilities with good performance scores (>75%) in blood film examination improved from 60% to 100%. The onsite mentorship may have improved the quality of malaria microscopy among laboratory technicians at health facilities. The use of mentors from local health management teams can bridge the gap of limited resources to reach a larger group of laboratory staff who may not have access to formal MDRT.

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EXTERNAL VALIDATION OF THE WORLD HEALTH ORGANIZATION INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESS (IMCI) PROTOCOL FOR MALARIA TESTING IN LOW MALARIA RISK AREAS

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In low malaria risk areas, the WHO Integrated Management of Childhood Illness (IMCI) chart booklet recommends testing for malaria only in febrile sick children with no obvious cause of fever. The safety of this approach is unclear since the clinical presentation of malaria is unspecific. We performed an external validation study to assess the predictive performance of identifying malaria in febrile children using the IMCI protocol in low malaria risk areas. We used data from ePOCT+, a digital clinical decision support algorithm that helps primary care health workers in the management of sick children in Rwanda and Tanzania. Sick children aged 2-59 months, presenting with fever or a history of fever to a health facility located in a low malaria risk area (i.e. malaria positivity in <5% of febrile children) were included. Follow-up visits and presence of IMCI danger signs made up exclusion criteria. Primary outcome was a positive malaria rapid diagnostic test (mRDT) or the detection of Plasmodium spp by microscopy (thick blood smear). Two diagnostic strategies were evaluated: 1) malaria test only in patients with no obvious cause of fever, 2) malaria test in patients with no obvious cause of fever or with recent travel history. Between December 2021 and January 2023, 7'209 patients from 11 Tanzanian and 15 Rwandan health facilities tested for malaria were included. 126 (1.8%) cases had a positive malaria test. The first strategy had a sensitivity of 24.6% (95%CI 23.6-25.6%) and a specificity of 87.0% (86.2-87.8%). If health workers had adopted this testing strategy, 75.4% (95/126) of febrile children with malaria would not have been identified and thus probably not treated (symptomatic and incidental parasitaemia cases combined). When adding travel history, sensitivity rose to 27.0% (26.0-28.0%) and specificity stayed stable at 86.3% (85.5-87.1%). The sensitivity of the IMCI chart booklet was low and the inclusion of travel history did not increase it significantly. Given the results of this study and considering the trade-off between the need to detect malaria cases and the avoidance of wasted tests, alternatives to the IMCI approach should be explored.

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IMPROVING MALARIA DIAGNOSIS THROUGH QUALITY ASSURANCE IN RWANDA FY 2021-2022

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Malaria remains a leading cause of morbidity and mortality in Rwanda, with almost 1 million malaria cases and 71 deaths reported in 2021-2022. Significant progress in malaria control has been made through the implementation of various interventions, including the scale-up of community-based management of malaria to include adults. However, the diagnosis of malaria continues to be a challenge, with the accuracy of diagnosis at health facilities (microscopy), and community level (malaria rapid diagnostic tests (mRDT)) needing improvement. To improve the quality of malaria diagnosis, an external quality assessment/quality control (EQA/QC) was conducted in selected health facilities and at the community level in all the 30 Rwanda districts. At the community level, the EQA/QC of mRDT was performed by direct observation of community health workers (CHWs) performing the test. At the hospital level, assessment of the laboratory settings and microscopy procedure was done. Fifteen slides per hospital visited were selected and retested by eight WHO accredited malaria microscopists from Rwanda National Reference Laboratory. A total of 704 CHWs were observed. 92% of these were trained on mRDT testing, and the main steps of performing mRDTs were correctly followed in 95% of cases. A total of 42 hospitals were visited and 630 slides retested. Discrepancy from two observers for positive and negative results was 1.5%. Two hospitals exceeded the acceptable range of discrepancy. Over 80% of the laboratories assessed had adequate laboratory space, infrastructure and good quality supplies to undertake microscopy work.

The staining SOPs were followed in 88% of cases. Improvements are needed in accurately recording the opening date and validation of new Giemsa solution, regularly undertaking QC of health centers' blood films, and reporting parasites density for positive blood films. Overall, the EQA/QC identified areas that need improvement. Performance of mRDT by CHWs was good. However, continuous monitoring and evaluation of malaria diagnosis is crucial for appropriate treatment and referrals.

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THE TESTSMART TRIAL: RESULTS FROM A CLUSTER-RANDOMIZED TRIAL OF MALARIA DIAGNOSTIC TESTING AND CONDITIONAL SUBSIDIES TO TARGET ACTS IN THE RETAIL SECTOR IN KENYA AND NIGERIA

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We present the results from an innovative, multi-country cluster-randomized trial (CRT) designed to improve targeting of artemisinin combination therapies (ACT) to individuals with confirmed malaria infection who seek treatment in private medicine retailers (PMR). The majority of ACTs in sub-Saharan Africa are distributed through PMRs. Unnecessary consumption of ACTs purchased over the counter in PMRs is widespread due to their low price, high perceived efficacy, and absence of diagnostic tools to guide drug use. We hypothesized that creating price differentials through targeted ACT subsidies dependent on malaria testing status (untested, negative, positive) could improve targeting and use of ACTs among clients of PMRs. From January 2021 to February 2023, we tested a client-directed intervention in the form of a diagnosis-dependent ACT subsidy combined with a provider-directed incentive for testing against a comparison arm in 48 PMRs in Lagos, Nigeria and 39 in Bungoma and Transnzoia counties, Kenya. All PMRs were provided access to low-cost malaria rapid diagnostic tests (RDT) which they sold to clients who wished to purchase one. PMRs in the intervention arm received 0.1 USD for performing a RDT and were instructed to give a free ACT to any client with a positive test for which they were reimbursed. Information from 5695 clients in Kenya and 3879 in Nigeria was collected through exit interviews.Preliminary results show that the program substantially increased testing uptake in both arms relative to baseline, which in turn improved targeting of ACTs. For example, in Kenya, 67.8% of untested clients received an ACT, compared to 24.1% of malaria negative clients. However, the price differentials did not have an additional impact on test uptake or ACT consumption in the intervention arm compared to the control. These findings provide additional insight into point-of-care decision making for fevers and suggest that although RDTs can be integrated into PMR practices, client level subsidies may not be optimal for modifying purchasing decisions. We plan to present final and detailed findings from Kenya and Nigeria during the scientific session.

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IMPLEMENTATION OF TWO-STEP MALARIA RDT DETECTIONPFHRP2/PLDH COMBINING WITH POINT-OF-CARE TESTS FOR BACTERIAL INFECTIONS IN THE MANAGEMENT OF FEBRILE DISEASES IN CHILDREN UNDER-5 YEARS IN BURKINA FASO

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In low and middle incomes countries (LMICs) such as sub-Saharan Africa (SSA), the management of febrile diseases remains challenging given the lack of practical diagnostic tools to screen the real cause of fever and the limits of malaria rapid diagnostic tests. In order to improve the management of febrile diseases in children under 5 years, this study has been conducted. The study was conducted at the Field Station of Sigle, set-up by the Clinical Research Unit of Nanoro (CRUN). All patients from 6-59 months attending the outpatient clinic of the health facility of Bologho in the health district of Nanoro (Burkina Faso), with documented fever or history of fever within the pass 7 days were invited to participate to the study. Participants were randomized either the intervention package (e-Algorithm or RDT-decisional algorithm arm(RDT-DA)) or routine system. The intervention package was constituted by the following PoC tests: two-step malaria RDT detection PfHRP2 and pLDH, CRP, white blood cells (WBC) count, oximetry, Group A Streptococcus, and Salmonella/Shigella. Antimalarial prescription was 42.05% (164/390) in e-Algorithm arm, 43.65% (172/394) in RDT-DA and 52.30% (232/392) in standard practice system [risk difference (RD): -10.25% (p p<0.001) for e-Algorithm and -8.65% (p<0.001) for RDT-DA). Antibiotics were prescribed in 46.92% (183/390) in e-Algorithm arm, 50.25% (198/394) in RDT-DA arm and 76.28% (299/392) in routine system [RD: -29.36% (p<0.001) for e-Algorithm and -26.03% (p<0.001) for RDT-DA]. The reduction of antibiotic prescription greater in children without malaria [RD:-64.79% (p<0.001) for e-Algorithm arm and -61.62% (p<0.001) for RDT-DA algorithm arm. In conclusion, implementation of two-step malaria RDT and PoC tests for bacterial infections has potential to improve the management of febrile diseases in children under 5 years and reduce inappropriate prescription of antibiotics. Nevertheless, the use of CRP test is not suitable differentiate bacterial to non-bacterial infections in children with malaria.

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SEROLOGICAL MARKERS PREDICT PLASMODIUM VIVAX RELAPSES IN A RETURNING INDONESIAN SOLDIER COHORT

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Relapses from latent liver-stage parasites (hypnozoites) are a key challenge for Plasmodium vivax elimination. Relapses are responsible for >80% of blood-stage infections. There are currently no tools to detect hypnozoites, but P. vivax blood-stage infections induce strong antibody responses arising quickly after infection and decaying slowly over time. Antibodies are thus markers of both current and recent past infections, allowing identification of people recently exposed to P. vivax and thus at risk of carrying hypnozoites. This study aimed to test the ability of antibody signatures to a validated set of 13 antigens to predict relapse risk in two cohorts of soldiers (n =

592) who returned to a malaria-free area from a 9-month deployment to a malaria-endemic area between 2018 and 2022. All soldiers were assessed by Luminex serology on the day of recruitment and followed actively every two weeks and at time of febrile symptoms until first recurrent P. vivax parasitaemia, for up to 6 months. An optimised machine learning Random Forest classification algorithm was used to classify soldiers as exposed during the previous 9 months. Over 110 soldiers experienced relapses during follow-up with significant heterogeneity in relapse risk between the two cohorts (Cohort 1: 25, Cohort 2: >85). Soldiers who relapsed had higher median antibody titers for most of the biomarkers compared to those who did not relapse. In cohort 1, our diagnostic tool had 75% sensitivity and 93% specificity at identifying future relapses using blood samples from recruitment day. Recurrent infections strongly boosted antibody titres both in sero-positive and initially sero-negative soldiers. Analyses of the 2nd cohort are ongoing but preliminary results indicate a comparable performance. This demonstrates the ability of serological markers to identify people at risk of relapse with high accuracy. In our presentation, we will present the final results across both cohorts and discuss the implications of these results for the development of a novel public health intervention P. vivax serological testing and treatment (PvSeroTAT) for relapse prevention.

6080

THRESHOLD LIMITS OF DETECTION AND QUANTIFICATION OF MALARIA PARASITES IN DRIED BLOOD SPOT: A COMBINED APPROACH OF MID-INFRARED SPECTROSCOPY AND MACHINE LEARNING

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Mid-infrared spectroscopy (MIRS) combined with machine learning (ML) have shown potential in detecting malaria infections. The technique is reagent-free, simple to use and cost-effective, but its malaria parasite detection thresholds remain unknown. This study aims to investigate the lower limits of detection and quantification of MIRS-ML approaches under different hematocrit levels, including anemia, to further evaluate its potential for malaria control. The study was conducted at the Ifakara Health Institute laboratory in Tanzania. Blood samples were obtained from PCR-tested malaria-free individuals, and parasite cultures were performed using Plasmodium falciparum strains of NF54 and FCR3. Hematocrit ratios (50%, 25%, and 12.5%) and malaria parasitemia levels (6%, 0.1%, 0.002%, 0.00003%, and 0%) were created through two-way matrix serial dilutions. Dried blood spots were analysed using MIRS and ML classifiers and regressors to detect and quantify malaria parasites at different parasitemia levels and in the presence of anemia.We created two logistic regression models, one including only the highest parasitemia (6%) and negative control, and a second model that included all parasitemia levels. The first detected malaria infections at accuracy of 97%, 90%, and 90% for Normal (50%), mild (25%), and severe (12.5%) anemia, respectively. The second model was 100% accurate in detecting malaria infections at 6%, 0.00003% and negative control, but less accurate in detecting of 0.1% and 0.002% (>80% and >50%, respectively). When Support vector machine regressor were used in the analysis, this model outperformed other regression ML models, quantifying five-class malaria parasitemia with a Root Mean Square Error, RMSE = 0. MIRS-ML approaches can detect and quantify at low parasitemia (1-10 malaria parasites/µl of blood) with > 95% accuracy. Importantly, malaria parasite detection and quantification by MIRS-ML approaches were not affected by anemia. These initial findings indicate that MIRS-ML approaches could be valuable for detecting and quantifying malaria infections, particularly in resource-limited settings.

6081

DETECTION OF PLASMODIUM MALARIAE AND PLASMODIUM KNOWLESI THROUGH IMPROVEMENTS IN MICROSCOPY SERVICES IN CAMBODIA

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The primary method of malaria diagnosis in Cambodia is the use of Rapid Diagnostic Tests (RDTs), particularly outside hospitals. Currently available RDTs only detect Plasmodium falciparum (Pf) and P. vivax (Pv). P. malariae (Pm) and P. knowlesi (Pk) are detected primarily in research studies using molecular diagnostic tools. Training and support for microscopy diagnosis has recently taken place in six provinces managed by the Ministry of Health, with financial and technical support from USAID/PMI through the Cambodia Malaria Elimination Projects (CMEP and CMEP2) and the World Health Organization. This includes 5-day training courses on microscopy diagnosis and organization of national competency assessments for malaria microscopists to ensure quality diagnosis at the point of care. If patients test negative by RDT but malaria symptoms continue, then a blood smear is taken for microscopy. If the blood smear is positive for Pm/Pk, a blood smear and dried blood spot are taken for confirmation at the National Center for Parasitology, Entomology and Malaria Control (CNM) through both microscopy and polymerase chain reaction (PCR). This investment has led to a corresponding rise in Pm and Pk cases diagnosed through routine CMEP2-supported activities from zero to 58 (Jan 2021-Feb 2023). Slide confirmation by CNM through microscopy examination classified 50 cases as Pm, six as Pk, and two were not definitive. PCR is used as it can be difficult to differentiate between Pm/Pk by microscopy. The PCR results showed that 42 cases were confirmed as Pm, nine as Pk, one as Pf/Pm and six were not definitive. The majority (79%, n=58) of these cases occurred during the rainy season (May-Oct 2022). These results suggest there is likely ongoing Pm/Pk transmission that is undetected in areas without microscopy services in Cambodia. Microscopy services at health centers remain limited and updates to the suspected case definition may be needed to ensure all Pm/Pk infected patents are tested. As Cambodia is aiming for the elimination of all human malaria species by 2025, introducing and sustaining quality microscopy will be essential to detect all forms of malaria species.

6082

LOW PREVALENCE OF PLASMODIUM FALCIPARUM HISTIDINE-RICH PROTEIN 2 AND 3 GENE DELETIONS—A MULTIREGIONAL STUDY IN CENTRAL AND WEST AFRICA

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Treatment of malaria parasite-infected individuals and the effectiveness of malarial control efforts may be compromised by Plasmodium falciparum parasites with deletions of P. falciparum histidine-rich protein 2 (PFHRP2) and pfhrp3 genes because such parasites may not be detected by PfHRP2-based rapid diagnostic tests (RDTs). Here, we assessed the frequency of parasites with pfhrp2 and pfhrp3 deletions at four different

study sites: Gabon and Republic of Congo in Central Africa and Nigeria and Benin in West Africa. Using a highly sensitive multiplex qPCR (4plex qPCR), we analysed 534 samples from Gabon, 917 from the Republic of Congo, 466 from Nigeria, and 120 from Benin. Low prevalences of single deletions in pfhrp2 (ranging from 0% to 1%) and pfhrp3 (ranging from 0% to 0.03%) were observed across all study sites, namely Gabon, Republic of Congo, Nigeria, and Benin. In addition, P. falciparum parasites with two deletions were found exclusively in Nigeria, accounting for 1.6% of all samples that were analysed. Thus, our pilot investigation suggests that, currently in Central and West Africa, there is a low risk for false-negative RDT results caused by deleted pfhrp2/pfhrp3 genes. However, continuous, and comprehensive monitoring is warranted to detect any (potentially fast) changes in this status and to make sure that RDTs continue to be an appropriate method for monitoring and diagnosing malaria in these regions.

6083

HIGH PREVALENCE OF PLASMODIUM FALCIPARUM HRPII-DELETED VARIANTS ASSOCIATED WITH LOW RAPID DIAGNOSTIC EFFICACY 13 YEARS AFTER INTRODUCTION OF MALARIA RDTS IN EASTERN ZIMBABWE

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Malaria has receded from most of Zimbabwe over the past decade following scaled-up vector control and artemisinin-based combination therapy (ACT) interventions for possible elimination of the disease. The advent of Plasmodium falciparum histidine-rich protein II (PfHRPII)-based rapid diagnostic tests (RDTs) and ACTs at inception of the 21st millennium ushered in a new era of complementary test-and-treat campaigns to accelerate towards malaria elimination, including mandatory RDT confirmation of clinical cases before the administration of ACT. However, the emergence of PfHRPII-deleted parasite variants is undermining RDT accuracy and posing a growing threat to prompt/effective testing and treatment for malaria control and elimination. We examined P. falciparum HRP-II RDT diagnostic performance on 1,125 presenting febrile suspected malaria cases using microscopy as gold standard. We report poor RDT efficacy on the presenting febrile cases, at 49% sensitivity, highly associated with rampant (61%) PfHRPII-deleted malaria parasite variants (OR [95%CI]: 14 [6.6 - 29.6], n = 331) 13 years after introduction of RDTs in Mutasa, Zimbabwe. Our data show ten-fold higher odds (OR [95%CI]: 10 [3.2 - 31.0]) of PfHRPII-deleted variants among malaria cases of 2021 compared to 2004 (pre-RDT introduction). RDT false-negative rate correspondingly increased from baseline 9% to 51%, suggesting formidable parasite adaptation to RDT use. Akin to the Horn of Africa our study is concerning for emergence of diagnostic resistant parasites in Southern Africa that may undermine regional elimination efforts.

6084

A DIGITAL MICROSCOPE FOR THE DIAGNOSIS OF PLASMODIUM FALCIPARUM PARASITES WITH HRP2 AND HRP3 DELETION AND P. VIVAX

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The most frequent and most sensitive class of rapid tests for Plasmodium falciparum diagnosis rely on detection of the HRP2 and HRP3 proteins. Deletions of the hrp2/3 genes are a major concern and where the frequency of the deletion is high, alternative diagnostic tools are needed. The Noul miLab is a portable digital microscope for malaria diagnosis. The miLab conducts smear preparation from a droplet of blood, staining, and imaging. An algorithm detects infected RBCs, and displays them on a screen. Time-to-result is approximately 20 minutes, with less than two minutes hands-on time. We evaluated the miLab among 659 febrile patients in Gondar, Ethiopia, where co-transmission of P. falciparum and P. vivax, and high frequency of hrp2/3 deletions make diagnosis challenging. By qPCR, 76.2% of patients tested positive; 40.4% for P. falciparum, 12.3% for P. vivax, and 23.8% with mixed infection. 34.7% of P. falciparum infections carried hrp2 deletion, and 91.5% hrp3 deletion. The miLab diagnosed 51/52 (98%) of P. falciparum infections with hrp2 deletion at densities >20 parasites/µL. The sensitivity of the miLab for P. falciparum at densities >200 parasites/µL (as determined by qPCR) was 93.6%, and 90.2% at densities >20 parasites/µL. The miLab was more sensitive than an LDH-based RDT and local microscopy with sensitivities of 80.3% and 82.1% at densities >20 parasites/µL. For P. vivax, the sensitivity of the miLab was 83.9% at densities >200 parasites/µL, and 82.7% at densities >20 parasites/µL (RDT: 64.4%, microscopy: 56.7%). Specificity of the miLab was 84.5%. At densities >20 parasites/µL, the miLab misclassified 4/100 P. falciparum mono-infections as P. vivax, and 4/36 P. vivax mono-infections as P. falciparum. Further, it identified only 5/23 mixed infections correctly. In conclusion, the Noul miLab is more sensitive than microscopy and thus a valuable addition to the toolkit for malaria diagnosis in particular in areas with high frequencies of hrp2/3 deletions. Incorrect diagnosis of species and low sensitivity for mixed-species infections are currently being addressed through updates to the algorithm.

6085

FITNESS COST OF PFHRP2/3 GENE DELETION & K13 R622I MUTATION IN NATURAL INFECTIONS IN ETHIOPIA: TRANSMISSION POTENTIAL OF PARASITES EVALUATED BY DIRECT MEMBRANE FEEDING ASSAYS

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Parasites with pfhrp2/3 gene deletions are fast spreading, especially in the Horn of Africa. Its unique heterogeneous spatial distribution is also evident at lower scales. In our previous studies, we confirmed its co-occurrence with parasites carrying the R622I kelch mutation. From Sept 2022 - March 2023, we examined the transmissibility of P. falciparum parasites with & without pfhrp2/3 gene deletion to colony-maintained An. arabiensis mosquitoes (n=5290) in direct membrane feeding assays (DMFA) in Ethiopia. A total of 182 microscopy positive patients were screened & 53% had negative result using HRP2-based RDT. They had pfhrp2 (88%, 83/94) & pfhrp3 (95%, 89/94) gene deletion by digital PCR. The median HRP2 antigen concentration (multiplex bead-based assay) was higher in the RDT positive (1,060pg/mL; IQR 675-1284; p=0.001) than RDT negative samples (10; IQR 9-16). Transmissibility of parasites with pfhrp2 deletion was higher (80%, 20/25) than without deletion (70%, 19/27). Overall, 47% of mosquitoes were infected with no difference between the two groups. The oocyst density in infected mosquitoes was higher in parasite without deletion (median 13, IQR 4-53) than with gene deletion (4, 2-17; p=0.082). Infectivity to mosquitoes was strongly associated with total parasite by 18S based qPCR (ρ=0.376, p=0.006) & male (ρ=0.381, p=0.006) & female (ρ=0.375, p=0.007) gametocyte densities measured by sex specific RT-qPCR. These were not different between pfhrp2 deleted & undeleted parasites. In conclusion, the overall prevalence of pfhrp2 (50%, 89/179) & pfhrp3 (90%, 161/179) deletion substantially increased in this study compared to our previous study in 2021. Parasites with pfhrp2 deletion were as transmissible to mosquitoes as wild type parasites. Currently, we are analyzing sequence results from the amplicon NGS to examine the association of drug resistance markers such as R622I with the above

outcomes. Based on our previous study, the frequency of R622I mutation was high in the same area (49%). We are also collecting more samples & doing extra DMFAs to boost the observation in the short transmission season (April-May 2023).

6086

PERCEPTIONS OF FACILITY-BASED AND COMMUNITY HEALTH WORKERS IN KENYA: IMPLICATIONS FOR PROGRAMS BASED ON FINDINGS FROM THE KENYA MALARIA BEHAVIOR SURVEY

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Facility-based health workers and community health volunteers (CHVs) play essential roles in malaria prevention and treatment. Community perceptions of health workers, however, remain under-examined in Kenya. In 2022, Kenya's Division of National Malaria Program (DNMP) and Breakthrough ACTION Kenya implemented the Malaria Behavior Survey in the malaria-endemic Lake region of Western Kenya. 1,787 women and 466 male partners participated from 1,456 households. Descriptive and bivariate analyses assessed differences in community perceptions of health workers by socio-demographic characteristics. Perceptions of health workers were also key covariates in multivariable logistic regression models of prompt and appropriate care-seeking for fever. Favorable perceptions were based on agreement with statements about facility-based health workers and CHVs overall and for case management. Scores were summarized and dichotomized for analysis. Most respondents reported overall favorable perceptions of facility-based health workers (95%) and CHVs (82%). Favorable perceptions of both types of health workers were significantly higher among female than male respondents. 61% of respondents had favorable perceptions of CHVs regarding malaria care-seeking and treatment in particular, and this varied significantly by respondent sex (female: 64% vs. men: 57%; p<0.01). 43% and 50%, respectively, of respondents perceived that CHVs always have 1) medication to treat malaria and 2) rapid diagnostic test kits to see if a person has malaria. Caregivers reporting favorable perceptions of CHVs had 1.9 times increased odds of reporting prompt and appropriate care-seeking for a child under five who had a fever in the past two weeks (AOR: 1.9; 95% CI: 1.1-3.4). The associations between CHV perceptions and care-seeking are cross-sectional yet suggest that service delivery and social and behavior change programs can improve perceptions of the quality of care and trustworthiness of CHVs. Perceptions that CHVs do not have supplies they need could be addressed by correcting supply issues and subsequently assuring communities that supplies are available.

6087

A NOVEL HUMANIZED MURINE MODEL TO ASSESS PRIMAQUINE-INDUCED HEMOLYSIS IN G6PD DEFICIENCY

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Approximately half a billion humans have some form of glucose-6-phosphate dehydrogenase deficiency (G6PDd), limiting the ability to safely achieve radical cure of Plasmodium vivax using primaquine or tafenoquine due to risk of hemolysis. Because most G6PDd is caused by an unstable enzyme variant, very young RBCs have increased G6PD activity and are resistant to hemolysis. As such, primaquine can have a "self-limiting" character if given in regimens that promote controlled early hemolysis and reticulocytosis. Accordingly, modified primaquine regimens have the potential to be both safe and effective in G6PDd patients. Historically, there has been no mouse model of G6PDd that recapitulates an RBC age-dependent gradient of G6PD activity, limiting testing of primaquine dosing strategies. We report the generation of two new strains of mice in which the murine G6PD gene was replaced with either the (A-) deficient or non-deficient (ND) human genomic DNA. RBC G6PD activity and protein levels were measured by spectrophotometric assay and Western blot, respectively. In vivo biotinylation pulse chase was used to visualize "young RBCs" from 1-6 days of age, which were isolated by streptavidin-coated magnetic bead depletion. "All age" RBCs from A- mice had 12.8% normal G6PD activity (p<0.0001) and only trace amounts of G6PD protein. In contrast, 1-6 day old A- RBCs had 56% normal G6DP activity and easily detectable G6PD protein. qPCR showed no difference in G6PD mRNA in bone marrow from A- and ND mice. After 4 days of primaquine challenge (50mg/kg/day), A- mice had a 17% drop in hematocrit compared with ND mice (p<0.001). A- mice also had increased reticulocytes (14.5%) compared to ND mice (4.9%) (n=12, p=<0.0001). Essentially 100% of cleared RBCs were older than 6 days. RBCs from ND mice had normal G6PD activity and protein, with only subtle effects of primaquine challenge. 3 out of 3 primaquine challenge experiments had similar results. While great care must be taken in translation of therapeutic details from mice to humans, the newly described mice serve as a tractable platform to test general primaquine dosing strategies.

6088

PREDICTING OPTIMAL ANTIMALARIAL DRUG COMBINATIONS FROM A STANDARDIZED PLASMODIUM FALCIPARUM HUMANIZED MOUSE MODEL

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The development of new combinations of antimalarial drugs is urgently needed to prevent the spread of parasites resistant to drugs in clinical use and contribute to the control and eradication of malaria. In this work, we evaluated a standardized humanized mouse model of erythrocyte asexual stages of Plasmodium falciparum (PfalcHuMouse) for the selection of optimal drug combinations. Firstly, we showed that the replication of P. falciparum was robust and highly reproducible in the PfalcHuMouse model by retrospective analysis of historical data. Secondly, we compared the relative value of parasite clearance from blood, parasite regrowth after suboptimal treatment (recrudescence), and cure as variables of therapeutic response to measure the contribution of partner drugs to combinations in vivo. To address the comparison, we first formalized and validated the day of recrudescence (DoR) as a new variable and found that there was a log linear relationship with the number of 46 viable parasites per mouse. Then, using historical data on monotherapy and two small cohorts of PfalcHuMice evaluated with ferroquine plus artefenomel or piperaquine plus artefenomel, we found that only measurements of parasite killing, (i.e., cure of mice) as a function of drug exposure in blood allowed direct estimation of the individual drug contribution to efficacy by using multivariate statistical modelling and intuitive graphic displays. Overall, the analysis of parasite killing in the PfalcHuMouse model is a unique and robust experimental in vivo tool to inform the selection of optimal combinations by pharmacometric PK/PD modelling.

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MODELLING THE HAEM DETOXIFICATION PATHWAY IN PLASMODIUM FALCIPARUM TO AID IN TARGET DECONVOLUTION AND MECHANISM OF ACTION STUDIES

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The parasite Plasmodium falciparum (Pf) causes the deadliest form of malaria. Critical to parasite survival is the haem detoxification pathway. This biochemical pathway, which occurs in the parasite digestive vacuole (DV), results in the digestion of haemoglobin (Hb) and subsequent formation of an inert crystal, haemozoin (Hz). Disruption of this pathway is an attractive antimalarial target as it includes numerous biophysical and biochemical targets such as protease enzymes, endocytosis mediators, transporters and molecules required for Hz. Incorporating these parameters and others into a mathematical model would aid in mode of action studies and may inform rational drug design. Numerous parameters are imperative for model development. In the current study, the volume of the DV lumen and the rate of Hb uptake were found to be crucial to the model, and were studied herein using confocal microscopy techniques. Validation of the model, by way of pathway perturbation, was studied using a cellular fractionation assay that assessed the impact of inhibitory chemotypes on the levels of Hb, free haem and Hz. To study the lumen volume, red blood cells pre-loaded with pHrodo™ dextran beads were incubated with Pf trophozoites to allow reinvasion. Following incubation, individual parasites were visualised with an Airyscan LSM 980 confocal microscope and image processing was carried out using ImageJ. These studies revealed that lumen growth in NF54 followed a Gompertz growth curve, while Dd2 followed a sigmoidal growth trend. We also examined differences in lumen volume of other Pf strains with a varying degree of sensitivity to piperaquine. Finally, parasites were treated with a set of endocytosis and protease inhibitors to perturb the pathway. Using cellular fractionation assays, treatment with butanedione-2,3 monoxime (an endocytosis inhibitor) caused a decrease in the levels of haem and Hz; whereas E-64 (cysteine protease inhibitor) caused a dramatic increase in the levels of undigested Hb and a subsequent decrease in the levels of Hz. These mechanistic studies help define haem perturbation properties characteristic of various inhibitor classes.

6090

THE ACTIVITY OF NOVEL SLOW-ACTION ANTIPLASMODIAL 1,3,4-OXADIAZOLES IS ASSOCIATED WITH A PLASMODIUM FALCIPARUM PALMITOYLTRANSFERASE

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New chemoprevention drugs are needed to help protect vulnerable populations in areas of high malaria endemicity as we move towards eradication. We have identified novel N,N-dialkyl-5-alkylsulfonyl-1,3,4-oxadiazol-2-amines as a new antiplasmodial chemotype with a different action to delayed-death slow-action drugs like clindamycin. Structure activity relationship analysis of >60 analogues identified multiple compounds with potent activity against drug-sensitive and drug resistant asexual stage Plasmodium falciparum parasites (IC50 <40 nM) and >2,500 selectivity for P. falciparum versus human cells. Genome sequencing of P. falciparum parasites selected for in vitro resistance to representative members of this series identified mutations in a palmitoyltransferase gene. This phenotype was confirmed using CRISPR/Cas9 mediated gene editing. Further studies are underway to investigate whether this P. falciparum palmitoyltransferase is the target of slow action 1,3,4-oxadiazoles and thus a new chemoprotection drug target, or alternatively, a mechanism of resistance to these compounds.

6091

A SYSTEMS BIOLOGY APPROACH TO UNDERSTAND THE MECHANISMS OF ACTION OF KALIHINOL, A POTENT NEW ANTIMALARIAL

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The Kalihinol analogues belong to the Isocyanoterpenes (ICT) family of chemical compounds. ICTs have been shown to have potent activity against multiple microbial pathogens including the human malaria parasite Plasmodium falciparum. Our work shows that the kalihinol derivative retains its potency against both drug-sensitive and -resistant parasites with IC50 values in the low nM range. This activity translates into transmission-blocking potential, as the compound inhibit sexual differentiation in vitro. Through phenotypic analyses and cell biological assays we demonstrate that the apicoplast is one of the sites of action of the drug in the P. falciparum-infected red blood cell. Drug-drug interaction studies as well as chemical rescue using isopentenyl pyrophosphate (IPP) confirmed that one Kalihinol analogue exerts its antimalarial activity through alteration of apicoplast metabolic processes. We also confirm, through metabolomic profiling and drug-protein interactions assays, that our analogue interacts with several proteins involved in apicoplast membrane biogenesis and lipid trafficking. Prolonged drug pressure assay followed by whole genome sequencing and CRISPR-cas9 genome editing, identify the mode of resistance acquired via the vesicular trafficking system. In vivo studies in humanized mice model demonstrate that Kalihinol analogues suppress P. falciparum growth with good pharmacokinetic and safety properties. We also confirmed the efficacy of the compound against P. knowlesi growth. Altogether our multi-omics approach not only unraveled a novel of mode of action for an antimalarial, but also mechanism involved in drug resistance. The unique properties of this class of antimalarials, their high potency, excellent therapeutic profile, and the limited capacity of the parasite to mount resistance make them ideal compounds to further develop as a potential next generation of drugs for the treatment and elimination of malaria infection.

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EVALUATION OF THE IN VITRO GAMETOCYTOCIDAL ACTIVITY OF TAFENOQUINE IN COMBINATIONS WITH METHYLENE BLUE AND OTHER ANTIMALARIAL COMPOUNDSTAFENOQUINE IN COMBINATIONS WITH METHYLENE BLUE AND OTHER ANTIMALARIAL COMPOUNDS

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Resistance to artemisinin-based combinations in Southeast Asia is jeopardizing malaria control and elimination efforts. There is an urgent need for new antimalarial drugs, especially those with potent gametocytocidal properties to reduce malaria transmission. Tafenoquine (TQ) possesses hypnozoitocidal, but poor blood schizontocidal and gametocytocidal properties. Ideally, TQ should be used in combination with a partner drug with strong schizontocidal and gametocytocidal activities. We have

previously shown MB to synergise the in vitro blood schizontocidal activity of TQ. In the present study, we evaluated in vitro gametocytocidal activity of TQ in combinations with antimalarial drugs including chloroquine (CQ), dihydroartemisinin (DHA), lumefantrine (LUM), piperaquine (PPQ), pyronaridine (PRN), methylene blue (MB) and 10-aminoartemisinins compounds, artemiside and artemisone, with potent blood schizontocidal and gametocytocidal activities. Plasmodium falciparum 3D7c gametocyte viability was assessed by measuring adenosine triphosphate (ATP) production. TQ inhibited ATP production in stage II-III and stage IV-V gametocytes with IC50 values of 2,453 ± 1,054 nM and 3,616 ± 1,360 nM, respectively, whereas MB was highly active against stage II-III and stage IV-V gametocytes with IC50 values of 27.7 ± 6.5 nM and 50.9 ± 24.5 nM, respectively. Addition of MB synergised the gametocytocidal activity of TQ against stage II-III gametocytes with summary fractional inhibitory concentrations (ΣFIC) of 0.52-0.73, but was mildly antagonistic against stage IV-V gametocytes with ΣFIC of 1.37-1.60. TQ-DHA and TQ-artemisone combinations were additive against early and late stage gametocytes, while TQ-artemiside was mildly antagonistic with ΣFIC of 1.09-1.33 and 1.99-2.30 against stage early and late stage gametocytes, respectively. Addition of CQ, PPQ, LUM and PRN at fixed concentrations corresponding to their maximum physiologically achievable concentrations to TQ had no significant effect on gametocytocidal activity of TQ. Our data suggest that MB can be considered as a potential partner drug with TQ for malaria elimination.

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A FIRST-IN-HUMAN SAFETY, TOLERABILITY, AND PHARMACOKINETICS STUDY OF MMV367, A NEW CANDIDATE ANTI-MALARIAL AGENT FOR ACUTE UNCOMPLICATED MALARIA

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MMV367 is a first in class, fast acting, pyrrolidinamide blood stage inhibitor of Plasmodium falciparum co-developed by MMV and GSK with an anticipated novel antimalarial mechanism for treatment of acute uncomplicated P. falciparum malaria. It is highly active against mutant and resistant strains including field isolates, demonstrating absence of cross resistance. This FIH study sponsored by MMV (NCT05507970) evaluated the safety, tolerability, and PK of MMV367 in 47 healthy male and female volunteers. Part 1 was double-blind randomised, placebo (Pbo)-controlled with 4 sequential fasted cohorts (6 active and 2 Pbo, each) receiving a single, ascending dose of 100, 300, 750 and 1500 mg. Part 2 was an open-label, crossover, fed-fasted cohort (n=8) dosed with 440 mg. 400 mg QD for 3 days was tested in Part 3 (6 active and 2 Pbo). At the writing of this abstract, the study is completed, and data are still blinded. Unblinded study results will be presented. No serious or severe adverse events were reported. 14 treatment emergent adverse events (TEAEs) - all causality - were observed. 2 mild TEAEs (abdominal pain - epigastric pain) reported by the same participant in the 750 mg cohort, were judged as IMP-related. No other IMP-related TEAEs, clinically relevant ECG, vital signs or laboratory tests changes were reported. Cmax values were achieved 2 - 4 h post-dose in Part 1. MMV367 mean t½ values across cohorts ranged from 16.3 to17.5 h. Compared to the fasted state, geometric mean relative bioavailability after a high fat meal based on Cmax, AUC0-last and AUC0-inf were 161, 133 and 133%, respectively. Median Tmax were 3.5h (fasted) and 5h (fed) post-dose. Accumulation ratio after 3-day QD dosing was 2-fold. MMV367 demonstrated safety, tolerability and PK warranting further clinical development. This new candidate will be further tested against induced blood-stage malaria in healthy participants to provide a PK-PD model supporting Phase 2 study design.

6094

EFFICACY OF PRAZIQUANTEL FOR TREATMENT OF PLASMODIUM FALCIPARUM INFECTION IN ASYMPTOMATIC GABONESE ADULTS

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To date praziquantel (PZQ) is the only licensed drug for the treatment of schistosomiasis. Also, there is preliminary evidence that PZQ may have an effect on Plasmodium parasites. This potential effect was assessed by the CORMA-MAL study, a phase 2a, single-center, randomized, blinded, placebo-controlled trial recruiting semi-immune, Gabonese adults with an asymptomatic Plasmodium falciparum parasitemia ranging from 200 to 5000 parasites/µl. PZQ was administered once daily as 40mg/kg dosage for three days (D0, D1, D2); Placebo was administered also once daily for three days. An effective antimalarial treatment was given to all participants at the end of study on D7, as well as to those reaching pre-defined rescue treatment criteria. Recruitment and follow-up of all 44 study participants was completed in February 2023 and the first preliminary results are presented here. 14% (3/22) of participants in the Placebo arm needed to receive the rescue treatment versus 5% (1/22) in the PZQ arm (p=0.29). The median (IQR) parasite reduction in the PZQ arm was 87% (0% to 99%) on D3 compared with 36% (-193% to 58%) in the Placebo arm (p=0.037) and 93% (45% to 100%) versus 68% (-228% to 100%), respectively on D7 (p=0.2). Linear regression models indicate a significant hourly decrease of log10(parasitemia) between D0 and D7 in the PZQ arm (y= -0.006*x + 2.4; p<0.0001), while there was a non-significant trend of decreasing log10(parasitemia) in the Placebo arm (y= -0.0018*x + 2.3; p=0.16). Out of 22 participants in the Placebo arm there were 3 (14%) participants with microscopic parasite clearance, compared with 7 (32%) out of 22 in the PZQ arm (log-rank test p=0.15). Computing the area under the curve (AUC) of log10(parasitemia) between D0 and D7 indicated that total parasite mass was lower in the PZQ arm (Mean AUC: 335) than in the Placebo arm (Mean AUC: 415), although not significantly (p=0.12). Concluding, preliminary data indicate some anti-plasmodial activity of PZQ in comparison to Placebo, however, further research is needed.

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ETHIOPIAN PLASMODIUM VIVAX HYPNOZOITES FOR MATION DYNAMICS AND THEIR SUSCEPTIBILITY TO REFERENCE ANTIMALARIAL DRUGS

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One of the key obstacles to malaria elimination is largely attributed to Plasmodium vivax's ability to form resilient hypnozoites in the host liver that cause relapsing infections. As a result, interruption of P. vivax transmission is difficult. P. vivax transmission occurs in Duffy-positive individuals and have been mainly thought to be absent in Africa. However, increasing studies using molecular tools detected P. vivax among Duffy-negative individuals in various African countries. Studies on the African P. vivax has been severely limited because most of malaria control program focus mainly on falciparum malaria. In addition, there is a scarcity of laboratory infrastructures to overcome the biological obstacles posed by P. vivax. Herein, we established field transmission of Ethiopian P. vivax for routine sporozoite supply followed by liver stage infection in Mali. Furthermore, we evaluated local P. vivax hypnozoites and schizonts susceptibilities to reference antimalarial drugs. The study enabled the assessment of local African P. vivax hypnozoite production dynamics. Our data displayed the ability of the African P. vivax to produce hypnozoite forms ex vivo at different rates per field isolate. We report that while tafenoquine (1µM) potently inhibited both hypnozoites and

schizont forms; atovaquone (0.25μM) and the phosphatidylinositol-4-OH kinase (PI4K)-specific inhibitor KDU691 (0.5μM) showed no activity against hypnozoites forms. Unlike hypnozoites forms, P. vivax schizont stages were fully susceptible to both atovaquone (0.25μM) and the (PI4K)-specific inhibitor KDU691 (0.5μM). Together, the data revealed the importance of the local platform for further biological investigation and implementation of drug discovery program on the African P. vivax clinical isolates

6096

VIRTUAL SCREENING OF THE NATURAL COMPOUNDS LIBRARY IDENTIFIES NATURE IDENTICAL SYNTHETIC COMPOUND METHYL GREVILLATE AS A NOVEL PFHDAC1 INHIBITOR WITH STEREOSPECIFIC MULTISTAGE ANTIMALARIAL ACTIVITY AND IN VIVO EFFICACY

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Malaria control relies on treatment with effective antimalarials. Although artemisinin (ART) combination therapies (ACTs) are currently the first line of treatment for Plasmodium falciparum (P.f.). As part of identifying specific inhibitors and novel targets essential for P.f survival, we focus on histone deacetylase 1 protein (PF3D7_0925700, PfHDAC-1) as a potential protein target. To identify hits from natural compound libraries potentially able to block PfHDAC1, we performed CADD based screening of n=135,335. These screening efforts identified commonly found tricyclic diterpenes/ terpenoid compounds. The hit library was negatively screened against human HDAC proteins. Methyl grevillate (MetG) among others was found to the top interacting compound with PfHDAC1 and had no binding affinity with human orthologue. MD simulation studies were conducted to validate the top hits, MetG had an energy score of -56.32. The MetG along with other top compounds were tested against erythrocytic stages which showed IC50 of 35.298±2.63 nM. Enzymatic validation assay revealed that MetG specifically blocks with inhibition curve fitting on competitive inhibitor models. In-vitro antiplasmodial efficacy testing of MetG in asexual stages confirmed its potent activity against both PfD6 (CQ-sensitive) and PfW2 (CQ-resistant) parasites. Anti-gametocidal evaluation showed distorted morphological changes in the nucleus of the RBC-dwelling parasites. Further testing in mice models of P. berghei blood stage and liver-stage malaria, showed in-vivo inhibitory activities. Most importantly, the evaluation using field isolates from clinical samples showed equally effective inhibition with IC50 of 198.45±6.1 nM. In addition, cytotoxicity testing showed negligible toxicity with 100x the IC50 in PBMCs, HEK293 and Huh 7.1. Notably, MetG was active against the pathogenic liver stage of the malaria parasite with IC50 of 78.91 nm. Taken together, these results suggest that MetG is a potential target-specific multi-stage inhibitor of P.f. malaria.

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POPULATION PK ANALYSIS OF CHLOROQUINE IN A HUMANIZED MOUSE MODEL OF PLASMODIUM FALCIPARUM MALARIA

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The Plasmodium falciparum humanized mouse model is a validated tool to predict the efficacy of new drugs in humans. The aim of this work was to develop a population PK model of chloroquine in a P. falciparum humanized mouse model to investigate the relationship between model PK parameters and evolution of parasitaemia. Thus, human erythrocytes were engrafted into 60 immunodeficient female NODscidIL2Rgammanull (NSG) mice and they were infected with P. falciparum intravenously. The pharmacological treatment started when the percentage of parasitaemia in mice reached either 1 or 10 %. Single and repeated doses of chloroquine from 2.5 to 300 mg/kg were administered orally once daily for 1 to 6 days. Drug concentration data from all dosing schedules were modelled using Phoenix® NLMETM 8.3 and FOCE method. The relationship between physiological or pathological covariates and parameter estimates were explored. Since the animals were examined at different occasions, the inter occasion variability in individual parameters was also evaluated. Model parameters, diagnostic plots and internal validation techniques (VPC and bootstrap) were evaluated for model performance. Overall, 466 chloroquine concentration data were available and were successfully characterized by a 1-compartment model with linear elimination associated to an additive error model. Of the covariables tested, concentration of parasitized erythrocytes significantly influenced volume of distribution. The volume of distribution was lower when the concentration of parasitized erythrocytes was higher. Our results demonstrate that the PK of chloroquine in this model is highly dependent on the concentration of P. falciparum in peripheral blood, suggesting that this fact should be taken into account to understand and model the PK behavior of chloroquine.

6098

WHOLE GENOME SEQUENCE ANALYSIS OF CANDIDATE GENES IDENTIFIED THREE LOCI POTENTIALLY RELATED TO MEFLOQUINE NEUROPSYCHIATRIC SIDE EFFECTS

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Despite effective once-weekly antimalarial prophylaxis, mefloquine has fallen out of favor due to neuropsychiatric effects. While genetic susceptibilities have been identified, pharmacogenomic testing guidance is not currently available for mefloquine. Volunteers with a history of exposure to mefloquine with or without adverse neuropsychiatric symptoms were invited to participate in a cross-sectional case-control study based on medical review of past mefloquine exposures. Pharmacogenomic analysis was performed on previously suspected 7 genes with 15 associated variants including ORM1 (S, F1, F2); MTHFR (A1298C, C677T); MDR1 (C1236T, G2677T, C3435T); PYK2 (rs2883490); HT2A (rs7997012, rs1928040, rs6311, rs6313); ADA (G22A); and ADORA2A (A2A) (T1976C, C2592T). There were 50 participants enrolled into one of four groups: those who had 1) mefloquine exposure and long-term adverse effects (AEs) greater than 6 months (n = 23); 2) exposure with subsequent AEs less than 6 months (n = 12); 3) exposure and no AEs (n = 8); and 4) a control group with a history of post-traumatic stress disorder (PTSD) but no mefloquine exposure or

traumatic brain injury (n = 7). Among volunteers exposed to mefloquine, the rs141942830 ADORA2A variant was potentially over-expressed among volunteers who had either long-term or short-term AEs compared to those who did not. Two additional variants were under- or over-represented relative to the comparable gnomAD population frequency, suggesting differences from reference controls. MTFHR was enriched for variation for volunteers who had long-term side effects compared to those with short-term or no side effects. A pharmacogenomics approach may help develop a mechanism to integrate test data and clinical findings to guide safer mefloquine use. These non-silent variants may serve as mediators to alternate pathways for signal transduction or drug metabolism, which may be future routes of research.

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OPTIMAL DOSING OF SINGLE LOW DOSE PRIMAQUINE FOR TRANSMISSION BLOCKING OF P. FALCIPARUM IN CHILDREN.

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Single low dose primaquine (SLDPQ) to block the transmission of artemisinin-resistant Plasmodium falciparum and curtail its spread was first recommended in 2012 but insufficient data at that time precluded the WHO from suggesting age- and weight based dosing tables. Dosing in young children is challenging because limited if any suitable paediatric forms are available at the right tablet strength and a lack of pharmacokinetic data mean that approximation methods used for children, notably, allometric scaling are used to derive regimens. However, such regimens may not be optimal and require tablet fractions. Our group is developing child-friendly paediatric primaquine, in the form of flavoured uncoated tablets of 2.5, 3.75, 5, 7.5 & 15 mg, for optimal dosing regimens for transmission blocking and radical cure. Pharmacokinetic data from age dosed SLDPQ were analysed and models developed to predict primaquine maximum concentrations and exposures as surrogates of the bioactive oxidative metabolites that are gametocytocidal and haemolytic in G6PD deficiency. Analysis is ongoing and we will present optimal weight-based SLDPQ regimens for stand-alone use and adapted to the different dosing bands of the artemisinin based combination therapies in common use.

6100

ASSESSMENT OF PLASMODIUM VIVAX BURDEN IN A MALARIA PRE-ELIMINATION CONTEXT AMONG HARD-TO-REACH POPULATIONS: P. VIVAX SEROLOGY AND PCR AMONG CLANDESTINE GOLD-MINERS IN THE GUIANA SHIELD (2015-2019)

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In a context of malaria pre-elimination in Suriname and French Guiana, residual transmission persists among hard-to-reach and mobile populations such as illegal gold miners. Plasmodium falciparum has been adressed by specific strategies but P. vivax (Pv) is particularly challenging, due to high proportion of asymptomatic carriers and low access to radical treatment leading to relapse. Our work aims to estimate the burden of Pv in the gold miner population in this region and its evolution between 2015 and 2019. Data derived from two cross-sectional surveys, conducted in 2015 and 2019 at the border between Suriname and French Guiana. Illegal gold miners having returned for less than 7 days from a gold mining site located in French Guiana were enrolled (questionnaire and collection of a venous blood sample). Samples were analyzed by qualitative polymerase chain reaction (PCR) according to the Snounou method. A serology specfic for Pv (described by Longley et al. In 2020) was used to identify individuals who had probably presented with Pv infection during the last 9 months. A total of 411 individuals were included in 2015, 378 in 2019. Among them, 36 (8.7%) had PCR detected Pv parasitemia in 2015 and 15 (3.9%) in 2019. For serology, a threshold corresponding to 63% sensitivity and 90% specificity was identified as the most appropriate for the study population: under these conditions, 45% of the participants in 2015 and 28% in 2019 had probably had a recent acute Pv infection, and were therefore potentially carriers of hypnozoites. In total, 40 (13.9%) of the 288 seropositive individuals had a positive PvPCR. Among the 51 positive PvPCR, 78% were Pv seropositive. In a context of low malaria prevalence, the proportion of individuals with serological markers of recent exposure to Pv remains significant. This species represents a major challenge for malaria elimination, and must targeted by tailored interventions. Moreover, these biological methods could be used as evaluation methods for new strategies for Pv elimination.

6101

IMPLEMENTATION OF MALARIA COMMUNITY CASE MANAGEMENT (MCCM) IN TANZANIA: SUCCESSES, CHALLENGES, AND WAY FORWARD

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The World Health Organization recommends community case management of malaria to improve access to prompt, effective testing and treatment by trained community members living in proximity to patients. In Tanzania, many rural areas with high malaria endemicity are difficult-to-reach with malaria health services; however, Tanzania's new 2021 policy restricts community-based malaria testing and treatment only to licensed medical personnel called Community-Owned Resource Persons (CORPS), not Community Health Workers (CHWs). To evaluate the implications of this policy, the National Malaria Control Program conducted a pilot of malaria community case management (mCCM) between June and December 2022 in 311 villages across 10 councils with high malaria burden and low access to health services. One CORPS per village was recruited; following placement, CORPS conducted malaria rapid diagnostic testing (mRDT) for patients with suspected malaria and provided treatment for uncomplicated malaria following national guidelines. Cases exhibiting severe malaria were referred to the nearest health facility. During the pilot, 35,409 patients sought health services from the CORPS. Of these, 33,030 (93.3%) were tested by mRDT, and 10,631 (32.2%) were positive. Initially, only 104 CORPS could be recruited because of the licensing requirement, and only 77 (74.0%) of these CORPS were retained during the pilot, serving only 24.8% of the 311 villages. The most cited reason for leaving CORPS duties was other employment opportunities. Of the 77 CORPS, 23 (29.9%) were not residents of their assigned village, and among these 8 (34.8%) faced poor acceptability from the community. Meanwhile, there were 434 CHWs who also resided in the 311 villages. Studies in Tanzania have shown CHWs are widely accepted within their communities. Coverage of malaria diagnosis and treatment achieved by relying on CORPS was lower than expected. Further evaluation might identify successes in the provision of services and reasons for limited coverage and attrition of CORPS to help expand access to community case management.

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LESSONS LEARNED FROM MADAGASCAR NATIONAL MALARIA PROGRAM PERFORMANCE REVIEW 2022

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To reduce the malaria burden in Madagascar and accelerate to elimination, the National Malaria Program (NMP) in collaboration with partners have implemented several interventions including free distribution of insecticide-treated bed nets (ITNs), targeted indoor residual spraying (IRS), prompt diagnosis and treatment, malaria surveillance, monitoring and evaluation (SME) between 2018 and 2022. The NMP and technical partners carried out a desk and document review of annual reports, specific study reports, from 2018-2022 to document progress and inform the development of the national strategic plan 2023-2027. Regarding reporting system performance, the completeness of reporting increased from 94.4% in 2018 to 97.9% in 2022, while timeliness of reporting increased from 46.7% (2018) to 90.4% (2022). The use of artemisinin combination therapies for treatment of confirmed malaria cases increased from 81% in 2018 to 96.6% in 2022, although this remained under the national target of 100%. The coverage (%) of three courses of Intermittent preventive treatment in pregnancy increased from 32.96% (190397/577582) in 2018 to 42.5% (302803/711426) in 2022, although below the national target of 60%. Overall, malaria incidence per 1,000 persons increased from 36.7 in 2018 to 81.9 in 2021, then decreased to 63.8 in 2022. Three regions (Atsimo Atsinanana, Anosy and Atsimo Andrefana) accounted for 60% of the malaria cases. The objective of reducing malaria morbidity by 30% by 2022 was not achieved; however, incidence decreased by 29% between 2021 and 2022. Regarding malaria mortality, a reduction of 69% was reported between 2018 (927 deaths) and 2022 (287 deaths). This review was useful to document progress toward the NMCP's objectives over the past five years. It also identified the main challenges to consider in the national strategic plan 2023-2027, which emphasize on subnational actions on hotspots and strategies to accelerate malaria elimination in Madagascar.

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GENERATION OF PLASMODIUM-RESISTANT ANOPHELES GAMBIAE

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The vector-born parasite Plasmodium falciparum is the major etiological agent of human Malaria, causing more than 200 million clinical diseases per year and accountable for the majority of the deaths (~0.6 million per year globally). Vector control strategies like insecticide-treated nets (ITNs) or indoor residual spraying (IRS), have been the only effective approach leading to lasting malaria eradication. The reduction in efficacy of insecticides and parasite drug-resistance call for new tools to be developed to stop the transmission of the parasite. Advances in mosquito gene drive technologies has opened the door to develop the new approaches for malaria control. Our current strategies involve CRISPR-Cas9 mediated knockout (KO) of mosquito host factors that facilitate the parasite and transgenesis-based overexpression, or CRISPR-Cas9 mediated knock-in (KI), of effector molecules targeting malaria parasites at essential Plasmodium life cycle stages. One challenge with targeting the early parasite stages in the mosquito blood bolus using transgenic technology is the expression of effectors that can reach those parasites immediately upon ingestion of infected blood. Towards this goal, we are exploring the expression of early parasite stage -targeting effectors in the saliva that can be ingested, and blended, with the gametocyte-containing blood in the mosquito midgut. Here we discuss this approach along with other transgenic parasite-blocking approaches that show prominent reduction in prevalence and ookinetes number after an infectious blood meal.

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ENTOMOLOGICAL MONITORING IN ZANZIBAR TO SUPPORT MALARIA ELIMINATION EFFORTS

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Zanzibar is in the malaria pre-elimination phase with multiple ongoing vector control interventions, including the distribution of insecticide-treated nets (ITNs) and indoor residual spraying (IRS). The Zanzibar Malaria Elimination Program has 10 sentinel sites (6 in Unguja and 4 in Pemba) established for entomological monitoring of the malaria vector population and bionomics to track the impact and for timely adjustment of vector control strategies. Between October 2021 to September 2022, adult Anopheles mosquitoes were collected during two consecutive nights per month from each sentinel site. Methods for collecting mosquitoes included indoor and outdoor human landing catch, indoor CDC light-trap, pyrethrum spray catch, and pit trap. A total of 3,206 female Anopheles mosquitoes were collected (1,628 from Unguja and 1,578 from Pemba), with an average of 94% composed of Anopheles gambiae sensu lato, and the remaining a mixture of An. funestus s.l, An. coustani, and An. rufipes. Of the 2,813 successfully amplified specimens of An. gambiae s.l., 2,714 were An. arabiensis, dominating on average 96% of species across the two Islands, with An. merus and An. gambiae sensu stricto contributing the remaining proportion. An. arabiensis exhibited early peak biting time before typical sleeping hours (before 9:00 PM), and predominantly outdoor feeding. These feeding behaviors were generally consistent across sentinel sites. An. arabiensis is the predominant malaria vector in Zanzibar, and its early and predominantly outdoor biting behaviors may be attenuating the impact of personal protection provided by ITNs and IRS. This calls for complementary vector control strategies coupled with social behavioral change to address the risk of outdoor malaria transmission.

6105

USING EVIDENCE-BASED RESEARCH TO IMPROVE TIMELY DETECTION, DIAGNOSIS, AND TREATMENT OF MALARIA IN GUATEMALA'S PUSH FOR ELIMINATION

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Since 2012, reported malaria cases in Guatemala have fallen by nearly 70%, totaling fewer than 1,900 in 2022. In a 2021 surveillance assessment, the National Malaria Control Program (NMCP) estimated that only 44% of cases began treatment within the WHO-recommended 72 hours of symptom onset. To address this gap, the NMCP sought to describe the barriers and facilitators that cases experience in successfully starting treatment within three days of symptom onset. We conducted a mixed-methods study in 2022 in Alta Verapaz, Escuintla, and Izabal - Guatemala's

three most endemic regions comprising 89% of cases nationwide. We administered a cross-sectional survey to 160 randomly selected cases from the NMCP's 2021 database. We also conducted 60 semi-structured interviews with key stakeholders, including cases, vector control technicians (VCTs), and community health workers (CHWs). Our survey results showed that 41% of cases self-medicated with analgesics, antimalarials, or other medications prior to seeking care. Those who self-medicated were 37% less likely to initiate treatment within 72 hours compared to those who did not ($p < 0.02$). We also found that CHWs conducted just 9% of tests but captured 57% of all cases. However, cases captured by CHWs experienced more extreme delays in starting treatment compared to those captured by VCTs (median: 1 vs. 2 days; range: 0-42 vs. 0-16 days). Self-reported treatment completion was high (98%) and most cases (87%) received direct observed therapy (DOT) for the entire 14-day treatment scheme. In interviews, VCTs reported challenges with DOT and CHW supervision due to funding gaps for vehicles and fuel, while CHWs reported frequent stock outs of rapid tests. Cases reported that feeling too ill to leave home was their primary barrier to seeking care. Some did not associate their symptoms with malaria. Others delayed care seeking due to a fear of being tested or vaccinated for COVID-19. As Guatemala pushes towards their 2025 malaria elimination goal, there is an opportunity to use evidence-based research to plan targeted education campaigns, improve commodity access, and strengthen CHW supervision.

6106

CLUSTERING OF ASYMPTOMATIC MALARIA INFECTIONS IN NEIGHBORING HOUSEHOLDS: REACTIVE CASE DETECTION REVIEW AND META-ANALYSIS FROM 2010 TO 2022

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Progress toward malaria elimination is increasing as many countries near zero indigenous malaria cases. In elimination settings, interventions will be most effective at interrupting transmission when targeted at the residual foci of transmission. These foci may be missed due to asymptomatic infections. To solve this problem, the World Health Organization recommends reactive case detection (RACD) triggered in response to index cases. The rationale of RACD is that local transmission potential is higher around index case households, leading to infection clustering. To test this hypothesis, pooled data from different RACD studies were utilized to determine the average risk of malaria among index case households and neighbors. Published studies between January 2010 - September 2022 were identified through PubMed and Google Scholar. Search terms included malaria and RACD, contact tracing, focal screening, case investigation, focal screen and treat. MedCalc Software was used for data analyses and the pooled studies' findings were analyzed using a fixed effect model. Summary outcomes were presented as forest plots and tables based on 54 studies reviewed. Of these studies, 7 met the eligibility criteria based on the risk of malaria in individuals living with an index case < 5 years old, 13 met the eligibility criteria based on the risk of malaria in an index case household member compared with a neighbor of an index case, and 29 met the eligibility criteria based on the risk of malaria in individuals living with index cases and were included in the meta-analysis. Individuals living in index case households with average risk (odds ratio 2.58; 95% CI 2.54 - 2.61) were more at risk of malaria infection and showed pooled results of high variation heterogeneity chi-square = 235.60, ($p < 0.0001$) $I2 = 98.88$ [97.87-99.89]. The pooled results showed that neighbors of index cases were 0.35 [0.30-0.41] times more likely to have a malaria infection relative to index case household members and this result was significant ($p < 0.001$). Evidence to support infection clustering in neighborhoods that necessitates the inclusion of neighboring households in RACD was presented.

6107

ACCESS TO MALARIA DIAGNOSIS AND TREATMENT IN ZAMBIA IN THE CONTEXT OF SCALING-UP COMMUNITY CASE MANAGEMENT

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The National Malaria Elimination Centre (NMEC) launched a pilot of community case management (CCM) for malaria in Southern Province, Zambia in 2009, and CCM was later scaled-up in an incremental fashion at national level between 2013-2020. The goal of this study was to: 1) examine the impact of CCM on treatment seeking behaviors among individuals of all ages with a febrile illness; and 2) assess the proportion of children less than five years old with malaria (defined as a positive rapid diagnostic test plus fever in the past two weeks) that received the first line malaria treatment artemether-lumefantrine (AL). We analyzed changes in these outcomes and their determinants over time using data from the Zambia Malaria Indicator Surveys (2012, 2015, 2018, and 2021) combined with distance to the nearest malaria provider at the time of survey from data on volunteer community health worker (CHW) expansion, as well as travel time from a friction surface from the Malaria Atlas Project. While results showed there was no significant increase in treatment seeking from 2012 to 2021 (overall seeking rate: 57.1% [52.7%, 61.0%]), time from fever onset to treatment seeking decreased significantly from 2.42 days [2.27 - 2.58] in 2012 to 1.71 days [1.56 - 1.86] in 2021. Children <5 with a fever in the previous two weeks were significantly more likely to have been taken for treatment compared to older age groups (ORs: 1.26 [1.12 - 1.42] for 5-19 years old and 1.48 [1.32 - 1.66] for 20 years and older). Respondents with a fever in the past two weeks who had access to a malaria provider (either CHW or health facility) within a 30-minute walking distance were significantly more likely to seek treatment compared to those further away (OR = 1.47 [1.29 - 1.67]). Across all survey rounds, among children with malaria and fever, 58.6% [51.2% – 65.5%] did not receive AL. Among children who had malaria and fever, those within a 30-minute walking distance to a malaria provider were significantly more likely to receive AL compared to those further away (OR = 1.59 [1.03 – 2.44]). While CCM in Zambia has been successfully scaled-up, gaps remain in malaria treatment access, especially in remote areas.

6108

HALT THE MARCHING OF ANOPHELES STEPHENSI IN AFRICA: FOLLOW INDIA'S INTERVENTION STRATEGIES

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Anopheles stephensi was reported from village Ellichpur (now Achalpur), Amravati district, Maharashtra, India. South Asia and the Arabian Peninsula is the home of this malaria vector. Now this species has been detected in Djibouti (2012), Ethiopia (2016), Sudan (2016), Sri Lanka (2017), Somalia (2019), and most recently in Nigeria (2020), Yemen (2021) and Ghana (2023). A recent modelling study using marine cargo traffic indicates that it may invade in more than half of the African countries. Since 2019 World Health Organization (WHO) to ASTMH 71st Annual Meeting at Seattle in 2022, and recently RMB Vector Control Working Group in Accra, Ghana

(6 to 8 February 2023) and WHO Regional Response meeting in Addis Ababa, Ethiopia (8 to 10 March 2023) have echoed the threat of perineal malaria transmission especially in urban settings. This species has three variants i.e. Type, Intermediate and mysorensis. They behave differently in terms of vector competence, bionomics and response to insecticides. Genomic studies and molecular diagnosis of these variants are possible developing isofemale homogenized lines. It is important to carry out detailed site-specific studies to plan strategic intervention strategies. Our study in Mangalore city, India revealed case-centric vector control response using smart digital surveillance devices brought down malaria at the lowest level leading to malaria elimination. Similar strategies would find a solution to prevent marching of Anopheles stephensi in Africa involving Indian scientists.

6109

REBOUND IN THE PLASMODIUM FALCIPARUM RESERVOIR FOLLOWING THE DISCONTINUATION OF INDOOR RESIDUAL SPRAYING AND IMPLEMENTATION OF SEASONAL MALARIA CHEMOPREVENTION IN NORTHERN GHANA

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It is now understood that the large reservoir of asymptomatic Plasmodium falciparum infections in all ages sustains malaria transmission in sub-Saharan Africa. If we are to achieve malaria elimination, the impact of current interventions to reduce this reservoir must be investigated. Here we present one of few contemporary studies to assess the efficacy of short-term indoor residual spraying (IRS) with non-pyrethroid insecticides and seasonal malaria chemoprevention (SMC) to reduce the reservoir of infection in all ages. Using data collected from an interrupted time series study in northern Ghana (2012-2020), involving four surveys each of ~2,000 participants, we examined the impact of two sequential interventions, IRS and SMC in combination with long-lasting insecticide-treated nets (LLINs), on the P. falciparum reservoir. We showed that the addition of IRS to LLINs reduced the size of the P. falciparum reservoir as measured using PCR, with participants of all ages being significantly less likely to be infected post-IRS in 2015 (41.6%) compared to baseline in 2012 (73.8%). Despite this reduction, in 2017, 32-months after IRS was discontinued, there was a rebound in prevalence to 64.2%. This rebound in the size of the P. falciparum reservoir was found in all age groups, except for the younger children (1-5 years) directly targeted by SMC. In 2020, over five years after IRS was stopped, but during the continued implementation of SMC and LLINs, P. falciparum prevalence remained high (50.0%) with younger children still being significantly less likely to have an infection compared to the older age groups. This rebound was also associated with higher median P. falciparum densities in 2017 and 2020, suggesting a loss of immunity in all ages due to reduced exposure to infection during the IRS. Molecular surveillance data will also be discussed. These results show that if high-burden countries, like Ghana, are to achieve a 90% reduction in the burden of malaria by 2030, they must develop strategies that can both reduce clinical disease and target the P. falciparum reservoir.

6110

"DON'T WAIT FOR SYMPTOMS!": INCREASING ROUTINE MALARIA TESTING AMONG FOREST-GOERS IN CAMBODIA

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Malaria transmission in Cambodia is highly localized among forest-goer populations. The Cambodia National Malaria Treatment Guideline includes systematic diagnostic testing for forest-goers exiting forests. Formative research indicated that adoption of routine malaria testing may be influenced by social norms and social support from family members to test. An SBC intervention was designed with communities to increase perceived social norms and social support among forest-goers for malaria testing after leaving the forest. Activities were implemented through various channels in 50 high-risk villages in three provinces under the slogan "Don't Wait for Symptoms!". Interpersonal communication was delivered by Village Malaria Worker (VMW) visits to forest-goer households to increase the positive social norm of testing and increase malaria risk perception. Additional behavioral nudges (banners, posters, audio messages) were delivered via placement close to forest exits and within forest-goer communities. Cross-sectoral surveys were conducted with random samples of forest-goers (n=360) from 50 villages before (May 2022) and after (December 2022) implementation to evaluate differences in perceived social norms and self-reported testing behaviors. No control group was interviewed, but routine data were compared with reports from non-intervention villages over the same period. Routine data recorded 12,338 VMW-performed community-wide tests of forest-goers upon returning from forest work during the intervention period, increasing 76% compared to the same period the previous year. VMWs in villages in the same catchment areas but not covered by the intervention recorded a 26% increase in testing. Survey data showed the percentage of forest-goers who believe other forest-goers consistently seek a malaria test when leaving the forest increased from 67% to 96% ($p<0.001$); self-reported malaria testing increased from 27% to 90% ($p<0.001$). Key messages reinforcing the social norm of malaria testing should continue, and explicit emphasis should be added on improving social support for forest-goer testing among family members.

6111

AN ONLINE SURVEY OF MALARIA ON MOBILE AND MIGRANT POPULATION AMONG INDONESIAN MALARIA MANAGERS: MINERS

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Miners are one of the malaria high-risk populations since they do outdoors activities and have poor access to health facilities. We conducted online survey from February to September 2022, with 514 district health managers as our participant, to determine their understanding of malaria problem in miners. The survey, which was developed in SurveyMonkey, inquired about the presence of miners with malaria issues, including but not limited to population size, distribution, malaria detection and diagnosis, vector control, obstacles, and future control programs. From the responses gathered, 114 (22.1%) districts reported having mining sites, with 29 (25.4%) of those experiencing malaria problems among the workers. Workers who contracted malaria received treatment from nearby primary healthcare and were mostly diagnosed using RDT. The types of mining minerals that had malaria problem at the sites were gold, coal, nickel, and tin. The distance to the sites varied, but they typically had to travel on rocky, damaged, and muddy roads to reach the sites. Majority of the districts also have influx of workers from other districts who could stay for more than three months at the sites. However, their departure and arrival times was unknown due to the uncertainty of mining projects in the area. More

than half of the districts had implemented interventions to control malaria with the most common being distributing long-lasting insecticidal nets (LLINs), health promotion, and vector control with larvaciding. LLINs were reported as the most effective intervention. Poor access to the sites and lack of funding were among many reasons that hampered malaria control efforts in miners. District health managers planned to build a cross-sectoral collaboration, train cadres, and conduct more migration surveillance in the future. This study provides insights into the level of perception, knowledge, malaria control strategy and efforts among the miners. The study findings will support in reformulating strategies to address potential obstacle and contribute to the National Plan to Eliminate Malaria in 2030.

6112

SAVING LIVES FOR CHILDREN UNDER FIVE YEARS THROUGH STRENGTHENING COMMUNITY TO HEALTH FACILITY LINKAGE; A CASE OF ICCM IMPLEMENTATION IN NORTHERN UGANDA

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Malaria Consortium is supporting 11 districts in Northern Uganda to improve community to health facility Linkage since September 2021. Several interventions have been undertaken and these include, among others, orientation of Village Health Teams (VHTs) Supervisors and VHTs on the new revised ICCM guidelines to manage HIV,AIDS,TB,Malaria,D iarrhorea,Pneumonia in the community and supporting quarterly VHTs coordination meetings with Health Facility health workers. Implementation is district led approach where District Health Teams (DHTs) are supported and facilitated to implement. Ministry of Health and TASO give technical support to ensure implementation according to the standard guidelines and policies. Community Data from District Health Information System 2 (DHIS 2) was downloaded and computations for selected ICCM indicators were done. Community reporting increased from 60.4% in September 2021 to 88.0% by the end of December 2022; the number of children under 11 months reportedly dying in the community decreased by 58.5%, from 270 to 112 children; the percentage of children with fever and danger signs reduced from 2.9% to 2.1%; the number of children under five years seen by the VHTs in the community every quarter increased from 120,281 to 350,890; the number average number of children seen by a VHT in a quarter increased from 11 to 33 children; the percentage of children with malaria treated within 24 hours increased from 59% when we started to 89% by the end of 2021. There have been challenges in stocks availability that have led to continuous low malaria testing rates (consistently below 80%) and significant referrals from the community, consistently at 15% - 16%, as reported previously. The results show that lives have been saved through interventions to strengthen health facility to community linkage in Northern Uganda. Demand and access to health services for children under five years from VHTs increased significantly during implementation. Gaps in stocks availability should be addressed to ensure access to quality services by the unreached vulnerable groups.

6113

CLINICAL PLASMODIUM FALCIPARUM DURING THE DRY SEASON IN AN ENDEMIC AREA OF MALI, TORODO.

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Plasmodium falciparum (Pf) clinical malaria is rare during the dry season in endemic countries, were the transmission mediating mosquitoes (Anopheles) are not prevalent at that time. Regarding all the effort made during transmission season and slow moving of the disease control and elimination program, additional strategies need to be explored to contribute to the existing one. Indeed, we addressed the following research question within one of our cohort studies: Can, Pf asymptomatic infected or non-infected individuals at the beginning of the dry season develop the disease at that period? Thus, from our cohort study of 250 participants (2 to 16 years old) in Torodo, 74 individuals (~29%) out of the 250 participants, were infected at the baseline (February 2022). Female represented ~44% of the positive group and the age group 7-11 years were more infected (13,2%). Looking at to the hemoglobin levels (which is one of the major indicators of Plasmodium falciparum acute or asymptomatic infection), it was higher in the negative group with a means around 11.5g/dl compared to the positive group (around 10.5). To track Pf clinical malaria during dry season we followed both group (Pf asymptomatic infected and non-infected groups) actively and/or passively from February to May 2022. During the follow-up, we observed 20 cases of Pf clinical malaria after PCR correction and 17 and 3 cases were respectively in the infected and non-infected groups from the baseline. These finding highlights that carrying asymptomatic Pf infection at the beginning of dry season can favor Plasmodium falciparum clinical malaria through all the dry season period, but also some new cases can happen in non-carriers, suggesting that an effort need to be addressed regarding malaria control and elimination program during that period.

6114

NEW SURVEILLANCE STRATEGIES FOCUSED ON ELIMINATION IN SOUTHERN ANGOLA

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Malaria incidence in southern border districts of Angola has seen a steady decline over the past years. This decrease in malaria cases is the result of joint efforts to reduce transmission and contribute to malaria elimination in neighbouring Namibia. As transmission declines, new surveillance approaches are required to tackle focal transmission. The objective of this study is to report the implementation of new surveillance strategies focused on elimination in southern Angola and to characterize transmission in line with case classification made. The implementation of case classification strategies started in November 2022 across 5 health facilities of Cunene and Cuando Cubango provinces. These health facilities have been shortlisted because they registered 5 or less cases per month on average over the past 3 years. Case classification was done for RDT/MO confirmed malaria cases using a structured questionnaire applied at health facility level focused on travel patterns and use of malaria preventive measures. Overall, 100% of the positive cases were classified (26). Of these, all were local, particularly 21 (81%) were considered as local L1 (own house) and the remaining L4 (out of usual accommodation but in the same province). Local cases had the following characteristics: 10 (38%) less than 15 years old, 16 (62%) more than 15 years old, 9 (35%) were females. It is likely to identify 12 foci of transmission based on the local guidelines that point out a focus of transmission to be the presence of more than 1 local case within a month. The data presented, the first of its kind in Angola, showcases the high proportion of local cases in areas targeted. Foci investigation, classification and response are key to tackle local transmission and gradually eliminate these scattered points of local transmission in the south.

6115

MATHEMATICALLY MODELLING THE IMPACT OF CASE MANAGEMENT AT BORDER AREAS ON MALARIA TRANSMISSION IN THE MOZAMBIQUE, SOUTH AFRICA AND ESWATINI REGION

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Eswatini and South Africa are in the path of malaria elimination but however, they share borders with Mozambique who has a high incident rate of malaria. Studies conducted show that most of the malaria cases recorded in both South Africa and Eswatini are imported cases from Mozambique. For these countries to attain their goal of malaria elimination, they need

to prioritise case management at border areas as their main strategy of malaria elimination. Will the use of rapid antigen tests at the border gate areas accelerate the elimination of malaria in the MOSASWA region? What impact will border management have on the malaria transmission in these countries? A Nonlinear stochastic ordinary differential equation model is used to simulate the impact of case management at border areas on malaria transmission in the MOSASWA region which consists of eastern Eswatini, the southern Mozambican provinces of Maputo, Gaza and Inhambane, and the north-eastern districts of the South African provinces of KwaZulu-Natal, Mpumalanga, and Limpopo. The results show us that malaria transmission can be reduced significantly if rapid antigen tests are conducted at the borders in the MOSASWA region. The results show us that malaria cannot be eliminated by this intervention but can reduce the malaria burden significantly in Eswatini and South Africa endemic regions. Border control is a vital strategy for malaria elimination in South Africa and Eswatini. However, malaria cannot be eliminated and hence this intervention combined with other interventions can contribute towards malaria elimination in the region.

6116

THE UGANDA HOUSING MODIFICATION STUDY - ASSOCIATION BETWEEN HOUSING CHARACTERISTICS AND MALARIA BURDEN IN A MODERATE TO HIGH TRANSMISSION SETTING IN UGANDA

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Scale up of proven malaria control interventions has not been sufficient to control malaria in Uganda emphasizing the need to explore innovative approaches. Improved housing is one such promising strategy. We describe the housing characteristics and their association with malaria burden in a moderate to high transmission setting in Uganda. In October-November 2021, a household survey was conducted in 1500 randomly selected households in Jinja and Luuka districts. Information on demographics, housing characteristics, use of malaria prevention measures, and proxy indicators of wealth were collected for each household. A finger-prick blood sample was obtained for thick blood smears from all children aged 6 months to 14 years in surveyed households. Febrile children were tested for malaria by rapid diagnostics test (RDT) and positive cases were managed per national guidelines. Hemoglobin (Hb) concentration was assessed in children aged 2-4 years, with anemia defined as Hb < 8 g/dL. Mixed effect models adjusted for age and wealth were used to estimate association between malaria burden and house type. Forty-four percent of households lived in modern houses (defined as built with finished roofs/walls/floors materials combined with closed eaves); the rest lived in traditional houses built with unfinished/natural materials. While most houses had closed eaves (85.5%), the use of other protective features like window and vent screens and having ceilings installed was limited (0.4%, 2.8%, and 5.2%, respectively). Malaria prevalence was 31.4% in 3443 children with smears collected. RDT test positivity rate was 56.6% among 1851 children with fever. Participants living in modern houses had a significantly lower parasite prevalence (adjusted prevalence ratio [aPR]=0.80; 95% confidence interval [95%CI] 0.71-0.90) and RDT test positivity rate (aPR=0.90; 95%CI 0.81-0.99) compared to those in traditional houses, with no significant impact on anemia. Our study found that even after adjusting for wealth, higher quality housing had a moderate protective effect against malaria, on top of the protection already afforded by recently distributed nets.

6117

IMPACTS OF ARMED CONFLICT FOR MALARIA PREVENTION AND ELIMINATION PROGRAMS IN ETHIOPIA: A TIME-SERIES ANALYSIS

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Ethiopia has experienced several conflicts during the last several years that have negatively impacted its health systems. This study aims to assess the impact of the conflicts in Northern Ethiopia on malaria prevention and elimination efforts, as well as the malaria surveillance system. We used routine district health information system data to quantify the changes in the levels of malaria prevention and control services from 2019 to 2021. We used interrupted time-series analysis and descriptive statistics to estimate the changes in intervention levels within the conflict-affected and surrounding districts. The routine malaria surveillance data showed that the reported national malaria cases increased by 20% from 2019 to 2021. Disruptions were found to vary across zones and districts with clear patterns by the intensity and duration of the conflict. There was a significant difference in test and incidence rates between affected areas and surrounding affected/not affected areas. In conclusion, While data limitations made it difficult to describe the level of disruptions to malaria prevention and elimination measures during the conflict (particularly in conflict-affected areas), these findings highlight a strong variation in the malaria incidence between conflict-affected and unaffected areas. Our study highlights the importance of peace and stability and preserving a functioning health system to sustain Ethiopia's progress toward malaria elimination targets.

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SURVEILLANCE OF PLASMODIUM MALARIAE INFECTION AMONG INHABITANTS AND ANOPHELES' MOSQUITOES IN RURAL AREAS OF SOUTHERN BENIN

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Among the Plasmodium species that infect humans, P. falciparum has been widely studied in malaria-endemic areas. However, P. malariae infection is less documented among the human population and mosquitoes. This study aimed to investigate the prevalence and distribution of P. malariae in southern Benin. A cross-sectional survey was conducted in Ouidah and Kpomasse from June to October 2019. At the time of blood collection from the participants and at the same time, mosquitoes were collected from the participants' households. Data on malaria infection were obtained by microscopic diagnosis and nested PCR in participants. In addition, the collected mosquitoes were identified morphologically and molecularly, and the infection status of Plasmodium species was investigated by qPCR. Considering the participants, according to microscopy, the prevalence of P. malariae mono-infection and P. falciparum/P. malariae co-infection was

2.3% and 1.2% respectively in our study area. This prevalence was higher ($P < 0.01$) than that reported ten years ago in the same study area with 0.7% and 0.3% of P. malariae and P. falciparum/P. malariae, respectively. Based on PCR analysis, the prevalence of P. malariae was 14.1%, of which 5.2% were mono-infected and 8.9% mixed with P. falciparum. Regarding the mosquito data, of the 415 mosquitoes collected, three species of Anopheles were identified with a predominance of An. gambiae s.l. (61%). Molecular speciation of this species revealed that An. coluzzii was the majority species 59.2% and 98.5% in Ouidah and Kpomassè respectively. The infection rate of Plasmodium spp. in An. gambiae s.l. revealed that 4.4% were infected with a predominance of P. falciparum (75%), followed by P. malariae (25%), and only An. coluzzii mosquitoes were infected. These results provide valuable evidence of the increasing prevalence of P. malariae infection and that An. coluzzii is the mosquito responsible for the spread of this parasite. This highlights the need for national malaria control programs to take P. malariae into account when designing future measures for effective malaria control and treatment.

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EVALUATING THE EFFECTIVENESS OF TRIMETHOPRIM-SULFAMETHOXAZOLE PROPHYLAXIS IN PREVENTING MALARIA IN PREGNANCY

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In sub-Saharan Africa, malaria in pregnancy remains a critical health concern for mothers and their babies. The WHO recommends sulfadoxine-pyrimethamine (SP) for the prevention of malaria during pregnancy. However, pregnant women living with HIV infection receive daily trimethoprim-sulfamethoxazole (TS) prophylaxis and therefore cannot safely also take SP. Previous studies have produced conflicting evidence as to whether TS prophylaxis adequately prevents malaria during pregnancy in women with HIV infection. We had the opportunity to evaluate the effectiveness of intermittent preventative treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP) in pregnant women without HIV infection compared to daily TS prophylaxis in pregnant women with HIV infection. We screened pregnant women with and without HIV infection for malaria enrollment in a clinical study and collected placental blood at the time of delivery from a cohort in a semi-rural area at one clinical site in southern Malawi. Dried blood spots from the enrollment visit in the second trimester paired with dried blood spots from the placenta after delivery underwent extraction and qPCR for 18S ribosomal DNA. Among 290 samples from pregnant women with and without HIV, we detected no Plasmodium falciparum infection. Our findings suggest that IPTp-SP and TS prophylaxis are equally effective in preventing placental malaria infection. We are currently testing enrollment samples from this cohort to characterize the burden of malaria infection when pregnant women initiate antenatal care. This will allow us to determine if the interventions prevented placental infection or if malaria transmission in the area was lower than anticipated.

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SPATIOTEMPORAL CORRELATION OF MALARIA INTENSITY AND VECTOR ABUNDANCE IN A PRE-ELIMINATION SETTING OF CHOMA DISTRICT, SOUTHERN ZAMBIA

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Choma District in Southern Province, Zambia, with malaria parasite prevalence by rapid diagnostic test of 2%, has long been targeted for elimination. However, low-level transmission with seasonal outbreaks has persisted, perhaps exacerbated by infectious secondary vectors. Previous geospatial risk maps of the area derived from remotely sensed data found that parasitemic individuals tended to be clustered in areas near streams at lower elevations. In this way, spatiotemporal analysis of low-level parasite prevalence and vector abundance has been critical in informing strategies targeting malaria elimination. This study aimed to produce malaria risk maps by assessing the spatial and temporal correlation of individuals with parasitemia by quantitative polymerase chain reaction (qPCR) and vector breeding sites within rural health center (RHC) catchment areas. Malaria case and entomological data were collected in 2022 and 2023 in Macha, Mapanza, and Simaubi RHCs. Passively-reported index case households and neighboring households within 250 meters of the index case household were surveyed from April 2022 to April 2023. Residents were tested for parasitemia using qPCR from dried blood spots. In October 2022, entomological surveillance began at 38 sentinel households, where each household was visited bimonthly. CDC light traps were set indoors and outdoors at each house and larval breeding sites within 500 meters were sampled. All households and larval breeding sites were geolocated. Intensity maps were created of the households of qPCR-confirmed parasitemic residents and confirmed breeding sites using kernel estimation with optimized bandwidths. Clustering was assessed using the K-function. We further compared the two intensity maps and clustering patterns with each other using the cross-K function. Analysis was done in R and ArcGIS. We will present the results of the malaria intensity mapping, K-functions for clustering, and cross-K function, and expect the results will inform further malaria risk mapping and targeted interventions in this pre-elimination setting.

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PLASMODIUM FALCIPARUM MALARIA IS ASSOCIATED WITH INCREASED KSHV SEROPOSITIVITY AND HIGHER KSHV ANTIBODY BREADTH AND MAGNITUDE: RESULTS OF A CASE-CONTROL STUDY FROM RURAL UGANDA

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We previously showed that children with asymptomatic Plasmodium falciparum (Pf) malaria infection had higher Kaposi sarcoma-associated herpes virus (KSHV) viral load, increased risk of KSHV seropositivity, and higher KSHV antibody levels. In the current study, we investigated the association between clinical malaria and KSHV seropositivity and antibody levels using an expanded immunoassay. Sick children (aged 5-10 years) presenting at a clinic in rural Uganda were enrolled in a case-control study. Pf was detected using malaria RDT and subsequently with qPCR. Children with malaria were categorized into two groups; RDT+/Pf PCR+ and RDT-/Pf PCR+. The seroprevalence of KSHV was 60% (47/78) among children who did not have malaria (RDT-/PfPCR-), 79% (61/77); among children who

were RDT-/PfPCR+ (Odds Ratio [OR] 2.41, 95% CI 1.15-5.02) and 95% (141/149) in children who were RDT+/Pf PCR+ (OR 10.52, 95% CI: 4.17-26.58; P (trend)<0.001). Furthermore, RDT+/PCR+ children followed by RDT-/PCR+ children had higher KSHV antibody levels and reacted to more KSHV antigens compared to malaria-uninfected children. Malaria infection in children is associated with both increased KSHV seroprevalence and antibody magnitude suggesting that malaria is affecting immunity to KSHV.

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TACKLING ASYMPTOMATIC MALARIA INFECTION IN PREGNANCY AS INTERVENTION TO IMPROVE PREGNANCY OUTCOMES IN BURKINA FASO

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Malaria in pregnancy is assumed to be asymptomatic in endemic area. The national malaria control program (NCMP) recommends to treat all malaria cases after confirmation either by microscopy or rapid diagnostic tests (RDT) before treatment. Asymptomatic infections have no clinical manifestation and thus remain undetected and untreated. Even asymptomatic, malaria infections are potentially harmful for both women and their offspring's. We therefore, sought to determine the prevalence of asymptomatic malaria infection among pregnant women at their first antenatal care (ANC) and the risk factors associated. A cross-sectional study was conducted in Nanoro district and all pregnant women attending the first ANC visit were recruited. Blood samples were collected to assess malaria infection using microscopy as gold standard and haemoglobin level using HemoCue®. Among the 418 pregnant women recruited, 318 were asymptomatic. The overall prevalence of asymptomatic malaria infection during first ANC was 25.5% (95% CI: 21.1 - 30.4) with a geometric mean parasite density of (95% CI): 790 (602 - 1036) parasites/µL. From the 86 pregnant women infected with malaria, those at the third trimester gestational age were significantly more prevalent 21.3% (13/61), followed by the second trimester 25.6% (66/258) and the first trimester 38.8% (7/18), P<0001. Younger age was associated with significantly higher odds of asymptomatic malaria compared to elder women. Furthermore, primigravida had 3.09 (95% CI: 1.52 – 6.26; p = 0.002) and secundigravida 3.02 (95% CI: 2.00 – 5.34; p = 0.001) folds higher risk than multigravida women. The mean haemoglobin concentration was 10.56 ± 1.55 g/dL and the prevalence of anemia was 59.1% (95% CI:53.9- 64.7). In multivariate analysis, asymptomatic malaria increased two times the likelihood of having anemia (AOR 2 95% CI:1.1-3.4; p < 0.001). Our findings highlight the importance of integrated strategies such as systematic screening with sensitive rapid diagnostic tests and treatment with effective malaria drugs during the first ANC to clear residual parasitaemia and thus improve pregnancy outcomes.

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INSIGHTS ABOUT MALARIA BURDEN AND CARE IN MALARIA-ENDEMIC, INDIGENOUS COMMUNITIES UNDER THE COVID-19 PANDEMIC USING CONVERGENT-PARALLEL APPROACH

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In Peru, the interruption of the malaria control program due to the COVID-19 pandemic increased the number of cases in urban areas. However, the impact on the burden and care in remote, indigenous areas was unknown. In this mixed-method study, we investigated malaria prevalence using molecular diagnosis and factors associated with malaria infections in indigenous communities in the Peruvian Amazon. Moreover, we explored the population's perceptions of the COVID-19 impact on malaria burden and care. We performed population surveys (2021 and 2022) and semi-structured interviews with inhabitants and local health workers (2022) in four indigenous communities of the Amazonas region. We identified the factors associated with malaria infection through multivariate modeling and assessed the participants' perceptions through a thematic analysis. The convergent parallel approach served to merge the quantitative & qualitative components through a pillar integration process resulting in a joint display. The overall prevalence of malaria varied between 2021 and 2022 (17.6% and 25.5%, n=528 participants). Living in some communities (OR=0.70) and having experienced previous malaria episodes (OR=0.07) reduced the likelihood of malaria infection.On the contrary, experiencing chills (OR=38.4) was associated with higher odds of malaria infection. Inhabitants and health workers pointed out the prioritization of COVID-19 interventions, leaving malaria control activities aside and affecting malaria prevalence. On the other hand, the population's behavior toward malaria prevention did not change during the pandemic. However, the participants highlighted the limited access to healthcare facilities during the pandemic and the absence of health posts in the two communities, which increased the likelihood of experiencing malaria (OR=0.19-0.47). The novel mixed methods approach facilitated the integration of quantitative and qualitative data to explain the malaria situation in indigenous areas better. Our findings provide relevant information to improve the current interventions for malaria control and elimination in Peru.

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TEMPORALITY AND MODALITY OF FIRST HEALTH CARE SEEKING AMONG MALARIA PATIENTS IN THE REPUBLIC OF GUINEA

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The temporality and modalities of seeking care are crucial in the fight against malaria. In Guinea, malaria is a public health problem, with a morbidity of 39.91% in health facilities. The prevalence among children under five of age was 17% in 2021. In addition, there are many opportunities to manage malaria, with conventional and non-conventional offers. The aim is to analyze the temporality and modalities of first health-seeking for malaria patients. This is a partial analysis of data from a cross-sectional study conducted between December 2022 and March 2023 in the health facilities of nine (9) health districts randomly sampled in the eight administrative regions. The data were collected using an Open Data Kit system and analyzed with R software. Early care-seeking was defined within 24 hours and late after 48 hours. The conventional modalities are the public and private health facilities and community health walkers, while the non-conventional are constituted by other offers not recommended by the national policy of malaria management. A total of 3300 confirmed malaria cases, of which 1632 (49.45%) were female, were interviewed in 60 health facilities. 1132 were less than 5 years old (34.30%) with a mean age of 27 months (SD=16). For the group of 5 years and older the mean age was 27 years (SD=18.7). Early care-seeking for all modalities was 53.2%, 95% CI [0.52-0.55]. With 63.60%, 95% CI [0.61-0.66] in the under 5 years and

47.83%, 95% CI [0.46-0.50] in the 5 years and older. The median time to first care-seeking was 24 and 48 hours, respectively. Early and appropriate seeking behavior was different in the age groups (p<0.0001) with 33.66% and 25.88% respectively. The median cost of the first referral varied according to age group, 54000 GNF and 49000 GNF, and referral modality, 110000 GNF for conventional and 6000 GNF for non-conventional. The partial analysis of this cross-sectional study shows proportions of early and appropriate care-seeking in the first intention, below 50%. This result demonstrates the importance of the next steps in this project whose goal is to provide evidence on patterns of malaria management service consumption and determinants.

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ANOPHELES MOSQUITO BITE EXPOSURE TESTING TO ASSESS THE IMPACT OF VECTOR CONTROL INTERVENTIONS IN THE COLOMBIAN PACIFIC REGION

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Previous studies have demonstrated that IgG antibodies against mosquito salivary proteins are a reliable tool to measure arthropod bite exposure and disease risk. In Colombia, Anopheles vectors belong to subgenus Nyssorhynchus (An. albimanus and An. darlingi) and subgenus Anopheles (An. pseudopunctipennis) among others. Thus, we measured IgG antibodies against four peptides designed from immunogenic salivary proteins of An. albimanus (Peroxi-P3 and Transferrin-2), An. darlingi (AnDar-Apy2) and the salivary biomarker gSG6-P1 to determine the degree of exposure to bites from mosquito species from subgroups other than Nyssorhynchus. In the first phase of the study, blood samples were collected from two regions of Cauca Department on the Pacific Coast of Colombia where two different malaria control interventions [insecticide treated bednets (ITNs) and indoor residual spraying (IRS)] are being implemented. To compare exposure to bites with previous exposure to Plasmodium parasites, we also determined the levels of IgG antibodies against Plasmodium vivax (PvCSP and PvMSP1) and P. falciparum (PfCSP and PfMSP1). The second phase of this study is underway, but our preliminary results from phase 1 showed a significant positive correlation between age and Peroxi-P3, Transferrin-2 and gSG6-P1 in people using bed nets. This correlation was not observed in people living in houses treated with insecticide suggesting that the type of mosquito control intervention shapes bite exposure dynamics in the population. So far in both study sites, we have observed a significant positive correlation between all salivary peptides and Plasmodium antigens suggesting an important association between exposure to mosquito bites and immune responses against Plasmodium in this area. Our results highlight the relevance of using antibodies against salivary proteins as an indirect tool to measure efficacy of vector control interventions in malaria endemic areas to support malaria elimination efforts.

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EPIDEMIOLOGIC RISK FACTORS TO URBAN MALARIA IN WESTERN AND COASTAL KENYA

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Most countries in Sub-Saharan Africa are reporting an increase in urban population growth. With Kenya still reporting a high endemicity of malaria in various urban regions, it is not known how urbanization will affect vector populations, disease transmission and control measures. Our prospective cohort study was conducted at two urban towns in Coastal (Ukunda) and Western (Kisumu) Kenya with demographic and risk factor surveys administered every 6 months between December 2019- February 2022. Participants were also interviewed any time they had a fever during the duration of the study. Blood samples were collected during the community survey and febrile (sick) visits for the detection of malaria by microscopy. Only survey responses at enrollment were considered in this preliminary risk factor analysis due to a high attrition rate and non-response during the follow up periods. The overall study prevalence for malaria in our study was 12.8 % (578/4534) with a significantly higher seroprevalence in Kisumu (20.1%,518/2521) than in Ukunda (3.0%, 60/2013) ,(OR=8.42, 95% CI =6.40-11.08;(p<0.01). 63.3 % (366/578) of all confirmed malaria diagnosis were from a febrile (sick) visit, 29.8%(172/578)were detected during the community survey, and 6.9% (40/578) during both the community survey and sick visit. Among the malaria-positive patients, 98.6% (570/578) of them were positive for Plasmodium falciparum, and 1.4 % had mixed infections of P. falciparum and P. malariae. There was an increased likelihood of malaria among children (<16 Years), (OR =1.43,95% CI =1.20-1.70 ; P < 0.01), those who had moved from their primary residence 6 months prior to the administration of the survey (OR =9.5, 95% CI =7.28-12.35 ; P < 0.01),and those with indoor occupations (OR =1.43,95% CI =1.20-1.70 ; P < 0.01).There was a decreased likelihood of malaria among households that had window screens, (OR =0.30, 95% CI = 0.22-0.41 ; P < 0.001).Gender, water collection, and insecticide use were not associated with malaria positivity in our study.Further studies are still needed to understand the epidemiology of malaria in urban settings in Sub-Saharan Africa.

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MAXIMIZING THE USE OF HUMAN POPULATION MOVEMENT DATA FOR MALARIA CONTROL AND ELIMINATION

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Malaria transmission through human population movement (HPM) poses a major obstacle to malaria elimination. We hypothesize that the collection of routine surveillance data on travel patterns of malaria patients in a country nearing malaria elimination could be used to maximize the use of HPM data for malaria elimination. From May 2017 to December 2021 we enrolled 6320 malaria patients from 107 health facilities Lao PDR. We obtained information on demographics, travel patterns, mobile phone use and ownership and collected dried blood spots. 27% were females, 73% males. Median age was 19 years. 58% had Plasmodium vivax, 40% P. falciparum, 1% mixed P. falciparum and P. vivax, 0.02% P. knowlesi and

0.02% P. ovale. The proportion of malaria patients travelling increased from 55% to 85%. Travel to the forest was most common, increasing from 53% to 75%. Attapeu was the most popular destination for inter-province travel (44-100%). During COVID, travel concentrated to Attapeu (from 46% to 60%) and Phouvong (from 26% to 53%), while inter-province and inter-district travel elsewhere decreased. The demographics of forest visitors remained unchanged. Males 25-49 years comprised the largest proportion of forest visitors and farmers remained the most popular occupation (59-69%). Visitors tended to stay overnight in the forest (71%). While mobile phone use in the general population was high (according to census), 24% of malaria patients owned or used a mobile phone. At district level, API was weakly negatively correlated with mobile ownership proportion (R2= 0.3, p-value= 0.005). Mobile phone ownership and use in both genders was significantly lower when compared to the general population (p<0.001), regardless of province, gender separated by province, age group and age groups separated by gender (P<0.001). In conclusion, routine collection of detailed travel surveys from malaria patients provide rich information to inform activities and future national malaria programmes. Low mobile phone ownership among malaria cases suggests use of cell phone data to analyze travel patterns will be relatively uninformative and travel surveys should be prioritized.

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POLICIES, KNOWLEDGE, ATTITUDES AND PRACTICES RELATED TO MALARIA, HELMINTHS AND SCHISTOSOMIASIS AMONG PREGNANT WOMEN IN GHANA: AN ETHNOGRAPHIC STUDY IN TWO GHANAIAN REGIONS

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The sub-Saharan African Region is burdened with high prevalence of malaria, helminth infections and schistosomiasis, which makes pregnant women within this region susceptible to infections. The study sought to explore policies on dealing with infections during pregnancy in health facilities and to describe knowledge, attitudes and practices among pregnant women related to malaria, helminths infection and schistosomiasis. This ethnographic study was carried out in two administrative regions in Ghana. It employed non-participant observation, in depth interviews (IDIs), focus group discussions (FGDs) and key informant interviews. Two sets of data were collected: (1) IDIs with health workers and health managers and (2) community key informant interviews with gatekeepers, IDIs with husbands and FGDs with pregnant women and lactating women. NVivo Version 12 was used to support thematic coding and analysis of data. All the health facilities implemented treatment guidelines on malaria during pregnancy based on WHO recommendations, however there were no uniform guidelines on treatment of helminths and schistosomiasis. Most of the study participants in the communities had knowledge on the causes and effects of malaria in pregnancy, but had little knowledge on the causes and effects of helminths infections and schistosomiasis in pregnancy. They mentioned health facilities as the place to seek treatment for malaria. FGD participants claimed that when they were pregnant or during their current pregnancy, they were not given dewormers and medicine to treat schistosomiasis at the ante natal clinic, so they did not view helminths infection and schistosomiasis as serious health issues needing attention. It was revealed that some pregnant women visited multiple sources such as health facilities for the treatment of malaria and other illnesses, but if they still felt unwell, they visited herbalists or self-medicated. Education on other infections that can have a negative effects on pregnancy should be intensified. The health service authority needs to provide clear guidelines for dealing with parasitic infections during pregnancy.

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INCREASING PATTERN OF MALARIA CASES IN LOW ENDEMIC DISTRICTS IN RWANDA

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Malaria remains a public health priority in Rwanda with the whole population being at risk of malaria infection. In 2016, Malaria stratification based on malaria incidence identified four epidemiological strata across the 30 districts of Rwanda. Since then, following core interventions have been deployed accordingly and based on availability of funds: early diagnosis and treatment both at health facility and community level, long Lasting insecticidal nets, indoor residual spraying in 12 high endemic districts, and information, education and communication as cross-cutting intervention. At National level, from 2020 to 2022, based on malaria cases reported from Health Management Information System, malaria incidence reduced from 114 to 76 per 1,000 persons with a 33% of reduction. While Rwanda malaria reduced in the last two years in high burden districts covered with core vector control interventions mainly IRS, low burden districts such as Musanze, Nyabihu, Burera and Gakenke mainly of Northern Province reported more malaria cases. Throughout this period, malaria incidence increased from 10 to 16 malaria cases per 1000 persons in these formerly lowest endemic districts, the number of malaria cases increased by 62% from 16,383 in 2020 to 26,591 cases in 2022. In Burera, malaria incidence remained constant at 5 per 1000 persons while in Gakenke malaria incidence increased from 25 to 41 per 1000 persons. Malaria incidence increased by 93% in Musanze and 67% in Gakenke. It was also found that malaria cases were heterogeneously distributed in sub-district in few sectors per each district. While the focus of malaria control over the last six years has been on high endemic districts, in low burden districts, malaria increase may not take adequate attention to malaria managers and pause a really threat to the population and sustainable of achievement in high endemic district. Therefore, it is important to continuously analyze data especially at sub-district levels, the sector, in order to determine most affected sub-areas and any changes in malaria epidemiology so as to deploy appropriate interventions in a timely manner

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THE ASSOCIATION BETWEEN MALARIA PARASITAEMIA, INTESTINAL PARASITE AND ANEMIA IN CHILDREN LESS THAN 6 MONTH IN SENEGAL: A CROSS SECTIONAL SURVEY

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Although malaria is declining in many countries in Africa, malaria and anaemia remain frequent in children. This study was conducted to assess the relationship between malaria parasitaemia, intestinal worms, and anaemia, in children under 6 months of age living in low transmission area in Senegal. A cross sectional survey was carried out in Lamarame in the central part of Senegal. A random sampling method was used to select study participant. Children under 6 months were enrolled after informed consent. For each child, blood thick and smear tests were performed, haemoglobin concentration was measured with HemoCue, and stool samples were collected and examined using the Ritchie technique. A total of 162 children were recruited. Malaria parasite prevalence was 0.75% (0.7-2.6); anaemia was found in 16.7% (11.3-23.3), while intestinal parasites and stunting represented 25.4% (18.5-33.4) and 22% (18.6-25.5), respectively. In a logistic regression analysis, anaemia was significantly associated with malaria parasitaemia (aOR= 6.3 (1.5-53.5)) and stunting (aOR = 2 (1.2-3.1)); The association was found between intestinal parasites and anaemia (OR=1.1(0.5-3.4). Malaria and anaemia remain closely associated

even when malaria is declining. Scaling up antimalarial interventions may contribute to eliminate malaria and reduce the occurrence of anaemia among children.

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SEASONAL DYNAMICS OF COMPOSITION AND DENSITY OF CO-ENDEMIC PLASMODIUM FALCIPARUM AND P. VIVAX IN ELIMINATION SETTING, SOUTH ETHIOPIA: IMPLICATIONS FOR ELIMINATION

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Malaria elimination requires targeting all remaining infections including the ones that do not elicit symptoms. It is important to evaluate the magnitude and parasite density of residual malaria in terms of species composition and season in elimination-targeted settings. To appraise these, longitudinal data were collected for one year between 2019 and 2020 covering major and minor transmission seasons and the dry season. Three elimination-targeted low transmission settings: Dilla town, Wonago, and Yirgacheffe were included. In each season, 504 individuals from 168 households were sampled. Microscopy, RDTs, ELISA, and 18S-based qPCR were performed. Overall, parasite prevalence was 7.3%, 6.8%, and 17.5% by microscopy, RDT, and qPCR, respectively. Microscopy (10.4%) and RDT (10.7%) missed infections detected by qPCR. The PvAMA1/PvMSP1/PfMSP1 antibody prevalence was 20.2%-30.4% based on the K-means algorithm. qPCR-based parasite prevalence showed seasonal variation with 12.5%, 18.3%, and 21.8% during the minor, peak, and dry seasons respectively ($p<0.05$). Of these, Plasmodium vivax infections were dominant during the minor (54.0%, 34/63) and dry (64.5%, 71/110) seasons. The highest malaria case burden was reported in the urban setting, Dilla town (29.6%, 149/504). High parasitemia was detected for both P. falciparum (median 159,44518S copies/µL) and P. vivax (median 140,321) for all seasons. A significant density of parasitemia was observed during the peak rain season ($p<0.05$). From the GEE model, study site, anemia, clinical status and bed net utilization ($p<0.001$) showed significant association with malaria. The over-dominance of P. vivax in two seasons implicates control measures need to consider tailored approaches. The considerable missing cases by conventional methods, even those parasite densities above the detection threshold of microscopy, may pose a challenge to elimination progresses. The noticed high malaria burden in urban settings and all seasons need spatial and year-round interventions through the elimination program. Also, the stratification of some settings as low transmission areas needs to be reconsidered.

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ASSOCIATION BETWEEN ANAEMIA AND PLASMODIUM FALCIPARUM AND HELMINTH INFECTIONS AMONG CHILDREN AND YOUNG ADULTS LIVING IN RURAL AREAS OF GABON, CENTRAL AFRICA

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The objective of this analysis was to describe in a cohort of school-aged children and young adults the profile of anaemia and its association with malaria and helminth infections. The study was longitudinal where participants were followed for 15-months. However, the present analysis was performed on data collected at six months follow-up. Blood samples were collected for the determination of haemoglobin parameters using an automated haematology analyzer, for the detection of malaria parasites using thick blood smear microscopy, and for the diagnosis of filariasis using leucoconcentration technique. Stool samples were collected for the diagnosis of soil-transmitted helminths (STH) while urine samples were collected for the diagnosis of schistosomiasis. Anaemia and its severity were defined using the WHO criteria for the level of the sea. General linear regression was used to assess factors associated with anaemia. A total of 217 participants were included in the present analysis. Of them, 73% (160, 95%CI: 67 - 79) were anaemic. Among the anaemic participants, most had a normal MCV value (42%, 95%CI: 34 - 50), compared to low (27%, 95%CI: 20-35) or high (31%, 95%CI: 24-39) values of the MCV. A low value of MCH (66%, 95%CI: 58 - 73) and MCHC (70%, 95%CI: 62 - 77) was observed in more than half of the participants. Anaemia was associated with Plasmodium infection (p-value=0.04) but not with STH infections (p-value=0.16), schistosomiasis (p-value=0.12) or filariasis (p-value=0.59). After multivariate analysis adjusted for age, sex, and helminth infections, participants with Plasmodium parasites had an adjusted odd of 2.44 (95%CI: 1.07 - 6.13), compared to those without Plasmodium infection. In conclusion, the prevalence of anaemia in children and young adults is high in rural areas surrounding Lambaréné, making anaemia a significant public health issue in our community. We reported malaria as the main parasitic infection associated with anaemia in the area also known to be endemic for STH infections, schistosomiasis, and filariasis. Our results, therefore, call for more interest in anaemia in the general population.

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ASSESSMENT OF THE BURDEN AND DETERMINANTS OF MALARIA TRANSMISSION IN SELECTED URBAN SETTLEMENTS IN NIGERIA

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Nigeria is the highest-burden malaria country. Unplanned urbanization may result in environmental conditions that promote heterogeneities in malaria risk. Identifying urban settlements with high malaria transmission risk will guide better targeting of interventions. We are conducting field epidemiological and entomological studies to understand the variations and drivers of malaria risk in formal and informal settlements, and slums in Kano and Ibadan cities. The design of our epidemiological and entomological assessments is informed by formative research. Study sites were chosen based on findings from multistakeholder dialogues which helped in defining and identifying settlement types. Focus group discussions, key informant interviews, and cognitive interviews were conducted to inform the design of quantitative instruments for epidemiological surveys. Our epidemiological surveys aim to estimate malaria prevalence and identify related factors among all ages, and pregnant women. To achieve this, we are conducting household and health facility cross-sectional surveys during the wet and dry seasons. We are also conducting 12-month longitudinal surveys to assess malaria seasonality and drivers among children under the age of 10 years. Dry and wet season entomological surveys (mosquito collection using CDC light trap and Pyrethrum Spray catches) are being conducted to establish the presence or absence of local transmission using various entomological indicators. Preliminary findings from the multi-stakeholders dialogue revealed that having a settlement plan, social amenities, and population densities were key factors useful for categorizing settlement types into formal, informal, and slums. During dry season entomological surveys, we captured two main malaria vectors - Anopheles Gambiae and Anopheles Funestus between the hours of 6 pm and 5 am in all settlement types, although most vectors were found in informal settlements. Results from the wet season cross-sectional surveys and early findings from the longitudinal surveys will be available for presentation at the annual meeting.

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PLACENTAL MALARIA AND BLOOD PRESSURE AT AGE FOUR YEARS: EVIDENCE FROM THE GHANA RANDOMIZED AIR POLLUTION AND HEALTH STUDY

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In sub-Saharan Africa, malaria and hypertension are one of the commonest causes of morbidity and mortality in children and adults respectively. Although previous studies have shown that malaria in pregnancy may increase the risk of gestational hypertension, the effect of placental malaria (PM) on blood pressure (BP) in childhood has not been well studied. The Ghana Randomized Air Pollution and Health Study recruited N=1414 non-smoking women prior to 24 weeks gestation in the Kintampo North Municipality and Kintampo South District of Ghana. PM was assessed by placental histology of full-thickness biopsies obtained at delivery. PM was first dichotomized as no infection or evidence of any infection followed by a more detailed classification: no infection, acute infection, chronic infection or past infection. At age four years, a subset of study children underwent two resting BP measurements, spaced five minutes apart after a 10-minute rest, using the digital OMRON BP742N BP monitor (OMRON Healthcare, CA, USA). We employed multivariable linear regression models to examine associations between PM and childhood systolic and diastolic BP. Of the N=1306 livebirths at 28+ weeks gestation, N= 639 had both valid PM and blood pressure data. The prevalence of PM was 24%. The mean systolic BP (SBP) and diastolic BP (DBP) at age four was 90.2 mmHg and 64.2 mmHg respectively. Following adjustment for child sex and BMI, maternal age and parity, wealth index and ethnicity, PM (any infection) trended towards increased DBP (β=1.51 mmHg; 95% CI -0.20 to 3.22; p=0.08) compared with no infection. Similarly, evidence of past PM showed a trend towards increased DBP (β=1.78 mmHg; 95% CI -0.27 to 3.82; p=0.09) compared with no infection. There was no evidence of an association between PM and SBP. PM may be associated with increased diastolic BP in early childhood. Given that childhood BP tracks into adulthood, larger longitudinal studies are needed to understand the effects of in-utero exposure to malaria and the risk of hypertension in childhood and whether this risk in sustained to adulthood.

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EVALUATION OF THE SEASONALITY OF MALARIA TRANSMISSION THROUGH ROUTINE DATA FROM HEALTH FACILITIES IN BURKINA FASO

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Malaria transmission is strongly seasonal peaking in the rainy season.in Burkina Faso and the country counts for the “high burden to high impact” initiative launched by WHO and the roll Back Malaria Partnership. Despite combined effective control measures include large scale distribution of long-lasting insecticide treated bed nets, the chemoprevention in pregnant women and the seasonal malaria chemoprevention in children 3-59 months, prevalence and incidence of malaria remain high, even though high proportion of diagnosed malaria are unconfirmed (either microscopy or rapid diagnosis test) despite continued effort to confirm malaria diagnosis. Thus, in this project, we aimed to investigate how the diagnosis of malaria in the absence of microscopy or Rapid Diagnosis Test confirmation is impacting malaria seasonality appraisal. Through the ACCESS-SMC project, we conducted a retrospective extraction of routine data from 40 randomly-selected health facilities in 8 different health districts spread all over the country from 2012 to 2016. Data collected included gender, age, clinical signs (fever, vomiting, diarrhea and other signs suggestive of malaria), the performance of rapid diagnosis test or not and the final diagnosis along with the treatment administrated. Overall, 826,199 consultations for suspected malaria were recorded over the study period. There was 36,34% increase in the testing rate between 2012 and 2016 (43.32 versus 79.66%). January to June considered as the low transmission period there were respectively 59.21% [range: 58.79%-59.64%] and 46.34% [range: 45.89%-46.8%] of unconfirmed malaria recorded while July to December considered as the highest transmission period, we recorded respectively 33.63% [range: 33.29%-33.96%] and 46.64% [range: 46.22%-47.06%]. Comparing these periods, the proportion of confirmed malaria is different between the two periods compared to the unconfirmed cases.

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MEASURING IMPACT OF SEASONAL MALARIA CHEMOPREVENTION ON MALARIA CASE DISTRIBUTION FROM ROUTINE DATA SOURCES COMPARED TO MODELLED PREDICTIONS IN BURKINA FASO

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Clinical trials assessing effectiveness of seasonal malaria chemoprevention (SMC) show high impact preventing around 80-85 percent of uncomplicated cases of malaria in children under 5. However, when implemented at scale, SMC programmes have not shown the expected impact in routine and administrative data. We are using a mathematical model to develop a framework for assessing impact of SMC programmes by bringing together relevant data such as prevalence, rainfall, health management information system (HMIS) case data, other interventions, implementation of SMC. We calibrated a malaria transmission model to malaria prevalence (Demographic Health Surveys [DHS]) over time for selected health districts in Burkina Faso using maximum likelihood methods by varying mosquito density. We simulated clinical cases in under 5’s during implementation of SMC in each district including rainfall, net use (Malaria Atlas Project), and treatment seeking (DHS). We compared model predictions of the proportion of clinical malaria cases in children under 5 out of children under 15 to district level rapid diagnostic test confirmed cases from the HMIS. The age distribution of cases aligns well with model simulations prior to SMC, however, model predictions show a larger change after SMC and this change varies by baseline transmission. This could be due to non-malarial fevers presenting at the health facility affecting seasonal patterns in routine data. We will present modelling analyses assessing the effect non-malarial fevers have on seasonal patterns and the extent to which these may mask the impact of SMC seen in routine data.

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MOLECULAR SCREENING SUGGESTS ANTAGONISM BETWEEN PARASITEMIA WITH PLASMODIUM FALCIPARUM AND P. OVALE IN TANZANIA

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Even as Plasmodium falciparum burden has declined in parts of sub-Saharan Africa in recent years, the prevalence of non-falciparum species, such as P. ovale, appears to be rising in the same populations. We employed cross-sectional molecular screening of over 6000 participants >5 years of age residing in coastal Bagamoyo, Tanzania, to examine rates of mono- and co-infection with P. falciparum and P. ovale and investigate possible cross-species interactions. Specifically, we calculated the prevalence ratio of ovale parasitemia between individuals who were positive and negative for falciparum parasitemia using a binomial logistic regression adjusting for age, sex, and seasonality. Of 6,258 participants screened between October 2018 and November 2021,1,929 (31%) were positive for P. falciparum and 644 (10%) were positive for P. ovale. These distributions show evidence of an antagonistic interaction, with individuals positive for P. falciparum having 0.67 (95% CI: 0.56, 0.82) times the probability of also having P. ovale compared to falciparum-negative individuals. This finding of fewer mixed infections than expected by independent assortment was detected in all age groups except adolescents, with age-stratified P. ovale prevalence ratios (95% CI) comparing falciparum-positive to falciparum-negative participants of 0.71 (0.52, 0.97), 1.14 (0.76, 1.74), 0.44 (0.28, 0.69), and 0.62 (0.42, 0.92) among participants ages 6-12, 13-18, 19-30, and >30, respectively. Potential explanations for these results could be that cross-protective immunity or competitive inhibition from the more-common falciparum malaria reduces detected co-infection by decreasing P. ovale susceptibility or parasitemia, or by suppressing ovale relapse infections. We plan to replicate this analysis using data from other molecular surveys in Tanzania and elsewhere in sub-Saharan Africa; if replicated, this interaction may help explain the relative resilience of non-falciparum species amidst declining falciparum burden.

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INTRA-HOST CLONAL DYNAMICS SHAPE CHRONIC PLASMODIUM FALCIPARUM INFECTIONS THROUGH THE DRY SEASON

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Plasmodium falciparum can persist in asymptomatic individuals for extended periods of time, which is particularly relevant in regions where malaria transmission is almost entirely interrupted by a long dry season. In Mali, up to 30% of children carry P. falciparum throughout the dry season without symptoms, comprising a genetic reservoir that bridges two transmission seasons. Our data show that the decreased virulence of the parasite during the dry season is likely not influenced by sensing of seasonal cues, but rather by the timing of inoculation and number of replicative cycles that individual parasite clones undergo within a host. We applied amplicon sequencing of a highly polymorphic gene (apical membrane-antigen 1) on longitudinal samples collected fortnightly in Kalifabougou, Mali, from gender-and-age matched individuals during one transmission season that maintained P. falciparum persistent infections during the 6-month dry season (n=92) or that cleared them due to either treatment during the season or to natural clearance (n=38). We observed that children with persisting parasites had a higher overall within-host diversity (measured by Shannon evenness of clonal abundance), even when taking into account differences in complexity of infection or parasite density, than those who did not. The ability of children with dry season persistent infections to control parasites more broadly suggests that immunity plays a role in structuring this diversity, and that clonal abundance is a predictor of persistence. We apply these data to inform mathematical models and intra-host simulations to determine drivers of persistence throughout and evaluate our predictions with longitudinal data collected monthly during the dry season in Torodo, Mali (n=74). Our findings highlight how the within-host clonal dynamics over time promote persistence and may inform new strategies for elimination in areas with highly seasonal transmission.

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EVALUATING MALARIA PREVALENCE IN NON-HOMOGENEOUS FOR MAL AND INFORMAL COMMUNITIES IN FREETOWN SIERRA LEONE: A MULTIPHASE CROSS SECTION SECTIONAL STUDY

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Limited resources for malaria, including in Sierra Leone, require national programs to stratify activities within urban areas. Simultaneously urbanization and changing transmission dynamics require innovative approaches for malaria control in urban areas. Catholic Relief Services (CRS) and the College of Health and Allied Sciences undertook a cross-sectional study from July 2021 to November 2022 to determine the prevalence of malaria in children 6-59 months old in four separate communities within Freetown. Two communities were identified as formal (Wilberforce and Hill Station) and two informal (Kolleh Town and Cockle Bay). Freetown, has two peak transmission seasons in May and the second in October/November, however, changing weather patterns have delayed rains in recent years. The three cross-sectional surveys were conducted within the four communities based on rainfall in the low transmission season (RD1, August 2021), mid-year transmission season (RD2, June/July 2022), and peak transmission seasons (RD3, November/December 2022). We observed a consistently higher malaria prevalence in the formal settlements [μ=14% - 11.1% RD1, 13.6% RD2 & 17.4% RD3] than informal settlements [μ=11.3%- 10% RD1, 8.7% RD2 & 15.2% RD3]. In formal areas 36% of houses were identified to be 'traditional' in construction suggesting that increased urbanization is leading to blended (non-homogeneous) formal areas. Other factors such as housing type, ITN ownership, and wealth quintile were variable in predictive association for malaria among households in formal and informal areas. The results demonstrate that increased urbanization has resulted in non-homogeneous areas of Freetown, and that malaria rates are higher than reported in national malaria surveys. New approaches including improved WASH, housing, and vector control are needed within urban areas to help stratify available malaria resources.

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HIGH-THROUGHPUT GENOTYPING OF PLASMODIUM VIVAX IN THE PERUVIAN AMAZON VIA MOLECULAR INVERSION PROBES

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Genomic epidemiology has enabled in-depth, high-throughput study of Plasmodium populations, antimalarial resistance, and importation. Molecular inversion probes (MIPs) have enabled efficient and affordable high-throughput genotyping of Plaasmodium falciparum populations in African contexts, but application to other species has lagged. P. vivax is the most widespread human malaria species and is an emerging threat in many areas with successful P. falciparum control. As such, there has been a recent proliferation in global P. vivax genomics studies facilitated by the superior PvP01 genome assembly. Leveraging the success of P. falciparum MIPs, we developed four P. vivax MIP panels covering: 1) known genes of interest (e.g. reticulocyte binding proteins, Duffy binding proteins, potential vaccine targets, potential drug resistance genes, and diversity markers); and SNPs identified in globally distributed (including Africa) whole genome sequences that are 2) highly geographically differentiating; 3) neutral and rare; and 4) neutral and common. We used these panels to study the population structure of 689 Peruvian P. vivax samples collected by NAMRU between 2011 and 2017 in the region around Iquitos. The panels consistently perform well with isolates at ≥ 200 p/µL, with some isolates <100 p/µL also performing well in initial sequencing. Across both our SNP panels and our genes of interest (e.g. RBP2), we detect a lack of rare alleles (Tajima's D > 2), which could indicate balancing selection in genes associated with RBC invasion that are under immune selection. Assessment of directional selection signatures in the population are ongoing, including evaluation of putative drug resistance alleles. Overall, we find minimal large-scale geographic or temporal structure among these samples based on PCA, consistent with a long-term panmictic population. However, at the local level we detect clusters within the same city and year that may represent local outbreaks and warrant further investigation. The new P. vivax MIP panels provide a high-throughput genotyping approach to interrogate genome-wide SNPs as well as genes of biological interest.

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PLASMODIUM VIVAX SHOWS HIGH GENETIC DIVERSITY AND RAPID LOCAL ADAPTATION IN A REMOTE COMMUNITY FROM THE PERUVIAN AMAZON REGION

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There is no a lot of information about Plasmodium vivax malaria transmission and parasite genetic diversity in remote hard to reach areas from the Peruvian Amazon that represent a challenge to achieve the long-awaited malaria elimination. The main objective of this work was to evaluate the P. vivax population genetics changes over time in the community of Santa Emilia, province of Loreto. Weekly active case detection and monthly screening were performed in 2013 and 2015-2016. A prevalence of 49% [IC 43-55] by microscopy and 82% [IC 77- 86] by PCR was found during all the surveillance activities. In addition, 350 out of 529 total samples were genotyped using sixteen neutral microsatellite markers. The result showed high genetic diversity (0.70 ± 0.10 in average) over time, high population differentiation (Fst> 0.5) between 2013-2015 and 2013-2016, and 40% of polyclonal infections. Additionally, we found the absence of a recent bottleneck in the population, with the presence of new alleles, supported by 14% of genetically unrelated parasites. Bayesian inference indicates that four more likely clonal populations (ΔK = 4) were circulating during this period of time. In conclusion, our results suggested that P. vivax had rapid adaptation and expansion in Santa Emilia and this community presents a high vulnerability to the importation of new parasites that support local transmission and high genetic diversity maintenance. This scenario may be due to the local human mobility, that should be better studied in these remote areas. This information is relevant to focalize or adapt the elimination strategies, already in place, mainly in remote communities.

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GENETIC ANALYSIS REVEALED HIGHLY RELATED LOCAL TRANSMISSION OF PLASMODIUM FALCIPARUM IN THE ISLAND OF SÃO TOMÉ

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The Democratic Republic of Sao Tome and Principe (STP) is approaching malaria elimination and aiming to eliminate it by 2025. However, continuous transmission and increasing cases have been seen in the past few years. To target effective control strategies, it is crucial to characterize local transmission and identify risk factors of transmission. Here, we collected 419 samples on the island of São Tomé between 2015 and 2016 and applied a multiplexed amplicon sequencing approach targeting 165 diverse microhaplotypes to obtain genetic data for each sample. To quantify transmission intensity and identify transmission clusters, we used MOIRE to estimate complexity of infection (COI) and within-host parasite relatedness, and Dcifer to estimate inter-sample relatedness. Preliminary results from 120 samples showed a very high proportion of monoclonal infections (96.7%, 116/120; average COI = 1.08) and high relatedness among a large proportion of samples. Most samples from 2016 (76.4%; 68/89) and a few from 2015 (9.7%; 3/31) were part of a single, predominant genetic cluster with high relatedness (range of pairwise relatedness from 0.9 to 1.0). The predominant cluster was transmitted throughout 2016 and sustained in Agua Grande (67.6%, 46/68) and Lobata (23.5%, 16/68) districts. Most 2015 samples outside the predominant cluster also showed a significant pairwise relatedness (> 0.5) to one or more samples from 2016. Overall, our results demonstrate extreme bottlenecking of parasite diversity in 2016, suggestive of sustained but low local transmission with limited importation of Plasmodium falciparum in the island of São Tomé. We are currently working with case surveillance data to identify risk factors of transmission, which may further guide targeted elimination strategies.

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GENOME STRUCTURE OF PFHRP2/3-DELETED PLASMODIUM FALCIPARUM: DELETION BREAK-POINTS AND CONSEQUENCES OF THE DELETION

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Deletions in Plasmodium falciparum histidine-rich proteins 2 and 3 (pfhrp2/3) cause false-negative RDT results, threatening malaria control efforts. These deletions occur as spontaneous rearrangements in P. falciparum, but the mechanism, break-points, and the extension of the deletions into flanking regions are not well-described. It is also unknown what impact these genome rearrangements have on the parasite genome, and on the phenotypic diversity and environmental adaptability of the parasite. In this study, we investigated the genome structure of P. falciparum with pfhrp2/3 deletions to understand how the deletions occur and the impact of the deletions on chromosome architecture. We derived whole genome sequence for two pairs of clinical and culture-adapted isolates using high-quality short-read genomic sequencing and carried out de novo assembly to investigate genome rearrangement. The genomes were annotated and synteny maps generated against the 3D7 reference genome. Genomic rearrangements including duplications, inversions and translocations were common in the sub-telomeric regions of most of the chromosomes in all parasite lines, suggesting this is a relatively common process in P. falciparum which can lead to pfhrp2/3 deletions. There is a clear common break-point for pfhrp2 at a location adjacent to it, spanning the distal 25-50 kb at the right end of chromosome 8. By contrast, pfhrp3 occurs at the end of a deletion block spanning 600 kb at the right end of chromosome 13. These differences may suggest that pfhrp2 deletion is a recent positive selection event but pfhrp3 deletion could be a passive consequence of genetic hitchhiking. The majority of genes deleted together with pfhrp2 and pfhrp3 encode variant surface antigens (VSA), possibly altering the parasite's immune evasion repertoire. We also observed gene deletions broadly involved in sexual cycle proteins predicted to impact the transmissibility of the parasites. Understanding whether the parasites acquire any advantage linked with deletions can aid in planning appropriate control strategies.

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DISTRIBUTION OF PLASMODIUM FALCIPARUM APICAL MEMBRANE ANTIGEN 1 CLUSTER ONE LOOP HAPLOTYPES AND THEIR ASSOCIATION WITH MALARIA SYMPTOMS IN BANDIAGARA, MALI

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Although overall malaria incidence has decreased sharply over the past two decades, progress has stalled since 2015. Vaccination is a control strategy that could limit malaria burden. While multiple malaria vaccines have been tested in phase 2 or phase 3 trials, and only one progressing to phase 4 trials, no vaccine has induced an overall clinical efficacy greater than 50% except the R21 vaccine. Understanding the parasite genetic factors playing a role in malaria pathogenesis could help identify essential proteins and aide in the design of an effective malaria vaccine. We hypothesize that clinical malaria phenotypes are a function of parasite density, genetic makeup of both parasite and host, starvation, co-infection, environmental factors, and potentially parasite and host epigenetic factors. To investigate the relationship between parasite genetics and clinical phenotypes, we have focused on apical membrane antigen 1 (AMA1), a parasite antigen involved in red blood cell invasion, which contains a cluster one loop (c1L) fragment that interacts with anti-AMA1 antibodies. Using ama1 gene sequences generated from samples collected from 425 children during a three-year malaria incidence study conducted in Bandiagara, Mali, we assessed the relationship between individual haplotypes and clinical malaria symptoms and disease phenotypes of those presenting with clinical malaria symptoms. AMA1 haplotype dynamics showed a gene under balancing selection. After adjusting for study participant location, using logistic regression, c1L haplotypes were not associated with malaria symptoms or disease phenotypes. None of the most frequent haplotypes were linked to clinical malaria, defined as any temperature greater than 37.5 degree Celsius and a parasitemia greater or equal to 2,500 parasites per microliter. Our findings suggest a lack of association between AMA1 haplotypes and symptomatic malaria. Likely, multiple factors are related to malaria symptomatology.

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A NOVEL PROBABILISTICALLY MODEL BASED ON GENETIC DATA FOR ESTIMATING PLASMODIUM VIVAX RELAPSES AFTER RADICAL CURE TREATMENT

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The diverse potential origins of recurrent infections after treatment against Plasmodium vivax make it difficult to estimate treatment anti-relapse efficacy. However, the genetics of parasite populations can support a more realistic estimation of the anti-relapse efficacy. Hereby, we developed a probabilistic statistical framework based on P. vivax microsatellite genotyping data from a cohort treated with chloroquine and primaquine in the Peruvian Amazon, aiming to estimate relapse events after treatment translated into anti-relapse efficacy. First, we performed multiple imputations to deal with missing microsatellite data using polytomous logistic regression models. Then, we proposed a probability of relapse integrating the prevalence of allelic profile and allelic dissimilarity index (multilocus comparison of pre-/post-treatment isolates). This informed to the binomial probability process to randomly impute the recurrent status (i.e., either reinfection or relapse), and multiply repeated to evaluate the uncertainty. Finally, Rubin's rules were applied to the final pooled estimates. Of 302 participants, 197 (65.2%) had at least one P. vivax recurrence during the 2-year follow-up. The pooled mean Nelson-Aalen cumulative hazard estimate of first heterologous recurrences was 4,0% at day 28 and increased gradually up to 2 years after treatment (45.7% at 6 months, 66.7% at 1y, and 88.5% at 2y). On the contrary, the first homologous recurrences only occurred from day 52 (0.35%) and were less frequent afterward (11.5% at 6 months, 13.5% at 1y, and 15,0% at 2y). The final pooled 6-month and 2-year cause-specific cumulative incidence function of first relapses after treatment were 0.22 (95% CI 0.17-0.28) and 0.29 (95% CI 0.23-0.35) for the overall study population. Our study proposes a statistical approach to identify the origin of P. vivax recurrences after treatment with a comprehensive assessment of the treatment's efficacy considering the parasite population's genetic features and the probability of relapse.

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MOLECULAR SURVEILLANCE OF MALARIA PARASITES IN AN INDIGENOUS COMMUNITY IN THE PERUVIAN AMAZON

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Hard-to-reach communities represent Peru's last challenge for malaria elimination, but information about epidemiology and transmission is scarce. We investigated the transmission dynamics/population genetics, drug resistance markers, and pfhrp2/3 deletions of Plasmodium vivax (Pv) and P. falciparum (Pf) in Nueva Jerusalén (NJ). NJ is a remote indigenous community in the Loreto region (~50 km from the Ecuador border) with persistent malaria transmission. We performed population surveys in 3 weekly consecutive active case detection (ACD) visits in November 2019 and by passive case detection (PCD) from December 2019 to May 2020. We analyzed a representative sample of positive-PCR isolates (Pv=70, Pf=64) using AmpliSeq NGS assays.The Pv population was genetically homogeneous during the study and had modest genetic diversity (He=0.27). In contrast, the Pf population had low diversity (He=0.08) and 3 clusters (one generated an outbreak).Moreover, Pf parasites carried resistance mutations in pfcrt (100%), pfdhfr (94%), and pfdhps (48%). No artemisinin resistance variants were found in pfK13. In addition, the most frequent haplotype was hrp2-/hrp3+ (62%). Compared to other remote areas, NJ's Pv parasites were highly differentiated from the ones from Yavari (district next to the Brazilian border, >480km distant from NJ) (Fst=0.45) but little differentiated from Mazan (riverine district, >350 km far away) (Fst=0.08). On the other hand, Pf in NJ had modest to high genetic differentiation with Santa Emilia (riverine community, >260 km from NJ) (Fst=0.19) and Mazan parasites (Fst=0.34). The Pf resistance markers and pfhrp2/3 haplotypes were similar among the areas, except in Mazan, where the double deletion was predominant. In this first report about malaria genomic surveillance in Peruvian indigenous communities, Pv & Pf population structure in NJ were different between them and also among other areas, highlighting the importance of performing regular surveillance in these communities in terms of imported infections and spread of drug resistance to promptly recommend the adaptation of the malaria elimination strategy in Peru.

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COMPARISON OF MOLECULAR SURVEILLANCE METHODS TO ASSESS CHANGES IN THE POPULATION GENETICS OF PLASMODIUM FALCIPARUM IN HIGH TRANSMISSION

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A major motivation for developing molecular methods for malaria surveillance is to measure the impact of control interventions on the population genetics of Plasmodium falciparum as a potential marker of progress towards elimination. Here we assess three established methods (i) single nucleotide polymorphism (SNP) barcoding (panel of 24-biallelic loci), (ii) microsatellite genotyping (panel of 12-multiallelic loci), and (iii) varcoding (fingerprinting var gene diversity, akin to microhaplotyping) to identify changes in parasite population genetics in response to a short-term indoor residual spraying (IRS) intervention. Typical of high seasonal transmission in Africa, multiclonal infections were found in 82.3% (median 3; range 1-18) and 57.8% (median 2; range 1-12) of asymptomatic individuals pre- and post-IRS, respectively, in Bongo District, Ghana. Since directly phasing multilocus haplotypes for population genetic analysis is not possible for biallelic SNPs and microsatellites, we chose ~200 low-complexity infections biased to single and double clone infections for analysis. Each genotyping method presented a different pattern of change in diversity and population structure as a consequence of variability in usable data and the relative polymorphism of the molecular markers (i.e., SNPs < microsatellites < var). Varcoding and microsatellite genotyping showed the overall failure of the IRS intervention to significantly change the population structure from pre-IRS characteristics (i.e., many diverse genomes of low genetic similarity). The 24-SNP barcode provided limited information for analysis, largely due to the biallelic nature of SNPs leading to a high proportion of double-allele calls and a view of more isolate relatedness compared to microsatellites and varcoding. Relative performance, suitability, and cost of the methods relevant to sample size and local malaria elimination in high-transmission endemic areas will be discussed.

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DIFFERENTIAL REGULATION OF PFMDR2 AND PFK13 TRANSCRIPTS IN KENYAN CHILDREN WITH SEVERE MALARIAL ANEMIA: POTENTIAL IMPACT ON ARTEMISININ-BASED COMBINATION THERAPY RESPONSES

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Severe malarial anemia (SMA: Hb≤6.0 g/dL, with any density parasitemia) is a common clinical manifestation of severe malaria in children under five in holoendemic Plasmodium falciparum transmission regions, such as Siaya County, western Kenya, and a primary cause of morbidity and mortality. To explore the impact of parasite-derived factors on malarial disease severity, we performed transcriptomic analyses on whole blood collected from children (3-36 months) with non-SMA (Hb>6.0 g/dL, n=40) and SMA (n=20) prior to treatment with artemisinin-based combination therapy (ACT). Next-generation sequencing was performed at a depth of >20 million high-quality mappable reads using Illumina NovoSeq and subsequently mapped to a reference genome for a Kenyan P. falciparum isolate (pfKE01) using the HTSeq platform. This resulted in the annotation of ~3200 distinct P. falciparum transcripts. RNA reads for each sample was normalized by calculating transcripts per kilobase million (TPM) per transcript. There were 688 differentially expressed P. falciparum genes between the SMA and non-SMA groups (P<0.05): 649 upregulated and 39 downregulated. Two P. falciparum transcripts related to ACT treatment responses were differentially regulated. Specifically, children with SMA had upregulated levels of multidrug resistance protein 2 (MDR2; Log2foldChange=1.33) and downregulated levels of kelch protein K13 (Log2foldChange=-0.47). These results suggest that children with SMA may have altered susceptibility profiles to ACTs. Further research is required to determine if altered gene expression patterns for MDR2 and K13 affect drug effectiveness and if

the driving force behind these observed patterns is due to pressure from the human host immune response and/or inherent genetic changes in the parasite.

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SPATIAL CONNECTIVITY, IMPORTATION AND TRANSMISSION FLOW OF PLASMODIUM FALCIPARUM IN MOZAMBIQUE USING MICROHAPLOTYPE DATA

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Malaria genomics represents a promising tool to improve current surveillance systems and tailor malaria control and elimination interventions. The GenMoz (Plasmodium falciparum genomic intelligence in Mozambique) project aims to operationalise a functional malaria molecular surveillance system in Mozambique to inform programmatic decisions on the use of effective diagnostic and treatment tools, targeted strategies for malaria elimination and effective intervention combinations to maximise burden reduction. For this purpose, a novel amplicon sequencing panel was developed to generate 272 genetic microhaplotypes targeting 250bp regions that are highly informative of diversity, misdiagnosis and drug resistance mutations, allowing precise estimates of relatedness for polyclonal infections. We studied the spatial structure of genetic connectivity of P. falciparum populations in Mozambique to assess the potential of genomics to characterise transmission flow and quantify the contribution of imported cases in low-transmission settings. We used the R package Dcifer to estimate identity-by-descent between sample pairs from various provinces, studying isolation-by-distance in a wide range of geographical distances, using Mandel tests. We quantified the contribution of imported cases in two low-transmission areas from the fraction of highly related pairs between samples from these areas and from other areas, correlating the statistics with travel history surveys. We found strong spatial genetic distinction across the country, with higher fractions of highly related pairs within regions (north-north or south-south) than between regions (north-south). The Mandel tests confirm strong isolation-by-distance at large scales (between provinces), but no statistical significance at small scales (within province). Few highly related pairs between samples in the targeted low-transmission areas and samples from different provinces of Mozambique were found, with no significant correlation with their travel history data, suggesting no significant contribution of imported cases in the low-transmission areas studied.

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EXPANDING THE GLOBAL WHOLE GENOME SEQUENCE DATASET OF PLASMODIUM FALCIPARUM

Richard D. Pearson on behalf of MalariaGEN

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Malaria control and elimination requires decision making regarding the use of vaccines, diagnostics and treatments, all of which can be informed by genomic surveillance of the parasite. Whole genome sequencing can play an important role in detecting new molecular markers associated with drug resistance, identifying regions of the genome that are under selection, and better understanding host-parasite interactions. We previously released the largest global resource of genomic data on Plasmodium falciparum, comprising over 20,000 samples from 82 partner studies in 33 countries. Since then, we have released further whole genome sequence data to MalariaGEN partners. We are working towards publicly releasing an expanded set of curated genotype data. As with previous releases, this will include genotypes at SNPs and short indels genome-wide, in addition to copy number variation calls at genes related to drug resistance and failures of rapid diagnostic tests. The latest release will include sample QC, identification of populations and characterisation of samples by inferred resistance status to major frontline anti-malarial drugs. In addition to an expanded set of samples, we aim to enhance the value of this data resource by making jupyter notebooks of typical analyses publicly available using a free-to-use cloud-based platform.

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PREVALENCE OF CYP2C8 POLYMORPHISM IN CHILDREN AGED 3 TO 59 MONTHS IN BOBO DIOULASSO, BURKINA FASO

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Cytochrome P450 2C8 (CYP2C8) is a key enzyme responsible for the metabolism of many drugs such as amodiaquine (AQ), which is a component of artemisinin-based combination therapy (ACT) and seasonal malaria chemoprevention (SMC) drugs. Polymorphisms present in this gene may have an impact on the pharmacokinetics (PK), efficacy and safety of this antimalarial. The objective of this study was to determine the prevalence of CYP2C8 mutation, associated with Plasmodium falciparum in children under 5 years of age in Bobo Dioulasso, Burkina Faso. Dried blood spots were collected from 1083 participants and extracted using the Qiagen kit (DNeasy Blood & Tissue Kit). The prevalence of the human CYP2C8*2 and CYP2C8*3 genotypes were determined by PCR-RFLP, and the identification of P. falciparum was done by the microscopy. The prevalence of P. falciparum was 7.20% (i.e. 78/1083) and the prevalence of CYP2C8*2 was 28.72% (i.e. 311/1083) in the study population. homozygous (*2/ *2) and heterozygous (*2/*1) participants for the CYP2C8*2 were 26.41% (i.e., 286/1083) and 2.31% (i.e., 25/108) respectively. The proportion of participants with the CYP2C8 mutation and with positive for P. falciparum was 0.74% (i.e. 8/1083). The influence of these CYP2C8 mutations on the metabolism of antimalarial drugs, in particular amodiaquine (AQ), needs to be further evaluated.

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INFERRING FOR CE OF INFECTION FROM MOLECULAR-BASED ESTIMATES OF MULTIPLICITY OF INFECTION IN FALCIPARUM MALARIA WITH AN APPLICATION TO INTERVENTION IN NORTHERN GHANA

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Force of infection (FOI), defined as the number of new Plasmodium falciparum infections acquired by an individual host over a given time interval, is a direct measure of exposure to Plasmodium falciparum blood-stage infection. It reflects risk of infection and clinical episodes, and relates local variation in malaria burden to transmission. It is thus suitable for monitoring the impact of antimalarial interventions and assessing vaccine or drug efficacy in clinical trials. Despite being recognized as

a key epidemiological parameter, FOI remains difficult, expensive, and labor-intensive to accurately measure, either directly via cohort studies or indirectly via the fitting of epidemiological models to repeated cross-sectional surveys. Molecular advances to sequence and type the var multigene family encoding for the major surface antigen of the blood stage of infection, provide a basis to estimate a sister "static" quantity, the multiplicity of infection (MOI, the number of genetically distinct parasite strains co-infecting a single human host), typically under sparse sampling schemes. Having extended this approach to a Bayesian framework to account for measurement error, we propose a general approach to obtain FOI on the basis of MOI. We specifically adapt two methods from queuing theory to derive FOI, and evaluate these with numerical simulations with a stochastic agent-based model. We then apply the methods to longitudinal surveys from northern Ghana before, during, and after a three-round IRS (Insecticide Residual Spreading) intervention. Both methods give accurate and consistent FOI estimates across various simulated scenarios. Their application to field surveys shows that despite a pronounced 60% reduction in FOI during IRS, transmission intensity rebounds almost completely in 32 months following IRS interruption. The methods should be applicable to many geographical locations where cohort or frequently-sampled cross-sectional studies are lacking but single-time-point surveys under sparse sampling schemes are available. They should also apply to other infectious diseases for which MOI has been obtained.

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POPULATION DYNAMICS AND GENOTYPIC VARIATION OF PLASMODIUM VIVAX IN A LOW-ENDEMICITY AREA OF SOUTH AMERICA BETWEEN 2012 AND 2020

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Ecuador is one of the countries that is part of the E-2025 initiative and would be able to eliminate malaria in the coming years. Nevertheless, elimination efforts have fallen short and cases have been increasing, particularly in the Amazon of the country. Plasmodium vivax is the main malaria parasite affecting the Ecuadorian population but little is known about the populations of P. vivax circulating in the country. We used nine microsatellite markers in 150 samples of P. vivax from the Ecuadorian Coast and Amazon regions collected between 2012 and 2020 to characterize their origin, distribution and population dynamics. We found that in Ecuador, there is higher genetic diversity and multiclonality of P. vivax in the Amazon region than in the coast of the country. In addition, there was evidence of gene flow and moderate genetic differentiation between Amazonian localities, but little gene flow between the Coast and Amazon. The coast of Ecuador shared lineages and had low/moderate genetic differentiation with coastal Colombian localities. Similarly, Amazon localities shared lineages and had low/moderate genetic differentiation with Peruvian Amazon localities. This study suggests a recent increase in P. vivax multiplicity of infection and diversity in the Amazon of Ecuador because of increased transmission. It confirms the importance of the Andes as a geographical barrier and underlines the importance of geographic corridors through the Pacific coast of South America and the Amazon rivers that help sustain malaria in the region and hamper elimination.

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GENETIC CONNECTIVITY AND TRANSMISSION METRICS OF PLASMODIUM FALCIPARUM IN ZAMBEZI REGION, NORTHERN NAMIBIA

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As malaria transmission declines, an increasing proportion of the parasite reservoir is clustered in subpopulations with shared risk factors and spatial hotspots. While the WHO recommends a targeted response in high-risk populations, there is limited evidence quantifying transmission between populations and the impact of targeted interventions. As part of a population-based evaluation of targeted malaria interventions in seasonal agricultural workers in northern Namibia (2019-2020), epidemiological data and samples were collected from cases at agricultural sites (n=35) and those presenting to nearby health facilities (n=511). All samples with parasite density ≥10 parasites/μL of blood by qPCR were sequenced using amplicon deep-sequencing panels including 175 highly diverse and differentiated loci. Population level and within-host genetic diversity measures, including effective complexity of infection (eCOI) and within-host relatedness were estimated by population (nationality and worker/community) and study arm, using an MCMC based approach. Preliminary results are reported from 25 cross-sectional and 280 incident cases. There was no difference in eCOI between agricultural workers and communities in control and intervention areas at either time point, but non-Namibians had a higher eCOI than Namibians, potentially indicating parasite importation from or increased connectivity with higher transmission settings. At endline, eCOI was lower in the intervention arm within both worksites and surrounding communities (median = 1.14 (95% CI: 1.13-1.16) and 1.16 (1.15-1.18)) compared to the control arm (1.21 (1.20-1.22) and 1.22 (1.21-1.23)). A similar, non-significant trend was observed for within-host relatedness and proportion of polyclonal infections in agricultural workers. Results suggest an impact of the intervention on transmission at worksites that may have spilled over to communities. Additional analyses will include data from all cases and evaluate genetic relatedness between infections using identity by descent and transmission networks within and between subpopulations at different spatial scales.

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BENCHMARKING IDENTITY-BY-DESCENT CALLERS FOR PLASMODIUM FALCIPARUM

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Genomic surveillance combined with traditional epidemiological analyses is important for identification of at-risk populations for targeted intervention in support of malaria control/elimination efforts. Identity-by descent (IBD) is one population genetic metric used to study genetic relatedness, effective population size (Ne), migration and population structure, and drug resistance-related selection in Plasmodium falciparum (Pf). Despite the wide use of IBD as a metric of genetic relatedness, a comprehensive evaluation of available tools for the identification of IBD segments in Pf has not been performed, and valuable information conveyed by individual IBD segments is not always well exploited. To date, existing IBD quality assessments either focus on the human genome (rather than Pf), use a loose definition of IBD accuracy or are biased toward long segments from pedigree-based simulations. In this study, we performed population-based simulations that account for the high recombination rate and shrinking Ne of Pf, and examine IBD segments spanning a wide length distribution. We benchmarked several IBD callers, including probabilistic (hmmIBD, isoRelate), Identity-By-State-based (hap-ibd, TPBWT), or other (Refined IBD, tree-based) methods, by comparing inferred IBD with genealogy-based true IBD. Our simulations suggest that hmmIBD-inferred IBD segments tend to be less biased for the determination of pairwise total IBD, length-specific population total IBD, and IBD-based demography estimates while remaining sensitive to IBD positional enrichment due to positive

selection. However, hmmIBD suffers from a high rate of false positive short IBD segments (<4cM), which should be excluded in sensitive analyses such as IBD-based Ne inference. Ongoing work will focus on the validation of benchmarking results in an empirical dataset with over 7000 worldwide Pf samples (including MalariaGen Pf6 and an in-house dataset) by evaluating the ability of different IBD callers to capture known selection signals and generate Ne and population structure estimates consistent with existing knowledge for each geographic region.

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THE RISK OF VACCINE GENOTYPE REPLACEMENT FOR PLASMODIUM FALCIPARUM

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Malaria vaccines represent a vital new tool in the fight against Plasmodium falciparum. Vaccines administered to children aim to prevent morbidity, while deploying vaccines to all ages aims to reduce morbidity and transmission, thus accelerating elimination. The first malaria vaccine, RTS,S/AS01, was recently approved, and many anti-infective (AIV), blood-stage (BSV), and transmission-blocking (TBV) vaccine candidates are under development or early clinical trials, such as R21. If targets of these vaccines are not conserved, there is a risk that vaccines confer variable protection between parasite genotypes due to antigen diversity. The risk of spreading vaccine-resistant or partially resistant P. falciparum is unknown, as are the factors promoting this spread. We adapted an individual-based model of malaria transmission to assess the spread of parasites partially or fully resistant to AIV and BSV when deployed to children and the spread of parasites resistant to an AIV when deployed alone or in combination with a TBV to adults or the whole population. For each vaccine type and use case, we assessed which biological, epidemiological, vaccine properties, and deployment factors drive the spread of resistant parasites and the impact of this spread on vaccine effectiveness. We estimated that even genotypes with low degrees of resistance could spread quickly for both use cases. Therefore, developing vaccines targeting conserved antigens and monitoring allele frequency and vaccine efficacy in implementation settings is essential. The estimated spread was faster for BSV than AIV and faster for more efficacious vaccines having longer half-lives and higher initial efficacies. Moreover, while favouring vaccine effectiveness, resistance spread is faster with a higher frequency of vaccine deployment and more extensive population coverage. Deploying a drug with a vaccine both increases the public health impact and reduces resistance spread. Additionally, deploying a TBV with an AIV to the whole population strongly delays the spread of AIV-resistant genotypes and increases the chance of elimination in some settings.

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INFLAMMATORY MARKERS ASSOCIATED WITH IN-HOSPITAL MORTALITY IN CHILDREN WITH SEVERE MALARIA

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Despite treatment with efficacious antimalarial therapy, severe malaria (SM) in children is associated with high mortality. The contributions of different pro- and anti-inflammatory cytokines and chemokines to mortality in severe malaria (SM) is not fully characterized. To better understand the pathogenesis of SM, we evaluated serum levels of 40 markers of inflammation, angiogenesis and chemotaxis by a Luminex assay in 596 Ugandan children 6 months - 4 years of age with severe malaria (SM) and 120 community children (CC). Children with one or more of the 5 most common forms of SM in Uganda (cerebral malaria, respiratory distress, malaria with multiple seizures, severe malaria anemia and prostration) were enrolled in the study. Levels of 21 of the 40 markers tested differed significantly between children with SM and CC ($p<0.00125$). To evaluate which markers were associated with mortality in SM, we compared levels of these 21 markers in children with SM who died (n=43) vs. those who survived (n=553) during the initial admission. Five markers were significantly elevated in children with SM who died compared to the children who survived ($p<0.0024$): a pro-inflammatory cytokine (IL-6), an anti-inflammatory cytokine (IL-1ra), a soluble programmed cell death ligand involved in immune suppression (sPD-L1), and chemokines involved in eosinophil (CCL11) and lymphocyte (CCL20) chemotaxis. In-hospital mortality increased (adjusted odds ratio [95% confidence interval] with natural log increase in the levels of IL-1ra (2.7 [1.57, 4.64]), IL- 6 (1.3 [1.11, 1.55]), sPD-L1 (2.7 [1.58,4.63]), CCL11 (5.2 [2.72,9.95]) and CCL20 (1.94 [1.51,2.49]). The study findings suggest that a complex combination of factors that regulate inflammation and cell chemotaxis contribute to severe disease and death in malaria.

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SEVERE THROMBOCYTOPENIA IS ASSOCIATED WITH AUTOANTIBODIES TO PHOSPHATIDYLSERINE IN *PLASMODIUM VIVAX* INFECTION.

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One of the most frequent hematological findings during Plasmodium vivax infections is a decrease in platelet count. One of the pathophysiological mechanisms proposed to mediate this hematological alteration is the production of autoantibodies directed against components of platelets, in particular phosphatidylserine (PS), which is exposed in the membrane of activated platelets during infections such as malaria. We hypothesized that platelet elimination may be a consequence of a previously described autoimmune response during P. vivax infection that includes anti-PS antibodies (PMID: 32687495). The purpose of this study was to determine the association of anti-PS antibodies in thrombocytopenia during P. vivax infections. An analytical, cross-sectional study was carried out between 2017 - 2019 an endemic area of Tierralta, Córdoba, Colombia. 163 patients monoinfected by P. vivax with different levels of thrombocytopenia were included (P. vivax + mild thrombocytopenia n=42; P. vivax + moderate thrombocytopenia n=53; P. vivax + severe thrombocytopenia n=31; P. vivax without thrombocytopenia n= 37) and 60 healthy volunteers without malaria or thrombocytopenia. Determination of anti-PS antibodies in the plasma of patients was performed by indirect ELISA and confirmation of PS exposure in platelets was determined by flow cytometry using Annexin V. It was found that the levels of anti-PS antibodies in the P. vivax patient group without thrombocytopenia were significantly lower compared to the group with severe thrombocytopenia ($p<0.05$). When comparing all patients in the cohort, the correlation between platelet counts and anti-PS antibodies was inverse ($r= -0.19$, $p<0.05$), with higher PS exposure in platelets from patients with severe thrombocytopenia. The results suggest that anti-PS antibodies binding to PS exposed on platelet membranes during P. vivax infection may be one of the pathophysiological mechanisms mediating the onset of severe thrombocytopenia in patients.

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MULTI-STAGE HUMORAL IMMUNITY TO PLASMODIUM FALCIPARUM MALARIA IN A LONGITUDINAL COHORT OF CHILDREN

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Acquired humoral immunity to Plasmodium falciparum prevents clinical illness. It predominantly targets the blood stages, but antibodies are also acquired to the pre-erythrocytic stage. The relative contributions of antibodies to different life stages in acquired immunity is not well understood, nor whether antibodies to different stages can act additively or synergistically to prevent malaria infection or illness. We have quantified antibodies to merozoites, parasitized RBCs, and sporozoite antigens in a longitudinal cohort of children in Papua New Guinea. We analyzed their acquisition and associations with protection, as well as the relationships between acquired responses. We quantified antibody magnitude as well as functional activity including complement-fixation and activation, antibody interactions with Fc-receptors and phagocytic functions, and growth inhibitory activity. Antibodies to merozoites, including antibodies with Fc-mediated functional activities, were more strongly associated with protection from symptomatic malaria than antibodies to parasitized RBCs, PfEMP1 on the surface of pRBCs, or sporozoite antigens. Associations with protection varied for different antigens, and for different functional antibody response types. Functional antibodies to sporozoites were acquired more slowly and substantial functional activity was only observed among a minority of children. However, higher magnitudes of Fc-mediated functional activities to the most abundant sporozoite antigen (CSP) were significantly associated with a reduced risk of malaria. Further statistical analyses and modelling is investigating potential synergistic effects of antibodies to multiple stages and antigens. These findings provide new insights into protective acquired immunity across the life-cycle of P. falciparum and may help inform the development of multi-stage vaccines for malaria.

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ASSOCIATION OF NOVEL IGG3 ALLOTYPE WITH MALARIA IN CHILDREN FROM SEPIK REGION OF PAPUA NEW GUINEA

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Malaria is a global health burden causing death and severe illness in children under five years of age in malaria endemic regions. Recent work has established the importance of malaria-specific IgG3 in malaria immunity. IgG3 via Fc region binds to Fcγ-receptors (FcγRs) on immune cell surface to instigate immunological defense against malaria. Changes in the amino acid sequences due to single nucleotide polymorphisms (SNPs) of IgG3-Fc regions give rise to IgG3 allotypes which can modulate IgG3 functions. A novel IgG3 allotype, G3m29, was recently reported in pregnant women from Sepik, Papua New Guinea, and has been shown to have enhanced affinity to FcγRIIa. We hypothesized that the prevalence of G3m29 in this population was associated with possible protection from severe or uncomplicated malaria in children. Here, we amplified the Fc region of IgG3 genes by polymerase chain reaction using heavy chain constant domains 2 and 3 specific primers, in a longitudinal study cohort of children aged 1 to 3 years (N=203) with multiple malaria episodes. We performed Sanger sequencing to identify SNPs and compared to the reference alleles of immunogenetics (IMGT) database. We identified that 78% of children in the cohort were either heterozygous (n=82, 40%) or homozygous (n=77, 38%) for G3m29 allotype. We also found a significant decrease in the total number of Plasmodium infections in children with G3m29 allotype compared to non-G3m29 allotype carriers (β= -1.736, 95% CI [-3.39, -0.079], p <0.05) via linear regression. This effect was most pronounced for effects of P. vivax infections. We are presently examining the relationship between allotypes and the levels of antimalarial antibodies and presence of anaemia in these children. Since polymorphisms arise in ethnic and isolated groups and persist in the population because of natural selection, the high prevalence of G3m29 allotype in Sepik region and its association with the number of malaria infections confirms that it is indeed under positive selection and might have a possible role in malaria immunity.

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A CONSERVED EPITOPE IN VAR2CSA IS TARGETED BY CROSS-REACTIVE ANTIBODIES ORIGINATING FROM PLASMODIUM VIVAX DUFFY BINDING PROTEIN

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In placental Plasmodium falciparum infection, VAR2CSA is expressed on the surface of infected erythrocytes (IEs) and mediates their sequestration in the placenta. Antibodies to VAR2CSA are largely restricted to women infected during pregnancy. These antibodies protect women in subsequent pregnancies but in an allele-specific manner. We discovered that VAR2CSA antibodies could also be elicited by P. vivax Duffy binding protein (PvDBP). We proposed that infection with P. vivax in non-pregnant individuals can generate antibodies that cross-react with VAR2CSA. To better understand the specificity of these antibodies, we took advantage of a mouse monoclonal antibody (3D10) raised against PvDBP that cross-reacts with VAR2CSA and identified the epitopes targeted by this antibody. We screened two peptide arrays that span the entire ectodomain of VAR2CSA from the FCR3 and NF54 alleles. Based on the array data, we designed a 34 amino acid synthetic peptide called CRP1 that maps to a highly conserved sequence in DBL3X and overlaps a previously defined CSA binding site. We showed by Isothermal Titration Calorimetry that this peptide can bind directly to CSA, and antibodies to CRP1 raised in rats significantly block the binding of IEs to CSA in vitro. In our Colombian cohorts of pregnant and non-pregnant individuals, at least 45% were seroreactive to CRP1. Most exciting, antibody reactivities to CRP1 and the 3D10 natural epitope in PvDBP region II, subdomain 1 (SD1), were strongly correlated in both cohorts. These findings suggest that antibodies arising from PvDBP may cross-react with VAR2CSA through the epitope in CRP1. These antibodies could contribute to protection against VAR2CSA by blocking a CSA binding site in DBL3X.

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THE PRESENCE OF DUFFY BINDING PROTEIN II PEPTIDES-SPECIFIC CD4+ T CELL RESPONSES IN PLASMODIUM VIVAX PATIENTS

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Plasmodium vivax Duffy Binding Protein region II (PvDBPII) is a leading vaccine candidate against blood-stage vivax malaria. Anti-PvDBPII antibodies potentially block parasite invasion by inhibition of erythrocyte binding. However, knowledge of PvDBPII-specific T cell responses is limited. Here, to assess immunogenicity of PvDBPII epitopes for induction of memory T cell responses in natural P. vivax infections, three cross-sectional

studies were conducted in recovered subjects. In silico analysis was used for potential T cell epitope prediction identified total 492 predicted peptides, which were further selected to obtain 29 peptides with lowest percentile rank. PBMCs from P. vivax subjects were stimulated with selected peptides and examined for cytokine production by ELISPOT or intracellular cytokine staining. From our analysis, six dominant T cell epitopes were identified. Peptide-driven T cell responses showed effector memory CD4+T cell phenotype, secreting both IFN-γ and TNF-α cytokines. Single amino acid substitutions in three T cell epitopes altered levels of IFN-γ memory T cell responses. Further analysis of antibody response to PvDBPII in individuals enrolled for detection of PvDBPII-specific T cell responses showed that 27.8% (5/18) displayed both IFN-γ T cell and antibody response, while 66.7% (12/18) exhibited only IFN-γ T cell response. Altogether, these findings demonstrate the response of CD4+ T cells and antibody to PvDBPII in natural infection. The knowledge of antigenicity could facilitate development of an efficacious vivax malaria vaccine.

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DYNAMICS OF NEUTROPHILS ACTIVITIES ACCORDING TO MALARIA INFECTION STATUS

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Neutrophils are the highest population in human leucocytes. They are considered to be the front-line fighters of the immune system against any invading pathogens including malaria parasites. Over the recent years, more insight has been gained from their role in inflammation. In addition to their phagocytizing property, it has now been admitted that activated neutrophils produce variety of pro-inflammatory cytokines and surface molecules. Recent technology advancement allows haematology analysers to go beyond the simple counting of neutrophils. Their activation status would it be their metabolic activity (cytokines production) represented by their reactivity intensity (Neut-RI) as well as their density or complexity (phagocytosis), represented by the cell's granularity (Neut-GI) can be differentiated. To elucidate that question, we assessed the neutrophils activation status in healthy, asymptomatic and symptomatic malaria in children aged between 3 months to 14 years. Blood samples were collected for full blood count and malaria microscopy. Among the 902 participants recruited, the prevalence of asymptomatic malaria (AM) cases, no malaria (NM) and clinical malaria (CM) were respectively 42.57% (384/902), 38.47% (347/902) and 18.96% (171/902). Regarding the neutrophils metabolic activity, Neut-RI were significantly ($p<0.001$) higher in CM compared to both AM and NM as well as in AM compared to NM ($p<0.001$). For the phagocytizing activity, the Neut-GI were significantly ($p<0.001$) higher in CM compared to both AM and NM participants while the difference was not significant ($p=0.3$) between NM and AM groups. There was a significant positive correlation ($\rho=0.30$, $p=0.0001$) between the metabolic or cytokines production activity with malaria parasite density in clinical malaria (CM) while this was not the case for Neut-GI ($\rho=0.04$, $p=0.6$). The metabolic activity of neutrophils is enabled regardless of the symptomatic status of malaria, whereas their phagocytizing activity is primarily seen in symptomatic cases. Furthermore, the metabolic activity is positively correlated with parasite density in malaria clinical manifestations

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BRAIN SEQUESTERED M1-LIKE MACROPHAGES EXPRESS ABUNDANT LEVELS OF CD163 DURING EXPERIMENTAL CEREBRAL MALARIA IN MICE

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Brain sequestered macrophages are one of the mediators of the pathogenesis of experimental cerebral malaria in mice. Likewise, accumulation and sequestration of macrophages in the brain during human cerebral malaria has also been reported. Despite their prominent role in cerebral malaria, the macrophage population(s) involved in malaria pathogenic processes remain poorly defined. Macrophages polarize into proinflammatory classically activated M1 macrophages or anti-inflammatory alternatively activated M2 macrophages. We examined macrophage polarization by measuring the expression of M1 markers (CD80 and CD86) and M2 markers (CD163 and CD206) on brain sequestered CD11b+F4/80high macrophages during the cerebral phase of a Plasmodium berghei ANKA infection in mice. Flow cytometric analysis showed that 82% of brain sequestered macrophages coexpressed the M1 markers CD80 and CD86. However, the majority (93%) of these CD80+CD86+ brain sequestered macrophages also expressed CD163, a scavenger (mainly hemoglobin/haptoglobin) receptor and a known marker for immunosuppressive M2c macrophages. In contrast, a minority (7.3%) of CD80+CD86+ brain sequestered macrophages expressed CD206, the mannose receptor and a known marker for immunomodulatory M2a macrophages. Our results suggest that brain sequestered macrophages may have an intermediate phenotype with mixed M1 and M2 features and CD163 may function to diminish the inflammatory response of M1-like (CD80+CD86+) brain sequestered macrophages because of its ability to produce anti-inflammatory heme metabolites. Lastly, due to exclusive expression on the monocytic lineage and abundant expression on macrophages at sites of inflammation, CD163 is currently being assessed as a target of immunotherapy for cancer and autoimmunity and also warrants consideration as a target of adjunctive therapy for cerebral malaria.

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IMPACT OF PLASMODIUM FALCIPARUM MALARIA ON SARS-COV-2 ANTIBODY RESPONSES IN KENYA AND BURKINA FASO (MALCOV)

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To investigate the impact of malaria co-infection on serological responses to SARS-CoV-2, we enrolled a cohort of 708 COVID-19 patients in Kenya and Burkina Faso, 139 (20%) of whom also had malaria. Median age was 33 years (IQR 24, 46), 10% were under age 15. We measured IgG antibody response against SARS-CoV-2 nucleoprotein (NP) and receptor binding domain (RBD) on days 1, 3, 7, 14, and 28 with a multiplex bead assay. Antibody responses with median fluorescence intensity (MFI) of ≥5000, >2000-5000, and ≤2000 were considered positive, intermediate and negative, respectively. At enrolment, 16.5% were positive for IgG against

both antigens simultaneously, 3% intermediate, 40% negative, and 40% had mixed responses to the different antigens. By Day 28, these were; 65% positive, 0.7% intermediate, 6% negative, and 29% mixed responses. Overall seropositivity at Day 28 was higher for NP than RBD (84% vs 67%) and lower in patients with recent or sub-patent (rapid diagnostic test-HRP2 positive, microscopy-negative) or patent malaria infection (microscopy-positive) than in malaria negative patients: 53%, 49% and 71%, respectively. The difference was mainly seen for RBD (NP: 75%, 77% and 88%; RBD: 53%, 49%, and 73%, respectively). There was no difference in the magnitude of antibody response in seropositive patients by malaria status. SARS-CoV-2 seroconversion occurred within one month in 35% of patients, regardless of the antigen. Persistent seropositivity, starting and remaining seropositive, was similar for RBD and NP (34% vs 29%), but persistent seronegativity was higher for RBD (15% vs 3.6%). Malaria co-infection had a limited impact on seroconversion. The largest observed difference was in the seroconversion to NP between patent malaria and malaria-negative patients: 45% vs 37%, respectively. Overall, antibody responses to SARS-CoV-2 RBD were lower than to NP. The effect of malaria on SARS-CoV-2 antibody response was dependent on antigen; there was no discernible effect on the response to NP, but responses to RBD were lower in individuals with patent or recent/sub-patent malaria.

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LOCAL GUT MICROBIOTA TOLEROGENIC HOMEOSTASIS NEGATIVELY IMPACTS ANTI-PLASMODIUM SYSTEMIC IMMUNITY

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Our laboratory researches the relationship between severe malaria and gut microbiome in mice. For that, we use Plasmodium yoelii and C57BL/6 mice from different vendors, which is sufficient for presenting diverse phenotypes in severity terms, recapitulated by introducing cecal or fecal material from the hyper-susceptible into the regular mouse, as well as onto germ-free mice. Although the causality is well established, the mechanisms are yet to be completed. Recently, we have shown that hypersusceptible mice present early contraction of germinal centers and consequently the lower quality of antibodies, leading to a parasitemia curve of 28 days instead of 14 and reaching up to 80% parasitemia instead of 20%. Tregs and T follicular regulatory cells are increased in the Peyer Patches and spleens of hyper-susceptible mice compared to the regular mice. Although both mice produced IL-10 on the serum and spleen on days 5-7 post-infection, the susceptible mouse failed to produce IFN-g, whereas the regular mice have a classic IFN-g/IL-10 ratio. To further evaluate the tolerogenic nature of the microbiota in the hypersusceptible mouse, we used sub-colitis doses of DSS, and they presented resistance to weight loss. In contrast, the regular mice showed weight loss and blood in their feces. Purified IgA-bound bacteria from the susceptible mice can recapitulate the phenotype in the regular mice. 16S sequencing of the IgA-bound bacteria presents an enrichment of invasive bacteria capable of causing septicemia in humans and rodents. These results provide insights into the impact of the gut microbiota on systemic immunity, an essential factor to consider in developing optimal malaria treatment and vaccines.

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ROLE OF IGE RESPONSE AGAINST MALARIA INFECTION IN CHILDREN UNDER FIVE YEAR OLD, LIVING IN MALARIA ENDEMIC RURAL AREA OF BURKINA FASO

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Despite these various measures, malaria remains one of the major health problems in the world, mainly due to the various forms of Plasmodium, as well as to the increase in resistance of vectors to insecticides and parasite to antimalarial drugs. The understanding of IgE responses dynamic, in children living in endemic area may help to optimize design interventions tools that could be used in malaria vaccine development. This study aimed to assess the relationship between IgE responses to Plasmodium falciparum and incidence of clinical malaria in children naturally exposed to malaria infection in Saponé (Burkina Faso) It was a secondary analysis of blood samples collected in 2007. Samples were collected during malaria low transmission season and at the peak of the high transmission season in malaria endemic area of Saponé, Burkina Faso. Sandwich ELISA was used to quantify IgE antibodies. Thick drop and blood smear were used for microscopic diagnosis of malaria. We combined levels of IgE to P. falciparum in plasma samples from 325 children with age, P. falciparum density, malaria transmission season and incidence. IgE quantification shows that IgE responses were higher among the parasitized children compared to non-parasitized. The means of IgE were respectively 1079.924 IU (CI95%= 943.8103 -1102.744) for parasitized children and 899.1933 IU (CI95% =718.0199 – 918.5753) for non-parasitized (p=0.045). In additional, the results show a statistically significant difference in IgE production during the two malaria transmission seasons. The mean IgE were respectively 993.25 IU (CI 95% =986.74- 1169.76) during low transmission and 854.37 IU (CI 95%=692.98-885.77) for high transmission season (p= 0.000134). IgE responses increased with age in both low and high malaria transmission seasons with respective p=0.00196 for low transmission and p=0.0531 for high transmission. In conclusion, IgE antibodies were produced in malaria infection. Its responses were associated with P. falciparum density, malaria transmission season and age. Key words: malaria, IgE, age, season of transmission and P. falciparum density.

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COMPARATIVE ANALYSIS OF PLASMODIUM FALCIPARUM TRANSCRIPTOME PROFILES REVEALS UPREGULATION OF HEAT SHOCK PROTEINS AND KINASES IN PEDIATRIC SEVERE MALARIAL ANEMIA

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The rapid emergence of resistance to anti-malarial therapy calls for the exploration of more anti-malarial drug targets to boost existing therapies. This can be achieved by harnessing vital pathways for the survival of Plasmodium parasite, the causative pathogen of malaria, in both the arthropod vectors and human host. Heat shock proteins (HSPs) and their co-chaperones are components of such vital pathways in P. falciparum parasites. The HSPs regulate the folding and stabilization of their client proteins that are essential for the parasites to survive temperature changes in the host during febrile illness. Among the client proteins of these HSPs are kinases, which have been shown to play roles in mediating the motility of sporozoites towards the liver cells and the subsequent attachment and entry into the hepatocytes. In addition, the egress of merozoites, infection of red blood cells and the adherence of the parasites in the endothelial vessels are equally dependent on kinases. To determine if parasite gene

expression levels of these proteins are associated with severe malarial anemia [SMA, hemoglobin, Hb, ≤6.0g/dL] pathogenesis, we examined P. falciparum transcriptome profiles derived from whole blood samples from two groups of pediatric malaria patients in Siaya County Referral Hospital, Kenya: SMA (n=20) and non-SMA (Hb>6.0g/dL, n=40). Our data reveal significant (P<0.05) upregulation of transcripts for the following P. falciparum HSPs and kinases in children with SMA: HSP110 (Log2foldChange=1.19), HSP90 (Log2foldChange=2.26), HSP60 (Log2foldChange=4.2), HSP40 (Log2foldChange=1.67), guanylate kinase (Log2foldChange=2.13), serine/threonine protein kinases (Log2foldChange=1.19), pyruvate kinase 2 (Log2foldChange=2.35), and phosphoglycerate kinase (Log2foldChange=1.58). Collectively, these findings provide novel information about the differential regulation of Plasmodium HSPs and kinases in SMA pathogenesis, and have the potential to facilitate the identification of new therapeutic targets, particularly for severe cases.

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PERIPHERAL BLOOD TRANSCRIPTOME PREDICTS ALTERED UBIQUITINATION PROCESS IN KENYAN CHILDREN WITH SEVERE MALARIAL ANEMIA

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Malaria remains one of the leading causes of childhood morbidity and mortality and manifests as severe malarial anemia [SMA, hemoglobin (Hb)<6.0g/dL] in western Kenya. Our recent studies revealed differential gene expression profiles of the host ubiquitination process in children with malarial anemia and temporal expression changes following ingestion of malarial pigment (hemozoin) by peripheral blood mononuclear cells. We extend these findings by determining the host transcript profiles of human ubiquitination process genes in children with non-SMA (Hb≥9.0g/dl, n=41) and SMA (n=25) presenting at Siaya County Referral Hospital in western Kenya. Total RNA was isolated from peripheral blood collected upon presentation at hospital for acute malaria prior to treatment. RNA sequencing was performed with coverage of >20 million high-quality mappable reads using the Illumina NovoSeq platform. Sequence reads were mapped to the human genome (GR-Ch38) using the STAR software. Differential gene expression analysis between the two clinical groups was performed using the EdgeR package. A MetaCoreTM network-building algorithm was used to identify direct functional interactions of significantly differentially expressed genes (DEGs). Results revealed 40 ubiquitination process DEGs (Padjust≤0.050) of which 26 were up-regulated and 14 were down-regulated in children with SMA. Specifically, 3 genes displayed a magnitude ≥1.5 fold-change (up-regulation) in SMA: UBE2H (Padj.=4.68E-19), RNF123 (Padj.=2.47E-10), and DDB1; (Padj.=9.73E-15). Functional analysis identified the βTrCP-MDM2-UBE2D2-UBE1L2-UBE2D1 network with UBE1L2 and MDM2 as central divergence and convergence hubs, respectively, both with 6 direct interactions. The top gene ontology process that emerged was Protein Ubiquitination (P=1.79e-60). Collectively, these results reveal DEGs in ubiquitination processes in children with SMA, suggesting that altered ubiquitination appears central to the pathogenesis of severe Plasmodium falciparum malaria.

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DIFFERENTIAL ANTIBODY RESPONSES TO DUAL-BINDING PFEMP1 ANTIGENS IN MALIAN CHILDREN WITH SEVERE MALARIA USING A CUSTOM PROTEIN MICROARRAY

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Plasmodium falciparum erythrocyte membrane protein-1 antigens (PfEMP1s) play an important role in virulence and immune evasion. Antibodies against PfEMP1s have been associated with protection from severe malaria, and distinct gaps in antibodies have been shown in children with cerebral malaria (CM) and severe malarial anemia (SMA) compared to uncomplicated malaria. We conducted a case-control study of severe malaria in Mali, West Africa, including cases of CM, SMA, and concurrent CM + SMA matched to uncomplicated malaria controls with and without a history of severe malaria. Controls were matched on age, sex, ethnicity, and date of presentation. We have recently found that cases of severe malaria had higher expression of PfEMP1s that bind both endothelial protein C receptor (EPCR) and intercellular adhesion molecule 1 (ICAM-1). We tested the hypothesis that children with severe malaria lack antibody responses to these dual-binding PfEMP1s. Sera was collected at the time of acute illness, during convalescence at day 21, and in the dry season after illness. We fabricated a custom protein microarray containing 158 PfEMP1 fragments from the 3D7 reference genome and 78 fragments from PfEMP1s associated with severe malaria. We selected PfEMP1 fragments containing consecutive domains from domain cassettes (DCs) previously associated with severe disease, including DCs 1, 4, 5, 8, 13, and 15 from the lab strains IT4, HB3, and Dd2 as well DCs 8 and 13 from clinical isolates collected from Malian children. Serological responses to these fragments were measured in 88 cases of severe malaria, including 57 that were matched to uncomplicated cases of malaria. Serological responses were also compared at the time of acute illness to day 21 of convalescence and to the dry season following infection. The results of this study could inform the design of vaccines and treatments against severe malaria.

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ASSOCIATION BETWEEN THE GUT MICROBIOME AND MALARIA INCIDENCE IN INFANTS LIVING IN MALAWI

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Studies in infants living in malaria-endemic regions have suggested a role for the gastrointestinal microbiome in establishment of Plasmodium infection, disease progression, and severity of infection. We hypothesize that malaria infection impacts the developing microbial community in infancy and, conversely, disruptions in the gastrointestinal microbiome may predispose infants to infections. Using 16S rRNA amplicon sequencing, we characterized the gastrointestinal microbiota in a longitudinal birth cohort in Malawi with active and passive surveillance for malaria infection and clinical disease from birth up to 2 years of age. Clinical malaria was defined as symptoms of malaria and a positive rapid diagnostic test (RDT), and malaria infection as any visit with P. falciparum DNA detected from dried blood spots by qPCR. Rectal swab samples were collected every 6 months, starting at 6 months of age. To identify whether the gastrointestinal

microbiota was associated with occurrence of clinical malaria, we compared the microbial species diversity, as measured by the Shannon Diversity Index (SDI), at 6 months of age in children who had subsequent malaria infections to those who did not. Among 60 children included in the study, 24 had clinical malaria between 6 and 12 months of age with a mean SDI of 2.69 (SD = 0.62) compared to a mean SDI of 2.85 (SD = 0.47) among those without malaria (p = 0.28). To account for the time between measurement of SDI and occurrence of malaria, survival analysis, adjusted for month of year and length-for-age Z score (a predictor of malaria) identified SDI at 6 months as associated with a non-significant decrease in the hazard of clinical malaria during the next six months (HR = 0.71, 95%CI = 0.33,1.54). Further analysis will identify temporal changes in the gastrointestinal microbiota associated with incidence and symptoms of malaria infection in this cohort. Our findings highlight the need to better understand the association between onset of malaria and microbial communities to develop novel strategies to reduce malaria susceptibility in infants.

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DEFINING THE PLASMODIUM PIPECOLIC ACID PATHWAY AND ROLE IN CEREBRAL MALARIA

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Cerebral malaria (CM) is a clinical syndrome and a leading cause of death from malaria, with a fatality rate between 15% to 30% in African children. CM occurs when Plasmodium falciparum infected erythrocytes accumulate within the cerebral microvasculature and cause vaso-occlusion, which is associated with high brain swelling, coma and seizures. The etiology of the coma is not well understood. Our prior studies demonstrated elevated blood pipecolic acid (PA) levels in children with CM and a corollary increase in PA in the brain lysate of mice during experimental cerebral malaria (ECM). PA is a non-proteinogenic amino acid metabolite of the lysine degradation pathway. PA has been associated with neuromodulation in humans and in animal models. Although Plasmodium generates PA, the parasite metabolic pathway is unknown. From this data, we will knock out pathway enzymes and measure pipecolic acid production to confirm the pathway model. Here, we will first confirm the production of PA in P. falciparum under in vitro growth conditions, using a quantitative liquid chromatography-mass spectrometry (LC-MS). Our second goal is to define lysine degradation pathway in P. falciparum using 13C labelled lysine in vitro to trace labeled pathway intermediates that gives rise to PA. Our preliminary data identified three 13-C labelled lysine pathway metabolites: (1) amino adipic semialdehyde. 2) piperideine-6-carboxylic acid and (3) pipecolic Acid. We mapped our model of lysine degradation pathway onto canonical KEGG pathway database which suggested that pyrroline-5-carboxylate reductase 1 (PF3D71357900) enzyme is involved in PA production in P. falciparum. To confirm the role of PF3D71357900 in PA production, we will use pargyline to inhibit PF3D71357900 in vitro. We will use the same labelling strategy to confirm this pathway model in vivo in P. berghei ANKA infected ECM model. This study informs our knockout strategy of pathway enzymes to disrupt PA production and examine the effect of PA on the neurological decline in ECM model.

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MALARIA- INTESTINAL PARASITES CO-INFECTION AMONG CHILDREN IN A LYMPHATIC FILARIASIS ENDEMIC REGION OF GHANA

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Malaria- intestinal parasites (IPs) co-infections are a major problem in tropical regions of the world including Ghana. This is mostly as a result of an overlap in their geographical distributions. Malaria and IPs are a major cause of morbidity in children, having severe consequences on their cognitive development and growth. This study was conducted to determine the prevalence of Malaria and IPs coinfections amongst children in the Ahanta West District of Ghana, a Lymphatic filariasis (LF) endemic region. The Study was done in the dry season where malaria transmission is expected to be low. Again, this region had ceased Mass drug administration for LF control for three years prior. The study utilized malaria rapid diagnostic tests (RDTs) such as NexTek, Bioline and First Response and microscopy to examine stool samples for IP. Out of 113 participants with a mean age of 12.10±2.3, 60 (53.1%) had malaria, 81 (71.7%) had IP, and 45 (39.8%) had malaria-intestinal parasite coinfection. Notably, 22.1% of participants had received malaria treatment three months prior to the study, and 66.4% had dewormed in the past three months. The overall prevalence of malaria, intestinal parasites and malaria-intestinal parasites coinfection were 60 (53.1%), 81 (71.7%) and 45 (39.8%), respectively. This high prevalence of asymptomatic malaria even during the dry season, may hinder current elimination strategies and drive malaria transmission. The impact of Malaria-IP coinfection is multifactorial, therefore, combatting parasitic infections simultaneously is essential to improve the health of these children.

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UNRAVELLING VAR COMPLEXITY: RELATIONSHIP BETWEEN DBLA TYPES AND VAR GENES IN PLASMODIUM FALCIPARUM

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The enormous diversity and complexity of var genes that diversify rapidly by recombination has led to the exclusion of assembly of these genes from major genome initiatives (e.g., Pf6). A scalable solution in epidemiological surveillance of var genes is to use a small 'tag' region encoding the immunogenic DBLα domain as a marker to estimate var diversity. As var genes diversify by recombination, it is not clear the extent to which the same tag can appear in multiple var genes. This relationship between marker and gene has not been investigated in natural populations. Analyses of in vitro recombination within and between var genes have suggested that this relationship would not be exclusive. Using a dataset of publicly-available assembled var sequences, we test this hypothesis by studying DBLα-var relationships for four study sites in four countries: Pursat (Cambodia) and Mae Sot (Thailand), representing low malaria transmission, and Navrongo (Ghana) and Chikwawa (Malawi), representing high malaria transmission. In all study sites, DBLα-var relationships were shown to be predominantly 1-to-1, followed by a second largest proportion of 1-to-2 DBLα-var relationships. This finding indicates that DBLα tags can be used to estimate not just DBLα diversity but var gene diversity when applied in a local endemic area. Epidemiological applications of this result are discussed.

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TRANSCRIPTOME ANALYSIS OF BLOOD-STAGE PLASMODIUM FALCIPARUM REVEALS UP-REGULATED PFHSP70 AND HISTONE TRANSCRIPTS IN SEVERE MALARIAL ANEMIA

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Malaria-related morbidity and mortality remain as significant health burdens in sub-Saharan Africa, accounting for 95% of 247 million cases and 96% of 619,000 global deaths. In Siaya, western Kenya, a holoendemic Plasmodium falciparum transmission region, severe malaria in children <5 years primarily manifests as severe malaria anemia [SMA, hemoglobin (Hb)≤6.0 g/dL]. Although the P. falciparum genome contains multigene families that influence parasite survival, it is largely unclear how differential expression of parasite genes influence human malaria severity. As such, the entire P. falciparum transcriptome was captured in whole blood prior to antimalarial treatment in children (3-36 months) who presented at hospital with non-SMA (Hb>6.0 g/dL, n=40) or SMA (n=20). Next-generation sequencing was performed at a depth of >20 million high-quality mappable reads using the Illumina NovoSeq platform. Reads were mapped to a Kenyan isolate reference genome (pfKE01) using the HTSeq platform, revealing ~3200 distinct P. falciparum transcripts. Differential expression analysis revealed 688 significantly differentially expressed genes in SMA (P<0.05) for which 3 heat shock protein 70 genes and 3 histone genes were upregulated: PfKE01_110038600 (PfHSP70-3, Log2foldChange=1.01), PfKE01_080037100 (Log2foldChange=0.51), PfKE01_090022300 (Log2foldChange=0.70), PfKE01_060023900 (histone PfH2A, Log2foldChange=1.51), PfKE01_110009800 (PfH2B, Log2foldChange=1.40), and PfKE01_060016500 (PfH3, Log2foldChange=1.97). Previous studies illustrate that the PfHSP70 family facilitates parasite proteostasis and protection from cytotoxic drugs, thus mediating parasite survival and potential pathogenesis. The P. falciparum histone family regulates parasite gene expression associated with its developmental stages, with the release of parasite histones into circulation stimulating pro-inflammatory mediators known to influence the pathogenesis of SMA pathogenesis. Collectively, these results support the PfHSP70 and PfHistone families as targets for small molecule inhibitors for novel therapeutic development.

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SINGLE CELL SEQUENCING OF BRAIN SEQUESTERED CD8+ T CELLS DURING EXPERIMENTAL CEREBRAL MALARIA

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Brain-sequestered CD8+ T cells play a prominent role in the pathogenesis of experimental cerebral malaria (ECM) in mice. A recent study has also shown that CD8+ T cells target the cerebrovasculature in children with cerebral malaria caused by Plasmodium falciparum. CD8+ T cells accumulate in the brain during the effector phase of a P. berghei ANKA (Pb-A) infection in mice and promote pathogenesis by inducing apoptosis of endothelial cells of the blood brain barrier. However, the molecular events associated with this CD8+ T cell-mediated pathogenesis remain poorly understood. To better characterize how brain-sequestered CD8+ T cells exert their pathogenic effect, we performed single cell sequencing of the transcriptome of CD8+ T cells isolated from perfused brain tissue of Pb-A infected moribund and non-moribund C57BL/6 mice and uninfected C57BL/6 mice. A single cell whole transcriptome library was prepared from RNA isolated from approximately 50,000 brain sequestered leukocytes that was also labeled with cell (TCRβ, CD3ε, and CD8α) and sample (mouse) specific antibody oligonucleotide conjugates. Approximately 2-2.5 billion clusters were then paired-end sequenced on a NovaSeq S4 PE100 flow cell and bioinformatic analysis was subsequently performed. Genes transcriptionally altered in brain sequestered CD8+ T cells and bioinformatic analyses-based biological pathways associated with the effector phase of ECM will be presented.

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IMPORTANCE OF INSULIN-LIKE GROWTH FACTOR : IGF-1 IN PLASMODIUM VIVAX MALARIA

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Malaria is a public health problem that causes millions of deaths a year. Plasmodium vivax is the most widely distributed etiological agent of malaria in the world. Malaria has been shown to have some relationship to insulin-like growth factor 1: IGF-1 is an important indicator of malnutrition, and acts as an acute phase reactant in infections and inflammation. The objective of this study was to evaluate the plasma concentration of IGF-1 and its relationship with fibrinogen, C-reactive protein CRP, body mass index, and anemia in patients with malaria caused by Plasmodium vivax. 23 individuals with malaria and 20 healthy individuals were included. This research was descriptive and analytical cross-sectional. Study zone: Tierralta, Córdoba, Colombia in a period of six months in the year 2022. Plasma fibrinogen concentration and IGF-1 were determined by ELISA and C-reactive protein was determined by latex agglutination in microtiter plates, using Anthro and Anthro Plus software, individuals were characterized according to height and body mass index according to age. The hemoglobin concentration was determined from automated blood table 7 of IV generation. A thick smear was made to calculate the density of parasites. The fibrinogen concentration increased significantly in patients with malaria (324.03± 59.87 mg/dl, compared to the control group 224.74± 34.88 mg/dl. The CRP increased significantly in patients infected with malaria 21.52± 35.59 mg/l compared to the control 2.43± 0.97 mg/l and the concentration of IGF-1 decreased 45.01± 0.53 significantly in malaria patients, who had a low body mass index, compared to controls. In conclusion, this study suggests that in patients with P. vivax malaria, a greater production of fibrinogen, C-reactive protein is induced, which promotes a decrease in IGF-1, associated with malnutrition and anemia.

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NON-FALCIPARUM SPECIES INFECTIONS AND MALARIA SEVERITY: PRELIMINARY FINDINGS IN HIGH TRANSMISSION SETTINGS IN SENEGAL

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In sub-Saharan Africa, non-falciparum species circulate at low prevalence and density of parasitemia, predominantly in co-infections with the dominant malaria Plasmodium falciparum species. The problematic diagnosis of non-falciparum parasites remains a challenge to accurately estimating their prevalence, contribution to the disease's burden, and potential role in severe malaria. This study assessed the contribution of non-falciparum parasites to malaria severity in Senegal. The study analyzed blood samples of 273 malaria patients (48,4% severe and 51,6% uncomplicated cases) enrolled in 2015, 2017 and 2020 from health facilities in Kolda, Tambacounda and

Kedougou, the three regions of Senegal with the highest malaria incidence. The Plasmodium positivity and Plasmodium species specific composition were determined by molecular methods. R Software was used for statistical analysis of non-falciparum species distribution concerning patients' demographics (age, sex), clinical malaria status (uncomplicated and severe), and the odds ratios of the relative risk of the disease severity associated with non-falciparum species infections. Non-falciparum species i.e P. ovale, P. vivax and P. malariae were retrieved at proportions of 37.36%, 28.20% and 1.83%, respectively, in tested samples. Among the non-falciparum species, P. ovale and P. vivax accounted for 6% of unique infections. Severe and uncomplicated cases are evenly distributed in age groups and gender. P. ovale infection was associated with a significant (OR=0,12) three-fold reduction of severe malaria, while P. vivax in co-infection increased, though non-significant (OR>1), the risk of malaria severity. These preliminary findings support a role of non-falciparum parasites species in the burden of malaria and potentially the severity of the disease in Senegal, and call for immediate attention from the control programs to sustain the limited success gained to date concerning malaria control in the areas.

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ACCEPTABILITY OF TECHNOLOGICAL INNOVATION IN MALARIA VECTOR CONTROL IN MALI: THE CASE OF ATTRACTIVE TARGETED SUGAR BAIT IN THE HEALTH DISTRICT OF KATI MALI

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Malaria is the leading cause of morbidity and mortality in Mali and it's among the ten countries with the highest number of malaria cases and deaths, accounting for 3% of cases and deaths worldwide and 6% of cases in West Africa. In Mali Malaria is endemic, where about 90% of the population is concentrated. Given the increase in resistance to the current generation of insecticides and the behavioral plasticity of the vectors that result in continued transmission of malaria despite the use of insecticide-treated nets (ITNs) or indoor residual spraying. Insecticides with new modes of action are needed, hence the need for Attractive Targeted Sugar Bait (ATSB). This qualitative research explores and assesses the perceptions and community acceptability on ATSB in Mali. Focus group discussions (12) and in-depth interviews (10) were conducted, and a mapping of distrust was done. Data were analyzed using Sphinx software. The results provided an understanding of the factors influencing the supply and community acceptability of ATSBs. Our data also show that ATSBs are perceived in different ways. On the one hand, they are an alternative to vector control. On the other hand, they are subject to mistrust regarding possible long-term environmental risks. Interpersonal communication with community authorities is a guarantee of the acceptability of ATSBs. Some ideas and strategies have been developed for the introduction of ATSBs on a sub-regional scale. The use of ATSBs offers hope in the fight against malaria in malaria-endemic areas. As with any innovation, its full and complete adoption requires a period of appropriation by the users.

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EFFECT OF SEASONAL MALARIA CHEMOPREVENTION ON ASEXUAL PLASMODIUM FALCIPARUM INFECTION IN CHILDREN AGED 5 TO 14 YEARS IN DANGASSA, MALI

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The effectiveness of seasonal malaria chemoprevention (SMC) in reducing malaria-related mortality and morbidity has been demonstrated through several studies. However, its effect on parasite clearance in asymptomatic carriers needs more investigation. This study aimed to determine the effect of SMC on the prevalence of Plasmodium falciparum infection. A secondary analysis was performed using the data from an open randomized study conducted in children 5-14 years in Dangassa to estimate the effect of an additional fifth round to the current SMC regimen (four rounds). A monthly follow up was done from July to December to collect data on parasitemia using smear microscopy in both intervention and control groups. Binomial generalized linear mixed regression was performed to estimate the reduction in the prevalence of P. falciparum infection in children under SMC adjusted on the age groups and the use of long-lasting insecticidal nets (LLINs) with a threshold at 5%. At baseline, the prevalence of P. falciparum infection was similar between the two groups (12.5% for the control group vs 13.4% for the intervention group, p=0.942). After adjusting for age groups and long-lasting insecticidal nets (LLINs) usage, a reduction of 60% in the prevalence of P. falciparum infection was observed in the intervention group (OR = 0.40, 95%CI [0.30 to 0.54], p<0.0001) compared to control group. Stratified by age groups, the same trend was observed with 58% and 61% reduction in prevalence, respectively in children aged 5 – 9 years (OR = 0.42, 95%CI [0.28 to 0.63], p<0.0001) and 10 – 14 years (OR = 0.39, 95%CI [0.26 to 0.58], p<0.0001). Our finding demonstrated the effectiveness of SMC in the reduction of asymptomatic parasitemia carriage among older children in Dangassa. Nevertheless, a large-scale study is warranted to assess the contribution of SMC in malaria transmission.

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FACTORS AFFECTING PREGNANT WOMEN'S ADHERENCE TO INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN THE NANORO HEALTH DISTRICT

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Malaria in pregnancy is still a public health issue despite progresses in case management and prevention. The later includes use of long-lasting insecticide treated nets (LLINs) together with administration of intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP). The national malaria control program (NMCP) has recommended at least 3 doses of IPTp-SP but available information suggests that only 30% of eligible women received this in 2016 despite observed high levels of antenatal care (ANC) attendance. Importantly, adherence to IPTp-SP may be affected by perceptions, acceptability and contextual factors that need to be understood and thus improve the effectiveness of health interventions. Therefore, we conducted a qualitative study to explore the socio-cultural factors limiting pregnant women's adherence to IPTp-SP in Nanoro, Burkina Faso. We have carried out 43 individual interviews and 4 focus groups with 84 people, direct observations between August 2021 to June 2022, targeting pregnant women, husbands, mothers in-low, traditional healers, community health workers and health workers. Participants were selected purposively. Interviews were audio-recorded and transcribed. Data were coded and thematic analysis was conducted using Nvivo 12. The results indicate that although pregnant women have popular beliefs about the causes of malaria, they still rely on medical treatment and do not use traditional care. Adherence to IPTp-SP is compromised by pregnant women's late initiation of ANC visits because they believe that pregnancy does not need biomedical care, as long as they are healthy, they do not need care. Also, the lack of awareness of IPTp-SP, the low perception of the seriousness of malaria during pregnancy by pregnant women, the difficulties related to the supervised intake and the stock-outs of SP are other reasons that explain the low adherence of pregnant women to IPTp-SP. To improve

IPT-SP coverage, awareness for early initiation of ANC should be increased and the conditions of the health facilities offer in terms of maternal health should be improved.

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LARGER FAMILIES ARE LESS LIKELY TO ACHIEVE UNIVERSAL LONG-LASTING INSECTICIDAL NETS COVERAGE IN ETHIOPIA

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In a population with a high risk of malaria infection, using long-lasting insecticidal nets (LLIN) is an essential malaria prevention method. Ethiopia has been distributing LLIN for free. However, ensuring sufficient access and use of LLINs requires close monitoring and evaluation. Hence, this study assessed ownership of LLINs in the Sidama Region in Southern Ethiopia. A community-based cross-sectional study was conducted in February and March 2023. Multi-stage cluster sampling was used to select representative households. We estimated LLIN coverage in terms of WHO's universal LLIN coverage (at least one LLIN for every two people) and national LLIN targets, which aim at 100% LLIN coverage of the population at risk with one LLIN per sleeping space. In addition, the LLIN distribution depends on the family size, with one LLIN for a family size of 1-2, two LLINs for a family size of 3-5, three for 6-7 and four for eight or more family members. We did not assess the quality of the LLIN. A total of 1647 households were included in the study. Most households were led by males (89%), farmers (63%) and persons who were unable to read and write (55%). The ownership of at least one LLIN per household was 85% (95% CI 83.5 - 86.9%; 1405 of 1647 households). About two-thirds (66%) of households had at least one LLIN for every sleeping space, and about half (49%) had the required LLIN per family size. Only 36% of households had universal access to LLIN. Moreover, only 33% of households with children less than under-five years of age or pregnant women had universal access to LLIN. Homes with larger families (Adjusted Odds Ratio (AOR): 8.14 [6.26, 10.58]) and female-headed households (AOR: 3.08 [1.47, 6.43]) were more likely to have unmet universal LLINs coverage. We conclude that the LLIN coverage was low compared to WHO-recommended universal LLIN coverage and national LLIN targets per sleeping space and family size. The National LLINs distribution standard should consider additional LLIN for larger families.

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CAREGIVER KNOWLEDGE AND CONFIDENCE IN SMC EFFECTIVENESS IN NIGERIA

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In 2012, the World Health Organization (WHO) issued a policy recommendation for seasonal malaria chemoprevention (SMC) as an intervention against Plasmodium falciparum malaria. It is aimed to protect children by clearing existing infections and preventing malaria infections during the season of greatest malaria risk. Caregivers are provided with basic information on the purpose of SMC, eligibility of targeted children, importance of SMC doses, duration of treatment and timing of the intervention. Caregivers with more information are likely to adopt positive behavioral change attitudes. Overall confidence in SMC was measured as caregivers' whose children received day1 dose of Sulphadoxine Pyrimethamine+Amodiaquine (SPAQ), importance of day 2/3 doses of Amodiaquine (AQ), what to do if their children experience any adverse drug events, and caregivers who reported confidence in the efficiency of SMC. We assessed knowledge of caregiver against their overall confidence in SMC. Data was extracted from 2022 end-of-round SMC coverage survey and analyzed data of 11,880 caregivers - child peer of sample from nine SMC implementing states of Nigeria. Mixed-effects multivariable logistic regression models were fitted to explore the association between SMC knowledge and caregivers' confidence in SMC. The proportion of caregivers with overall knowledge of the four SMC knowledge indicators assessed was low (56.6%) however, there were high odds of confidence of SMC among caregivers with knowledge of the purpose of SMC (OR: 1.7, 95% CI: 1.3 - 2.4, p<0.001), SMC age eligibility (OR: 1.4, 95% CI: 1.1 - 1.9, p=0.013), importance of receiving day 2/3 doses (OR: 5.0, 95% CI: 3.7 - 6.7, p<0.001), and what to do if their children experience any adverse drug event (OR: 2.1, 95% CI: 1.7 - 2.5, p<0.001). The study shows direct relationship between SMC knowledge and caregiver's confidence in SMC. Therefore, there is need to review SMC messaging either through orientation or direct social behavior change (SBC) intervention to ensure the right information and knowledge permeates the entire community space. This will have a positive influence on effective delivery of SMC.

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UTILIZATION OF LONG-LASTING INSECTICIDAL NETS AT HOUSEHOLD AND INDIVIDUAL LEVELS IN SIDAMA REGION, SOUTHERN ETHIOPIA

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Malaria is an increasing public health problem in Ethiopia, sometimes occurring as epidemics. The utilization of long-lasting insecticidal nets (LLIN) is an essential malaria prevention tool, and there is limited information on its utilization in the Sidama Region in Southern Ethiopia. This study aims to assess LLIN use in rural Sidama. Using multi-stage cluster sampling, a cross-sectional study was conducted in two districts in February and March 2023, including 1,647 households with 8,054 individuals. LLIN utilization was measured by the self-report of sleeping under LLINs the day preceding the survey and was estimated at household and individual levels. Descriptive statistics and binary logistic regression were performed. The mean age of house members was 23 years; half of the participants were males, and 47% could not read and write. Of 1647 households, 85% (95% CI 83 - 87%) owned at least one LLIN, from which 78% (95% CI 76 - 80%) used at least one LLIN the preceding night. However, the individual-level LLIN use showed that only 31% slept under a bed net the previous day. Females (Adjusted Odds Ratio (AOR): 1.5 (1.4, 1.7)) and members from large families (AOR: 1.3; 95% CI 1.1, 1.4) were more likely not to sleep under LLIN. Meanwhile, literate household members (AOR 1.2; 95% CI 1.1, 1.4) were likelier to sleep under bed nets than those who couldn't read and write. Our study shows that the proportion of the population in a malaria-endemic area who slept under LLIN the previous night was far below what is required to control malaria. Furthermore, our study shows that measuring individual LLIN use may give more appropriate information for control than using the household as a unit, as often recommended.

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IMPACT OF SCALING UP SEASONAL MALARIA CHEMOPREVENTION ON COVERAGE AND QUALITY OF IMPLEMENTATION IN KARAMOJA REGION, UGANDA

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Uganda scaled-up seasonal malaria chemoprevention (SMC) using sulfadoxine-pyrimethamine and amodiaquine (SPAQ) to eight districts in Karamoja region, where malaria transmission is highly seasonal targeting 209,405 children under five. This followed a pilot in 2021 that targeted 73,464 children in two districts. Delivery was through a door-to-door approach by village health teams (VHTs), supervised by health workers. In three districts, four cycles were delivered because of delays in finalizing funding arrangements. In five districts, five cycles were implemented in line

with the duration of peak transmission season. This study documented the impact of SMC scale-up on intervention fidelity. We assessed coverage, quality of delivery and beneficiary perceptions through end of round household surveys conducted before and after scale-up. A total of 1863 SMC eligible households were surveyed in 2021 and 1404 in 2022. Review of SMC implementation and adaptation processes and documents were conducted. In 2022, full coverage (proportion of eligible children who received all delivered cycles and the complete 3-day treatment course) was 78.2 % (95%CI: 76.0 - 80.3) across eight districts. Among eligible children who received day 1 SPAQ, 93.1% (95%CI: 91.6 - 94.4) received directly observed treatment (DOT). These were comparable to 2021 when 87.2% (95%CI: 85.2 - 89.1) of eligible children received all five cycles of SPAQ in the two districts, and 97.4% (95%CI: 96.4 - 98.3) received day 1 SPAQ by DOT. Similar to 2021, 98.0% of caregivers reported having heard of SMC in 2022, with VHTs a predominant source of information. Majority (> 90.0%) of caregivers knew the purpose, eligibility criteria, justification for giving SPAQ only to children under five, importance of amodiaquine doses on days 2 and 3, and how to respond when a child experienced an adverse event. Overall, 99.1% and 98.2% of respondents in 2021 and 2022 respectively, felt the program was effective in malaria control. SMC was successfully scaled-up in Karamoja region, increasing its access to beneficiaries at high coverage and quality, while adhering to the adapted implementation model.

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STAKEHOLDER PERSPECTIVES ON INCORPORATING A NEW VECTOR CONTROL TOOL INTO THE KENYA NATIONAL MALARIA VECTOR CONTROL POLICY

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New vector control tools are needed to reduce malaria transmission. It is essential to ensure the new tools reach the market as soon as possible and are accompanied by evidence-based policy recommendations. To complement a trial of the efficacy of a spatial repellent for malaria control, key informant interviews with national malaria control policy stakeholders were conducted. The national policy stakeholders were individuals or organisations that make and/or influence vector control policy and had first-hand knowledge about review, licensing, adoption, and distribution of vector control products. The interviews investigated the factors influencing policy adoption and the role that actors and evidence play in the policymaking process, to draw lessons to help accelerate the uptake of new vector control tools. The interviews were audio-recorded, transcribed, and analysed thematically. Stakeholders outlined the strengths and limitations of existing core interventions comprising long-lasting insecticidal nets, indoor residual spraying, and larval source management. The roles of various individuals and institutions in the processes of formulating vector control policies were also revealed. Upon submission of evidence of efficacy and safety of a proposed new tool, national experts and stakeholders hold discussions and critically analyse its strengths, weaknesses, opportunities, and threats. Additional considerations such as cost, acceptability, usability and complementarity to existing mosquito vector control tools, advocacy and buy in at various decision-making levels and source of funding are also key aspects influencing the adoption and integration of new vector control tools. This study provides insights into the nature of potential problems and solutions for adopting and integrating a new mosquito vector control tool into the national malaria control sphere.

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FACTORS ASSOCIATED WITH INSECTICIDE TREATED BED NET ACCESS AND USE IN SUSSUNDENGA, MOZAMBIQUE

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Insecticide treated bednets (ITNs) are the key malaria prevention tool used in endemic areas. However, there are several barriers to access and use of ITNs in many countries and particularly in rural areas. Mozambique has the fourth highest prevalence of P. falciparum malaria worldwide. Malaria incidence and prevalence follow a gradient of lowest in the south to highest in the north. Manica Province is located in the center of the country and has historically high malaria prevalence with seasonal peaks in incidence following the rainy season. The use of ITNs is the primary malaria prevention method available in this area. The aim of our study was to quantify access and use of ITNs in Sussundenga village, Manica Provice and determine factors associated with both access and use. Ninety-eight (98) households with 302 residents completed the study. The overall malaria prevalence by rapid diagnostic test (RDT) was 31%. Sixty-five percent (65%) of participants reported sleeping under an ITN the previous night. The primary reason given for not sleeping under an ITN was not having any in the household, or not having sufficient numbers for all of the residents of the household. ITN use the previous night was significantly associated with decreased risk of malaria infection measured by rapid diagnostic test (RDT). We constructed several generalized estimating equation (GEE) logistic regression models to quantify individual level and household level factors associated with access and ownership of ITNs, and use of an ITN the previous night. These finding are relevant for informing malaria control campaigns in the area to increase ITN ownership and usage. In 2020 this area was target with a large-scale ITN distribution, aiming to achieve universal coverage in Manica Province. The findings of this study can be used to improve use by identifying factors associated with regular use of ITNs.

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PREDICTING MALARIA INFECTION AND ANEMIA IN PREGNANCY AT FIRST ANTENATAL CARE ATTENDANCE

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Malaria in pregnancy is responsible for adverse effects both on mothers and their offspring's. To tackle these adverse events, WHO recommends the promotion and use of long-lasting insecticide treated nets (LLINs) together with administration of intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP) and appropriate case management through prompt detection and effective management. At least, 4 antenatal care visits (ANCs) and 3 doses of IPT-SP are recommended before delivery. Unfortunately, all these interventions are delivered through the antenatal care (ANC) channels. Knowing the characteristics of pregnant women attending ANC for the first time can help to customize interventions towards this specific group. We therefore, sought to determine the prevalence of malaria infection in pregnant women attending their first ANC visit and the risk factors associated. We conducted a cross sectional survey in 4 health centers of the district of Nanoro and all pregnant women attending their first ANC visit were recruited. Blood samples were collected to assess malaria infection using microscopy as gold standard and haemoglobin level using

HemoCue®. From the survey, less than 14% and less that 7% of pregnant women attended ANCs during the first and third trimester respectively. The prevalence of malaria infection and anemia were respectively 28.2% (n=118/418) and 70% (n=253/416). Being a primigravidae (Adj. OR=3, 95% CI:1.65-5.40) and at the first trimester of pregnancy (Adj. OR=0.28, 95% CI:0.08-0.91) were associated with higher risk of malaria infection. In addition, being primigravidae (Adj. OR=2.00, 95% CI:0.88-4.76), in the second trimester of pregnancy (Adj. OR=1.38, 95% CI:0.55-3.38) and malaria infection (Adj. OR=2.07, 95% CI:1.17-3.73) were strongly associated with the anemia. Socio-anthropologic studies with the objective to understand low and late ANC attendance should be performed and intervention strategies developed accordingly. Scale-up of these interventions is a key entry point for the effectivity of malaria prevention and control in pregnancy.

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IMPACT OF INDOOR RESIDUAL SPRAYING AT THE END OF THE RAINY SEASON IN A HOLOENDEMIC MALARIA TRANSMISSION SETTING IN NORTHERN ZAMBIA: A DEMONSTRATION PROJECT

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Nchelenge District in northern Zambia experiences holoendemic, perennial malaria transmission. Pre-rainy season indoor residual spraying (IRS) has been deployed annually since 2008 with distribution of insecticide-treated nets, yet Plasmodium falciparum prevalence by microscopy remains above 30%. Anopheles funestus is the most abundant vector and peaks in the dry season (May-July). We conducted a pilot trial to assess the effect of adding IRS at the end of the rainy season to the current IRS program on parasite prevalence. Four clusters of households were selected and two were sprayed with clothianidin pre- and post-rainy season; the remaining two clusters were sprayed only pre-rainy season. A total of 401 residents among 65 households were surveyed monthly from March to September. The primary outcome, measured monthly, was the presence of a parasite-positive episode by microscopy. Multilevel logistic regression with adjustment for socio-demographic and geographic variables found no significant difference in the odds of a microscopy positive episode comparing sprayed and unsprayed clusters pre- and post-rainy season spray (adjusted ROR 0.11, 95% CI: 0.01-1.19, p = 0.07). This same model found no significant difference in odds comparing pre- and post-spray at the end of the rainy season (adjusted OR 5.5, 95% CI: 0.57-52.6, p = 0.14). A time to infection analysis using a log-rank test and a Nelson-Aalen Cox proportional hazards model with baseline risk stratification found a statistically significant difference in hazards of a microscopy positive event across the sprayed and unsprayed clusters (log-rank test p<1x10-5). While the second round of IRS reduced hazard rates, we did not find a measurable impact on overall parasite prevalence. Given the limitations of this analysis and the p-value associated with relative odds of parasite prevalence comparing sprayed and unsprayed clusters pre- and post-spray (p=0.07), further investigation is warranted. Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

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FREE-LISTING OF MOSQUITO CONTROL STRATEGIES IN BUSIA COUNTY, WESTERN KENYA

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Additional mosquito vector control interventions are needed, and their potential effectiveness will be improved if user perceptions and practices regarding existing strategies are integrated into their design. To complement a trial of the efficacy of a spatial repellent for malaria control, listing of existing mosquito control products and behaviours was included. The free-lists allowed inferences to be made about the cultural salience of the strategies in the participants' mosquito control domain. Listed products and behaviours will be ranked to help the project understand perceptions of existing mosquito prevention measures. The data obtained will inform the potential and strategies for introducing the spatial repellent at scale. Using a free-listing approach, 61 participants were asked to name all the mosquito control strategies they know. The individual lists were entered into Excel to generate frequencies for each mentioned product. The generated list will be a basis for further inquiry about the items such as when, where, why, how, and by whom these items are used in a ranking exercise. In all, 317 products/behaviours were coded into 47 categories. Participants often mentioned insecticide treated bed nets, mosquito coils, draining stagnant water, creating smoke, and clearing the compound. Other less commonly mentioned mosquito control strategies included spraying insecticide and closing doors/windows early, applying mosquito repellent, and clearing the compound of garbage. The most frequently mentioned strategies were eleven, each mentioned by more than 10% of the sample. Because the spatial repellent is a supplementary tool to existing mosquito control strategies, its introduction must be carried out in a way that optimizes the use of the recommended strategies. The data gathered from the free-listing shows the more widely used strategies and ranking will provide specific insights on characteristics that make those strategies popular. This information will be considered for designing and large-scale distribution of the spatial repellent.

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FEASIBILITY AND ACCEPTABILITY OF GROUP ANTENATAL CARE FOR MATERNAL HEALTH CARE PROVIDERS AND SUPERVISORS IN RURAL HEALTH CENTERS IN BENIN

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Group antenatal care (GANC) is a model in which prenatal counseling and services are delivered monthly to groups of 8-15 pregnant women of the same gestational age starting in second trimester. This allows women to learn while building supportive social networks. GANC can increase uptake of key pregnancy interventions. We examined factors affecting the feasibility and acceptability of GANC for providers and their supervisors in rural Benin, in the context of a study assessing the effect of implementing GANC on uptake of antenatal care under routine programmatic conditions. Six health zone officials and 2-3 ANC providers (midwives, health aides) in each of 20 facilities with ~20-130 new ANC clients/month were trained on

GANC in 2021. Nine months after implementation began, semi-structured interviews (45-90 minutes long) were conducted with purposively selected supervisory health staff (7) and GANC providers (14) from 6 health centers selected to represent both low and high performing facilities with regard to GANC implementation. Data were analyzed through qualitative framework analysis. All participants expressed support for continued implementation and eventual scale-up of GANC. Providers appreciated the opportunity to build closer relationships with patients. They found GANC implementation challenging, particularly scheduling and reminding pregnant women about meetings, starting meetings on time, and accommodating late arrivals. Staffing shortages resulted in GANC meetings being disrupted so facilitators could attend to labor and delivery activities. Supervisors contended that additional supervisory personnel were required to support implementation, especially where there were shortages of qualified providers. Some facilities might need changes to physical layout, to make space for meetings. Providers appreciated the GANC model. Having an adequate number of providers is critical to implementation. Feasibility depends on identifying efficient GANC reminder systems, shortening meetings, and ensuring adequate personnel to support both meeting facilitation and care for emergencies and labor and delivery.

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INFLUENCE OF SEASONAL MALARIA CHEMOPREVENTION ON THE PREVALENCE OF MALARIA INFECTION, PLASMODIUM FALCIPARUM GENETIC DIVERSITY AND RESISTANCE PROFILE IN CHILDREN LIVING IN RURAL AREAS OF BURKINA FASO

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Seasonal Malaria Chemoprevention (SMC) is recommended since 2013 by WHO for the preventive treatment of malaria with sulfadoxine pyrimethamine (SP) plus amodiaquine (AQ) during periods of high or moderate transmission in endemic areas. Chemoresistance and genetic diversity of the parasite are among the major challenges in malaria control. The aim of this study was to assess the impact of SMC on the prevalence of malaria infection, Plasmodium genetic diversity and the prevalence of P. falciparum resistance molecular markers in rural children in Burkina Faso. The study consisted of 222 children participating in the SMC in the Saponé health district. Blood samples were taken for thick drop for microscopic diagnosis and blood spots for molecular analysis at Centre National de Recherche et de Formation sur le Paludisme molecular laboratory. Parasite DNA was extracted using Qiagen kits, the prevalence of malaria infection and genetic diversity were determined by nested PCR while molecular resistance markers were analysed by PCR/RFLP. The prevalence of malaria infection determined by PCR during SMC was 19.7%. The study of genetic diversity revealed a high polymorphism of the parasite during SMC. The prevalence of mutations associated with resistance to SP+AQ was very low in our study. However, the Pfdhfr59 mutation was very high in the study and averaged 92.31% respectively. These results showed a reduction in the mutation prevalence of Pfcrt genes associated with antimalarial drug resistance in Burkina Faso after the implementation of SMC. In addition, SMC contributes to the reduction of the prevalence of malaria infection, affects the genetic diversity of P. falciparum and the distribution of molecular markers of antimalarial drug resistance.

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ASSESSING THE IMPACT OF GROUP ANTENATAL CARE ON INTERMITTENT PREVENTATIVE TREATMENT IN PREGNANCY (IPTP3) UPTAKE IN ATLANTIQUE DEPARTMENT, BENIN: A CLUSTER RANDOMIZED CONTROLLED TRIAL

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In 2020, an estimated 33.8 million pregnancies occurred in malaria endemic areas of sub-Saharan Africa. WHO recommends HIV-negative pregnant women in malaria endemic areas receive at least 3 doses of intermittent preventative treatment in pregnancy (IPTp3). However, coverage remains low at 32%. Group Antenatal Care (GANC) is a service delivery model in which 8-15 women are assigned to a group at their first ANC visit, and subsequent care is provided in the group setting. GANC has been associated with higher quality and greater retention in ANC care. We conducted a cluster-randomized controlled trial in Atlantique Department, Benin, to assess whether GANC improved retention in ANC and uptake of IPTp3. Forty purposively selected health facilities (HF) were randomized 1:1 to control or GANC. Cross sectional household surveys were conducted before and after implementation, among randomly selected women who had given birth in the previous 12 months from each HF catchment, to measure uptake of ANC and IPTp. Changes in coverage were assessed using a difference in difference approach, adjusting for HF clustering. At baseline (N=1259), coverage of at least 4 ANC visits (ANC4) and IPTp3 was 52.8% and 48.0%, respectively, in the intervention arm catchment areas and 44.9% and 49.4% in the control catchment areas. At endline (N= 1280), coverage of ANC4 improved in both arms, to 56.7% in the intervention and 46.1% in the control. Accounting for baseline differences, the increase in the intervention arm was not significant (p = 0.51). Coverage of IPTp3 also increased, to 53.2% (intervention) and 49.7% (control) but was not significant (p=0.26). Only 140 women reported participating in GANC- 99 (15.6%) from intervention and 41 (6.5%) from control arm. Participation in GANC improved coverage of both ANC4 (65.0% vs 50.5%, p=0.002; Odds ratio (OR) 1.9, 95%CI 1.4-2.5) and IPTp3 (64.0 vs 50.6%, p=0.004; OR = 1.8, 95%CI 1.2-2.6). Among women who participated, GANC improved retention in ANC and IPTp3 uptake, but participation was limited. Understanding and addressing the barriers to participation will be critical if GANC is to be used more widely to improve IPTp coverage.

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COMPARING THE DURABILITY OF SYNERGIST LONG-LASTING INSECTICIDAL NETS PERMANET®3.0 AND CONVENTIONAL NETS YORKOOL© IN SOUTHEAST BENIN REPUBLIC AFTER NATIONAL MASS CAMPAIGN IN 2020

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Long-lasting insecticidal nets (LLINs) based on pyrethroids have been important in significantly reducing malaria cases in Africa, but insecticide resistance in Anopheles mosquitoes threatens their impact. The synergists

could help control insecticide-resistant populations. The LLIN PermeNet 3.0 (pyrethroid-piperonyl butoxide (PBO)) is an example. However, the longevity of PBO nets in Benin is not well known. To provide the National Malaria Control Program with evidence of physical and insecticidal durability, two of the LLIN brands deployed in similar districts, Massè (PermaNet®3.0), Adja-Ouèrè (Yorkool®) and Adingnigon (PermaNet®3.0) in the southeast during the 2020 mass campaign were evaluated. This is a prospective cohort study enrolling a representative sample of households six months after distribution. Over a 21-month period, all nets from the campaign in these households were marked and monitored. The primary outcomes were the "proportion of nets in good condition" based on measures of integrity and attrition in years. Insecticide results were determined by bioassay using the WHO cone test. A total of 1559 campaign nets (109% of target) from 546 households were included in the study. Final results could be determined for 70% of the nets in the cohort in Massè, 54% in Adja-Ouèrè and 74% in Adingnigon. After 21 months, all-cause attrition was 31% in Massè, 13% in Adja-Ouèrè and 37% in Adingnigon (p=0.199) and attrition due to wear and tear was 2% in Massè, 5% in Adja-Ouèrè and Adingnigon (p≥0.05). Survival in use at the last survey was 39% in Massè, 53% in Adja-Ouèrè and 45% in Adingnigon (p≥0.05). The multivariate Cox proportional hazards models suggest that the difference between sites was not primarily attributable to LLIN brand. Insecticidal efficacy was optimal for 100% of PermaNet®3.0 tested compared to 67% for Yorkool© after 21 months. In the southeast Benin environment, the PermaNet®3.0 polyester LLIN performed significantly better than the Yorkool LLIN, but both were below a three-year survival rate. Improved net usage behavior should lead to increased physical durability.

6195

PERENNIAL MALARIA CHEMOPREVENTION (PMC) INTEGRATION INTO MOZAMBIQUE'S ROUTINE HEALTH SYSTEM: A PLUS PROJECT CASE STUDY

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Malaria is endemic in Mozambique, accounting for 42.9% of cases among children under five in 2021. To develop a perennial malaria chemoprevention (PMC) model for Mozambique and discuss how PMC could be integrated into Mozambique's routine HMIS, the NMCP led a cascade of multi-day co-design meetings with participation from stakeholders and representatives from various health programs. In November 2022, Mozambique's Ministry of Health (MoH) adopted an overarching malaria chemoprevention strategy, which included PMC. In parallel with the design of a Mozambique-specific model of PMC resulting from the June workshop, additional work was required to fully integrate PMC into Mozambique's routine health system, which included updating paper-based data collection tools and the online HMIS database. A week-long workshop was held in September 2022 to adapt the existing healthy child consultation (HCC) data collection and reporting tools to include PMC data elements. The workshop was also spent discussing monitoring and evaluation plans, such as deciding on key performance indicators (% of sulfadoxine-pyrimethamine (SP) doses administered to target population, % of target population receiving one or more SP doses, % of PMC health facilities reporting no stockout of SP, and number of adverse events notified). Additional technical questions must still be resolved before PMC is fully integrated into the reporting system, such as the time it takes to fill SP information in the new register book column and plans for production of updated HCC register books. Integrating PMC reporting alongside routine health reporting is a vital step to ensuring timely data collection, accurate documentation, and comparable data sharing for this newly approved malaria chemoprevention policy. Results from this case study can be used by other provinces in Mozambique and other countries implementing PMC to ensure compatible data collection and sharing processes.

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EXPLORING NET USAGE, PREFERENCES, AND REPAIR HABITS: A QUALITATIVE STUDY ON MALARIA PREVENTION STRATEGIES IN KONONGO, GHANA

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Understanding insecticide-treated net (ITN) usage and net care and repair (NC&R) are vital for enhancing prevention strategies. There is currently a lack of research on current net usage and NC&R inhibitors, especially among non-net users. This study explored factors affecting ITN usage, preferences, and repair behaviors in Konongo, Ghana. By understanding NC&R habits, overall net retention methods can be improved We conducted 60 in-depth interviews with maximum variation purposive sampling. Participants consisted of 30% non-net users and 70% net users. Interviews covered net usage habits/preferences, NC&R habits/messaging, net damage, and malaria incidence, then qualitatively analyzed using MaxQDA. Average net age and household net count indicated nets were not lasting long and were below the recommended amount. Experiences with net damages were common, with few users attempting repairs. Quantitatively, 40% of net-using households reported net repair inhibitors such as lacking materials or knowledge on how to repair, or exposure to repair messaging. Furthermore, only 13% of families have been exposed to any form of repair messaging. Because of this, the majority of participants expressed a desire for a net repair kit, highlighting a potentially unmet need. A preference for polyester over polyethylene nets suggests comfort and usability impact usage. Non-users cited net damage, heat, and irritation as reasons, revealing areas for improvement in net design, distribution, and education.: In conclusion, To increase net use, it is crucial to address net use, repair, and maintenance inhibitors, and their concerns about heat and irritation. Understanding these factors can also guide targeted interventions and behavior change communication strategies, ultimately increasing overall net retention. Further research is necessary to explore the potential benefits of integrating the provision of materials and education on net repair into standard net distribution programs.

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EMPOWERING COMMUNITY LEADERS TO INFLUENCE ACTIONS AGAINST MALARIA AT HOUSEHOLD LEVEL. LESSONS FROM MOYO DISTRICT, WEST NILE REGION, UGANDA

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Over 90% of Uganda's population is at risk of contracting malaria. The West Nile Region, with an estimated population of 3,404,800 has one of the highest malaria prevalence rates in Uganda at 22% as reported in the Malaria Indicator Survey 2019. Moyo District hosts approximately 23,000 registered refugees, and an unknown number of self-settled refugees, mainly from neighboring South Sudan and Democratic Republic of Congo, posing unique vulnerability to malaria and other diseases. Improving risk perception, building structures, and implementing targeted malaria prevention interventions to empower communities to own the response process requires intense leadership engagement at the grassroots. The USAID PMI Uganda Malaria Reduction Activity (MRA), implemented by JSI, identified high burden villages using HMIS data. Malaria interventions were implemented in 318 households in Lefori and Laropi sub counties in Moyo District. Community leaders were empowered to improve malaria prevention

at household level. Monthly data review meetings were held at the village level led by the community leaders to track progress in malaria response activities. Household malaria response plans were developed, awareness and knowledge on malaria prevention improved. A total of 214 households were followed up ; 85% of the household had children under five sleep under mosquito nets, 80% of the households had pregnant women who attended antenatal care. Data enabled stakeholders to harmonize interventions and implementation approaches, contributing to more effective resource allocation. Community leaders addressed negative myths and misconceptions and social norms that limited community access to correct malaria information and health services. Involvement of leaders, community and health service providers formed an important structure for a supportive environment for households most affected by malaria.

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"AFTER A LONG DAY OF PLAY, I GET TIRED AND FOR GET TO UNFURL MY BEDNET": EXPLORING BARRIERS AND FACILITATORS OF BEDNET USE IN EASTERN UGANDA

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Insecticide-treated bednets are the most common form of malaria prevention throughout the world and understanding the factors that affect their use is critical. Self-reported use may not accurately measure actual practice due to social desirability bias and temporal variations in use. Electronic bednet monitors can provide more precise measures of use. Households in Tororo and Busia districts who were enrolled in an ongoing study with electronic bednet monitors underwent in-depth interviews about bednet use. Household members aged 8 and older were eligible. A survey guide was developed using an Information-Motivation-Behavioral (IMB) framework. A simplified guide was used for children under age 15. Thematic analysis was done using the IMB framework to categorize the data according to barriers and facilitators of use. Fourteen participants from 4 households were interviewed, including 7 adults (mean age: 42 years) and 7 children (mean age: 11 years; range 8 to 17). Ten of 14 participants (64.3%) were female. Facilitators of bednet use included knowledge of bednets as a low cost way to prevent malaria, more rooms in a house and more stable sleeping arrangements. The presence of the electronic monitoring devices was noted to promote bednet use, as were habits such as unfurling the bednet before bed time. Age was a moderating factor, with older people more likely to use bednets compared to the younger children. Barriers to use of bednets included ignorance about the cost of treatment, excessive heat and tiredness after a long day of play for the children. Children depended on parents for bednet use, leading to non-adherence when parents were unavailable. In this qualitative study of individuals undergoing observation with electronic monitoring of their bednet use, multiple factors were identified with heterogeneity between age groups that may present targets for improving bednet use in this population at risk of malaria.

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PREDICTORS OF ACCESS TO SEASONAL MALARIA CHEMOPREVENTION MEDICINES OUTSIDE HOUSEHOLD VISITS IN NIGERIA IN 2021

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In Nigeria, Seasonal Malaria Chemoprevention (SMC) medicines are typically delivered to children under five door-to-door through household visits by SMC community distributors during the high transmission season. Despite this recommended approach, some households access SMC through other means, including fixed point distributions, health facilities and private purchase. However, until now, analysis of access to SMC outside household visits has been limited. Our study aimed to identify household characteristics associated with access to SMC outside household visits. We analysed data from Malaria Consortium's 2021 Nigeria SMC end-of-round coverage survey, covering seven states. We described sources of SMC medicines using weighted percentages and performed univariate and multivariate logistic regression analyses to identify predictors of access to SMC outside household visits. We estimated adjusted odds ratios (AOR) with 95% confidence intervals (95% CIs). Of the 9,491 caregivers of eligible children included in our analysis, 96.32% received SMC, of which 1.36% accessed SMC outside household visits. The three most common alternative sources of SMC medicines were health facility personnel (36.29%), informal distribution in public by SMC distributors (25.81%), and family or friends (16.94%). Univariate model results showed that caregivers with higher educational attainment, being non-partnered, having less SMC-related knowledge, and not using indoor residual spray or mosquito nets were more likely to access SMC outside household visits. In the multivariate analysis with mutual covariate adjustment, we found higher levels of caregiver educational attainment are a positive predictor of accessing SMC outside household visits (AOR 2.30, 95% CI: 1.08–4.89 for post-secondary vs. none/informal) and having a household head born in the local state (AOR 0.46, 95% CI: 0.24–0.86) was a negative predictor. This analysis will be expanded to identify predictors of access to SMC via specific sources, and to explore the potential impacts of different SMC sources on caregiver SMC knowledge and adherence to the full course of SMC medicines.

6200

THE ROLE OF COMMUNITY DRUG DISTRIBUTORS IN THE QUALITY OF SEASONAL MALARIA CHEMOPREVENTION DELIVERY IN NIGERIA

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Seasonal malaria chemoprevention entails the door-to-door distribution of four or five monthly cycles of sulfadoxine-pyrimethamine and amodiaquine (SPAQ) to children 3 - 59 months as a malaria prevention strategy delivered by community drug distributors (CDD). CDDs are responsible for ensuring the first dose of SPAQ is given as a Directly Observed Treatment (DOT) informing the caregiver how to administer subsequent doses of amodiaquine (AQ) of days 2 and 3 and what to do in the event of any adverse reaction. Adherence to the three-day complete course of SPAQ is a measure of quality of implementation and is critical to the impact of the intervention in reducing malaria morbidity and deaths in children. We analyzed reported CDDs compliance with protocol against caregivers' adherence to subsequent SMC doses. Data were collected from 11,188 primary caregivers of eligible children randomly sampled from nine SMC-implementing states in Nigeria during the 2022 end-of-round household survey. Of the 94.8% (10,606) caregivers visited by CDDs, 89.0% (9957) reported CDDs' directly observed them giving the children SPAQ on day 1, 82.1% (9185) of caregivers received information on how to administer days 2 and 3 doses of AQ and 81.1% (9073) on what to do in the event of adverse drug reaction. When CDD-related factors predicting adherence to days 2 and 3 AQ doses among caregivers were analyzed, after controlling for other confounders such as caregiver's background demographics and female peer influencers' visit, caregivers whose SPAQ administration on day 1 was supervised by CDDs were almost 3 times more likely to adhere (aOR = 2.75, 95% CI = 1.69 -4.47 p<0.001), there was no association between those who received information on what to do in the event of adverse drug reactions (aOR = 0.950, 95% CI = 0.53 -1.69 p=0.86) or those who were informed on how to administer Days 2 and 3 doses (aOR=0.89, 95% CI=0.54 - 2.39 p=0.72). The study underscores the importance of CDDs observance of directly observed treatment in caregivers' adherence and highlights the need for further studies on the content and delivery of key messages to caregivers to determine its effectiveness and benefits.

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PERCEIVED FACTORS IMPACTING COMMUNITY HEALTH WORKERS' CAPACITY TO IMPLEMENT SEASONAL MALARIA CHEMOPREVENTION ACROSS DELIVERY SETTINGS: QUALITATIVE SECONDARY ANALYSIS FROM RECENT STUDIES IN MOZAMBIQUE, NIGERIA, SOUTH SUDAN AND UGANDA

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Seasonal malaria chemoprevention (SMC) is the intermittent administration of antimalarials to children from age groups at risk of severe infection in areas of seasonal transmission. Since 2012, Malaria Consortium has been implementing SMC at scale in the Sahel region of Africa as recommended by the World Health Organization (WHO). More recently, SMC implementation has been expanded to new geographies, including countries in East and Southern Africa. During the SMC round, corresponding to the peak transmission period, monthly courses of antimalarials are administered to age-eligible children. Community health workers (CHWs) play a role in SMC campaigns across implementing countries, either as community distributors, in the case of Boma Health Workers (BHWs) in South Sudan and Village Health Teams (VHTs) in Uganda, as community-based support to caregivers, in the case of lead mothers (LMs) in Nigeria, or in other key intermediary roles such as Agentes Polivalentes Elementares (APEs) in Mozambique. Previous studies have looked at the role of CHWs in SMC, however, questions around what factors impact CHWs' capacity to implement SMC across different delivery settings have remained relatively unaddressed. Aiming to bridge this gap, we conducted secondary analysis of recent (2021/2022) qualitative SMC studies in Mozambique, Nigeria, South Sudan and Uganda, comprising of focus group discussion (FGDs) and key informant interviews (KIIs) with stakeholders at various levels of the health system, including CHWs. Thematic analysis is ongoing and preliminary results point to some factors affecting CHWs' capacity to implement SMC across countries: CHWs' proximity to, and rapport with community members and/or caregivers; feasibility of, and synergies between multiple tasks performed by CHWs; level of motivation; areas to cover and number of CHWs; remuneration and allowances; selection criteria. Complete results from this secondary thematic analysis will be presented, focusing on identifiable commonalities and points of differences across delivery settings, to support the development of improved engagement strategies at community level.

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POPULATION DIFFERENCES IN VACCINE RESPONSE: THE ROLE, REVERSIBILITY AND MEDIATORS OF IMMUNOMODULATION BY CHRONIC INFECTIONS IN THE TROPICS PROTOCOL B: THE EFFECT OF INTERMITTENT PREVENTIVE TREATMENT FOR MALARIA WITH DIHYDROARTEMISININ-PIPERAQUINE ON RESPONSE TO VACCINES AMONG RURAL ADOLESCENTS

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Vaccines are key tools for infectious disease control, but several important vaccines differ in immune responses induced, and in efficacy between populations. We hypothesized that malaria infection suppresses responses to unrelated vaccines and that this effect can be reversed, at least in part, by monthly intermittent preventive treatment (IPT) of malaria in high-transmission settings. A randomized, double-blind, placebo-controlled trial was conducted to assess the effect of monthly intermittent preventive treatment of malaria with Dihydroartemisinin-Piperaquine (DP) on vaccine responses. Adolescents 9 to 17 years were recruited from primary schools in Jinja district, Uganda, where malaria is highly endemic, and randomized to monthly DP versus placebo. The DP/placebo was administered monthly, including twice prior to the first immunization. Participants received a standard portfolio of BCG, Yellow Fever (YF-12D), oral typhoid (Ty21a), HPV, and tetanus/diphtheria (Td) vaccines. There were three main immunization days (week 0 (BCG), week 4 (YF - 12D, Ty21a, and HPV), and week 28 (Td)). Primary outcomes were BCG-specific interferon-gamma ELISpot response at 8 weeks post-immunization, vaccine-specific IgG responses to YF - 17D, Ty21a, HPV at four weeks, and Td at 24 weeks post-immunization. The trial was conducted from May 2021 to August 2022. 341 participants were enrolled, 170 in the DP arm and 171 Placebo arm. 145 (85.3%) participants in the DP arm and 140 (81.9%) in the placebo arm were followed up to week 52. At enrolment, 60% of participants had malaria on PCR, this reduced to <5% among participants in the DP arm. The geometric mean ratio of BCG-specific interferon-gamma response at week 8 was 1.19 (95% CI 0.99-1.42) P = 0.064. There was no effect of DP versus placebo on IgG responses to TT (geometric mean ratio (95% CI) 1.12 (0.84-1.48), p=0.44), DT 0.97 (0.83-1.12), p=0.66), Ty21 (1.037 (0.82-1.32), p=0.76). Outcomes for YF-17D and HPV are being processed. IPT significantly reduced malaria in the DP arm. With exception of BCG, IPT did not affect immune responses to Td and Oral typhoid vaccines.

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COMMUNITY PERCEPTIONS ON FEASIBILITY AND ACCEPTABILITY OF SEASONAL MALARIA CHEMOPREVENTION IN AWEIL SOUTH COUNTY NORTHERN BAHR EL GHAZAL STATE SOUTH SUDAN

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Seasonal malaria chemoprevention (SMC) is an effective intervention to prevent malaria infection in children. SMC was implemented in Aweil South County in South Sudan targeting 17,000 children aged 3-59 months. With boma health workers (BHWs) already active in the area, acting as community distributors, children received courses of sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) in five monthly cycles from July to November 2022. A qualitative study to assess the feasibility and acceptability of SMC was conducted at the end of SMC campaign round. We held key informant interviews with national ministry of health officials (3), gender experts (2), community leaders (4), health facilities in-charges (4) and state ministry of health officials (4). We also conducted focus group discussions with caregivers of SMC age-eligible children (6) and BHWs (4). Thematic analysis using an inductive approach was conducted. Most respondents perceived positive impacts of SMC through reduction of malaria cases in children aged 3-59 months. Many reported that acceptance increased over time due to the perceived effectiveness of SMC and use community distributors from the same community. Majority of the key stakeholders cited proper sensitization of caregivers, commitment of the service providers, proper planning, timely logistics supplies, community engagement through sensitization meetings, adequate number of boma health workers to cover vast geographical distances between households, and proper training of boma health workers as key determinants for successful implementation of SMC. Some respondents reported need for gender inclusiveness in household's healthcare seeking behaviors, quoting women as chief decision makers for children healthcare unlike men for non-health related issues in a household. While most stakeholders spoke of the successful implementation of SMC, some implementation challenges were outlined, including the effects of floodings in the area and long distances between households. Many of the respondents asked for SMC to be extended and scaled up to additional areas.

6204

ASSESSING THE IMPACT OF EXTENDING SEASONAL MALARIA CHEMOPREVENTION TO FIVE CYCLES: FINDINGS FROM AN ANALYSIS OF ROUTINE DATA OF 19 DISTRICTS IN BURKINA FASO (2015-2021)

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Seasonal malaria chemoprevention (SMC) typically involves administering antimalarial medicines to eligible children over four monthly cycles, coinciding with the rainy season and period of high malaria transmission. In 2021, five monthly SMC cycles were introduced in some areas with longer high transmission seasons, including 19 of the SMC-eligible districts in Burkina Faso. There is not yet any evidence on impact of the additional cycle under programmatic conditions since 2021. We compared trends and estimates of key malaria outcomes between periods of four and five SMC cycles using routine health facility data (2015 to 2021) of 19 districts that transitioned from four to five SMC cycles in Burkina Faso. Newey-West interrupted time-series analysis (ITSA) was used to explore district-level monthly trends in malaria incidence and deaths from the period of four SMC cycles to that of five cycles. Negative binomial regression models were fitted to compare estimates of mean malaria incidence and deaths between four-cycle and five-cycle years. The models generated estimates of the impact of five SMC cycles relative to four cycles, in terms of incidence rate ratios (IRRs) and their corresponding 95% CIs, while controlling for district-level, time-varying factors such as population growth, health-seeking behaviour, health system capacity and seasonal trends in the outcomes of interest. ITSA trends showed a decline in the peak incidence of RDT-confirmed malaria cases in 2021 following the introduction of the fifth cycle. Compared with the four-cycle years, incidence of RDT-confirmed malaria was 10% lower in the five-cycle years, IRR 0.90 (95% CI: 0.84 - 0.97, p= 0.004). A more substantial decline in malaria-related deaths was observed in the five-cycle years relative to the four-cycle years, IRR 0.06 (95% CI: 0.04 - 0.08, p=0.001). The study provides early evidence on the additional impact of introducing the fifth SMC cycle in areas with longer high transmission seasons. Further research with more robust data over a longer period is needed for a better understanding of impact.

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EVALUATION OF THE LEVEL OF SATISFACTION OF AN INTEGRATED MALARIA INFORMATION SYSTEM USERS IN MOZAMBIQUE

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In 2019, the Mozambique National Malaria Control Program (NMCP) developed and has been implementing an Integrated Malaria Information System (SIIM/iMISS) that enables all NMCP staff to monitor key indicators, assess the impact of interventions and provide evidence for decision making. The study evaluated the level of satisfaction of the SIIM/iMISS among users at provincial, district and health facilities level. A cross-sectional study with data collected using a self-administered online Google survey with the link sent to all 645 active and inactive users. Data collected included access; ease of navigation; impact in improving quality malaria data reporting timeless, completeness and accuracy and usefulness in decision making. The study explored satisfaction of the platform among users and associated factors. Descriptive statistics were used to summarize results and logistic regression was used to examine factors influencing satisfaction. 415(64.3%) users completed the online survey. Majority of respondents (63%) were from the district level. 92.5% are active users. Among active users, 19% were data entrants and over 81% had access to all visualizations and automated analyses (data users). Most user; data entrants (92%) and data users (88.9%) reported SIIM/iMISS to be easy to use and simple to operate. 74.5% of the active users agreed that the use of the SIIM/iMISS has had an impact on the quality of malaria data reported with 99.7% active users reporting that it is useful for decision making. Overall, satisfaction was high with 69.5% of active users reported being satisfied and 24.5% very satisfied. Factors significantly associated with satisfaction included features accessed, and whether the users reported fast data update. Data users were more likely to be satisfied compared to data entrants (OR 3.87) and those who reported no fast data updates were less likely to be satisfied compared to those who reported (OR 0.37). Further improvement to achieve more satisfaction can focus on ensuring access to visualization features even to data entrants.

6206

COMMUNITY DATA USE; PIVOTAL TO IMPROVING THE UPTAKE OF MALARIA SERVICES BY PREGNANT WOMEN AND THE RESILIENCE OF COMMUNITY HEALTH SYSTEMS - THE CASE OF PHCS IN CROSS RIVER STATE NIGERIA

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Accurate, timely, and accessible health data is crucial for data use and evidence-based improvements of essential healthcare services during pregnancy. This study investigates the correlation between the change in some malaria indicators and the establishment of data quality and use teams. The teams were established across 20 high-volume facilities randomly selected in 7 LGAs of Cross River, Nigeria and trained on data quality and use in November 2021. Each team which comprised heads of facilities, record officers, representatives from all service delivery units, and the Ward Development Committee (WDC) held monthly meetings to present data and review the performance of malaria indicators. These routine meetings revealed issues such as low uptake of antenatal care services (ANC) and stock out of Sulphadoxine-Pyrimethamine (SP) in health facilities. The WDC used the data to engage communities on identified issues leveraging community development and religious meetings, and targeted advocacy on SP procurement to key stakeholders. These engagements helped communities mobilize pregnant women (PW) to attend ANC and further donate 10200 doses of SP to 15 out of 20 facilities, demonstrating ownership and resilience. A pre and post (twelve-month before and after the intervention) Wilcoxon signed rank test at 95% confidence level with an alpha value of 0.05 was conducted to assess malaria services uptake indicators for PW drawn from the National Health Management Information System. The findings revealed a significant improvement in PW receiving intermittent preventive treatment in pregnancy - second and third dose (IPTp2 & IPTp3) from 51% to 82% (p =0.008) and 27% to 51% (p=0.005) respectively. Similarly, the proportion of PW attending first ANC before 20 weeks and ANC 4th visit improved from 22% to 32% (p=0.009) and 27% to 40% (p=0.02) respectively suggesting an improved ANC early attendance and retention. The findings of this study support the hypothesis that data-driven community engagement may further improve the acceptability, accessibility, and uptake of ANC services with the potential to address and prevent health and gender inequities.

6207

MENTORSHIP IMPROVES QUALITY OF MALARIA IN PREGNANCY SERVICES IN PMI-SUPPORTED REGIONS IN TANZANIA

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Malaria Services and Data Quality Improvement (MSDQI) supportive supervision assesses the quality of services and competence of health workers at service delivery points including Reproductive and Child Health (RCH) clinics. It is expected that the competence gaps in the provision of quality services during antenatal care visits (ANC) identified during MSDQI assessments can be addressed through mentorship between MSDQI assessments. The PMI Impact Malaria project supported the regional and district health management teams to implement MSDQI at 512 health facilities in Lindi, Mtwara, and Katavi in Tanzania in 2021 using the RCH checklist and identified 47 facilities performing <50% in the key competence indicators of assessment of danger signs, clinical history taking and physical examination, laboratory testing, diagnosis and treatment, and counseling and communication. These facilities were later visited once by trained mentors to strengthen capacity. On average, the MSDQI visits in 2022 following mentorship revealed improvements in indicators from 2021 to 2022: assessment of danger signs (45% vs. 88%); clinical history taking and physical examination (35% vs. 82%); laboratory testing (43% vs. 76%); counseling and communication (65% vs. 82%); and diagnosis and treatment (35% vs. 88%). Facilities with high performance during MSDQI assessments in 2021 that received subsequent MSDQI visits in 2022 without intervening mentorship maintained performance in assessment of danger signs (78% vs. 79%), clinical history and physical examination (75% vs. 76%), laboratory testing (71% vs. 79%), and counseling and communication (91% vs. 90%); overall diagnosis and treatment performance increased from 79% to 90%. In poor performing facilities, mentorship led to improved competence in provision of malaria services to pregnant women.

6208

QUANTIFYING THE ADDED BENEFIT TOWARD MALARIA ELIMINATION BY COMMUNITY CASE MANAGEMENT IN THE DOMINICAN REPUBLIC

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A strong surveillance system is required to achieve certification of malaria elimination. As part of the elimination strategy in the Dominican Republic (DR), community health workers (CHWs) perform community case management in malaria outbreak-affected foci to supplement the passive surveillance system. We present a novel application of the previously reported "Freedom from Infection" (FFI) framework-- a set of surveillance methods adapted to malaria elimination settings that allow: (i) the estimation of the sensitivity of a surveillance system to detect cases in the community (SSe) and (ii) the probability that zero reported malaria cases effectively reflect the absence of transmission (Pfree). We aimed to estimate the added value of CHWs on the health system's ability to detect malaria. Routine malaria surveillance data from passive case detection (PCD) from 2018 to 2022 was collected in 47 health facilities, 9 of which included CHW data. Based on the results of the FFI model with the PCD data only, several facilities exhibited a high degree of uncertainty in the estimated SSe. Despite the high uncertainty, the preliminary results suggest that in some areas, malaria freedom is likely with 21/34 (0.62, 95%CI 0.44, 0.78) health facilities reaching Pfree equal to 1 in at least 1 month of observation based on the PCD data alone. However, where a high Pfree was achieved, it was only sustained between 1 to 50 of the 50 months of observation. When the CHW data was added, two additional facilities reached a high Pfree, and overall, the facilities with CHW data sustained Pfree from 48 to 52 months. The difference in the precision of estimates when CHW data was added to the model was 0.28, or a 0.4-fold increase in precision. Overall, results suggest that the addition of CHW data generally improves the sensitivity of a malaria surveillance system to detect infections if they are present.

6209

OPTIMAL STRATIFICATION STRATEGIES IN THE SELECTION OF SENTINEL SITES FOR AN INTEGRATED MALARIA SURVEILLANCE IN BENIN

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Despite massive investments in recent years, malaria remains the leading cause of care seeking in Benin with an incidence that has plateaued around 20% for several years and high mortality rate among children under 5 and pregnant women. This stagnation questions the effectiveness of current strategies and calls for a paradigm shift towards the improvement of the targeting of interventions. This is the rational of ongoing discussions around the selection of a set of sentinel sites that will allow for an integrated monitoring covering entomological, epidemiological, climatological… dimensions. This research is a contribution to these discussions. It aims to propose a stratification strategy based on the spatial distribution of malaria transmission risks, allowing for a data-informed choice of sentinel sites that ensures the representativity of the entire country in an integrated surveillance system. The methodology used, is based on the World Health Organization's conceptual framework for the control of Malaria from which, we selected several variables deemed to be determinants for malaria transmission. We then estimated a set of linear mixed-effects models on longitudinal data for all the country's districts over the period from January 2017 to December 2021, to confirm the validity of these determinants. Finally, using a hierarchical ascending classification consolidated with the k-means method, we classified the districts of the country, into reasonably homogeneous blocks that can shelter each, a sentinel site. The main contribution of this study is therefore to use statistical methods to propose a dynamic classification tool that allows the user to pick a number of sentinel sites to be operationalized, likely taking into account resource constraints, and to obtain in return, the optimal slicing with the selected number of geographical areas. Crafted on a rational basis, such optimal slicing of the national territory is expected to foster a well-tailored integrated surveillance system generating a better targeting of the interventions, for an effective reduction of the burden of the disease.

6210

IMPROVING MALARIA EPIDEMIC SURVEILLANCE THROUGH ACTIVE ENGAGEMENT OF DISTRICT LEADERS. LESSONS FROM BUSOGA REGION IN EASTERN UGANDA

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The World Health Organization surveillance guidelines 2018 consider transformation of malaria surveillance into a core intervention as one of the pillars of the global technical strategy. In 2001, Uganda adapted and began implementing the Integrated Disease Surveillance and Response developed by WHO for African region member states. However, human resource challenges and technical glitches with the online reporting system as well as stock out of HMIS tools have weakened malaria epidemic surveillance in Uganda. The PMI Uganda Malaria Reduction Activity implemented by JSI, works with the Ministry of Health to strengthen malaria prevention and response efforts at all levels in the five highest-burden regions of Uganda. A broad range of interventions to ensure data completeness, timeliness, and quality are implemented. In Busoga region, beginning in April 2022, technical assistance was provided to twelve districts to improve HMIS reporting rates and address existing data quality gaps. Weekly, surveillance data was shared on reporting rates, malaria diagnosis, case management and malaria commodities stock status. District health, administrative and political leaders from 12 districts were engaged to lead the process of following up with 517 health facilities to address reporting and data quality gaps. Monthly reporting rates improved from 76% between April and June 2022 to 99% between October and December 2022. The weekly surveillance reporting rates further increased from 55% in week 22 of 2022 to 84% in Week 37 and rose to 91% in week 48. As of 2023, in week 3 and week 4, the reporting rate peaked at 93%. District leaders made data reporting a key performance indicator for health facility managers in 9 of the 12 districts. Active participation of district leaders in data management triggers health workers to improve performance. Using data to inspire leaders to be involved in malaria epidemic surveillance and deploying the tools available is a critical approach in settings where human resources are less motivated to document and report quality malaria data.

6211

PLASMODIUM FALCIPARUM MALARIA MOLECULAR INDICATORS IN SOUTH WEST BURKINA FASO: COMPARISON OF ACTIVE AND PASSIVE CASE DETECTION

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The aim of this study was to compare the molecular indicators of P. falciparum during active and passive case detection. Samples of children aged from 1.5 to 12 years were collected from October 2020 to Mars 2021. Children below 5 years benefited on the National seasonal malaria chemoprophylaxis (SMC). All study participants received either supervised curative doses of artesunate (AS) or dihydroartemisinin-piperaquine (DHAPQ) to clear existing parasites prior their enrolment. Active and passive case detection methods were combined to capture all malaria clinical episodes during the follow up. Blood spots were collected and DNA extracted; alleles frequencies and msp-2 genes diversity investigated by nested polymerase chain reaction. A total of 458 (403 for active and 55 for passive cases) P. falciparum isolates collected from 176 participants (38.43%) were genotyped. The mean values of MOI were 2.91 [2.74-3.07] for active and 3.52 [3.04-4.00] for passive visit respectively (p=0.01) and those of FOI in active visit was 1.95 [1.76-2.15] versus 2.38 [1.75-3.01] in passive visit (p=0.16). No statistically significant difference in FOI values (p=0.92) was found between subjects who were on SMC (1.98 [1.57-2.39]) and those who were not (2.00 [1.82-2.18]). On average, 2.98 [2.83-3.14] clones parasitized our subjects during each infection and there was no statistically difference (p=0.75) between subjects on SMC (3.03 [2.69-3.38]) and the other group (2.97 [2.79-3.15]). This study shows that the molecular indicators of P. falciparum were higher in isolates from subjects with symptomatic malaria. Despite the current malaria control tools deployed in young subjects, variant patterns in young subjects, allelic variant profiles identical to those of subjects without SMC coverage are still observed. This may support the current hypothesis that school children should also be the target of malaria control tools.

6212

THE YELLOW FEVER OUTBREAK SHEDS LIGHT ON THE MISSED THREAT OF MALARIA IN ISIOLO COUNTY, KENYA 2022

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Malaria and Yellow Fever can be difficult to differentiate based on symptoms and signs, leading to delayed diagnosis and increased morbidity and mortality. In March 2022, in a suspected febrile illness outbreak in Isiolo, some samples collected were confirmed malaria. We investigated by retrospectively reviewing patient records, conducting malaria data quality audit and surveillance capacity in 16 randomly selected facilities from October 2021 through March 2022. A suspected case was any patient's record that had presented with fever and any of the following - headache, backache, chills, sweat, myalgia, nausea, and vomiting in Isiolo County during the review period, a confirmed malaria case was any patient's record tested positive for malaria through a blood smear test or rapid diagnostic test within the same period. We abstracted data on age, sex, visit date, diagnostic test, and laboratory results. Data Quality Assessment (DQA) evaluated timeliness, completeness, and data. Descriptive statistics utilized means, medians, frequency and proportions. We reviewed 5,527 records from three sub-counties; Garbatula contributed 45.03% (2,489) of the cases, Isiolo 46.35% (2,562) and Merti 8.61% (476) cases. Median age was 15 Years (IQR 5 - 30). Attack rate for ages under five was 6.54% (86/1.315), and above five was 10.87% (458/4,212). Approximately 10.3% (571/5527) cases tested positive — a case attack rate of 2.08 per 1000 population for Isiolo county. Garbatula had highest case positivity rate — 57% (323/571) an attack rate of 4.64 cases per 1000 Population, Isiolo was 1.26 cases per 1000 population and, Merti was 1.01 cases per 1000 population. Undetected case upsurges to alert thresholds noted on the 3rd, 4th and 5th epidemic weeks of 2022. Data completeness was 83% and timeliness 71%. At least 25% (4/16) facilities had significant stock-outs of mRDTs and antimalarials. Weak surveillance systems could have contributed to the missed upsurge of cases. We recommend strengthening support supervision, improving mRDTs access in facilities without laboratories, and redistributing antimalarials to strengthen malaria control and surveillance

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PIONEERING ELECTRONIC FORMS AND REPORTING IN SEASONAL MALARIA CHEMOPREVENTION IMPLEMENTATION AMID INSECURITY IN ZAMFARA STATE

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Malaria is the leading cause of morbidity and mortality in children under the ages of five (CU5) in Nigeria. In Zamfara state, SMC has been implemented among CU5 since 2015. SMC implementation contends with difficulties around payment of SMC personnel (Community Drug Distributors [CDD], health facility workers and Local Government teams) and incomplete submission of data, specifically, with heightened security risks. E-accountability tools - CDD nomination, CDD attendance, call-in data, and in-process monitoring forms were introduced in 2021 to overcome these challenges, and SMC personnel were provided practical training on their use. Throughout SMC implementation, monitoring and supervisory support was provided by state trainers on use of these tools. This assessment compared the SMC implementation processes and outcomes before (2020) and after the introduction of the e-tools in 2021. Deployment of CDDs e-nomination forms reduced the number of days for CDD selection and engagement from 6 to 2 working days, while deployment of the e-attendance increased CDDs daily attendance submission from 5% to over 85%. The daily call-in data received from health facilities on delivery of the SMC drugs increased from 14% to 80% and the field supervisors' submission of in-process monitoring reports increased from 35% to 100%. The duration of personnel replacement reduced from 20 to 3 working days, due to the establishment of a replacement protocol aided by the unique ID numbers linked to every registered personnel. The timeline for payment of SMC actors reduced from 30 to 3 working days. The e-tools improved microplanning by facilitating the inclusion of and provision for CU5 in internally displaced persons (IDP) camps and hard to reach communities. The introduction of e-tools during SMC implementation had a positive impact on overall program management, monitoring, commodity availability, personnel management, and payment processes. This has also contributed to the increased availability of real time data for prompt decision making, cost efficiencies throughout the process and improved SMC delivery including in security challenged area.

6214

INTEGRATING ANTENATAL CLINIC-BASED MALARIA SCREENING DATA AND MATHEMATICAL MODELLING TO CAPTURE THE TRAJECTORY OF MALARIA TRANSMISSION IN WESTERN KENYA IN THE CONTEXT OF THE COVID-19 PANDEMIC.

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In Siaya county, western Kenya, pregnant women are routinely screened for malaria at their first antenatal care (ANC) visit. Since 2016, screening has occurred alongside an all-age continuous household Malaria Indicator Survey (cMIS), providing a unique opportunity to understand how malaria infection trends at ANC map to general population prevalence, a metric by which ~85% of the world's malaria burden is estimated. As with much population-based disease surveillance, cMIS was halted in 2020 in the context of the emerging COVID-19 pandemic. Meanwhile, an insecticide treated net (ITN) campaign scheduled for mid-2020 was delayed to March 2021. In contrast, ANC surveillance remained ongoing and largely unaffected in 2020-2021. We assessed the relationship between ANC and population prevalence using binomial regression. We then incorporated this relationship within an existing dynamical malaria transmission model, using particle Markov Chain Monte Carlo to estimate transmission trends throughout the study period. Through k-fold cross-validation, we show that ANC-based surveillance accurately captured a rapid decline in population malaria prevalence from around 50% to 20% immediately after an ITN campaign in 2017. Our estimates suggest a near thirty-fold reduction in transmission from an entomological inoculation rate (EIR) of ~30 to ~1 during this period. By early 2020, both population prevalence and our estimates of transmission had rebounded to their pre-ITN peaks. During the pandemic, both ANC-based prevalence and our transmission estimates remained near their study-level peak throughout the year-long delay in ITN distribution, declining rapidly from March 2021 when ITNs were eventually distributed. This highlights the utility of ANC-based indicators in providing more granular estimates of population-level trends and as a data source likely to remain more robust to external shocks such as pandemics than other forms of population-based surveillance such as cMIS. These results also provide a quantitative example of the indirect impact the pandemic is likely to have had upon malaria control, transmission, and burden.

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TRACKING PROGRESS OF PROPORTIONAL USAGE ANTIMALARIALS FOR TREATMENT OF PLASMODIUM FALCIPARUM INFECTIONS IN CHILDREN, TWO DECADES OF ARTEMISININ-BASED COMBINATION THERAPY (ACT) POLICY IMPLEMENTATION

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A policy shift to Artemisinin-based combination therapy (ACT) for managing malaria cases contributed substantially to the reduction of malaria burden globally. Unfortunately, in the past few years progress stalls and that plateau trend continues. Possible explanation for the slowing down could be inequalities in the uptake of interventions in specific transmission foci and sector specific performances. Studies suggest that unregulated private sector may allow the use of ineffective antimalarial medicines resulting to poor clinical outcomes. Additionally, undetected poor performance at subnational levels may mislead correct allocation of control strategies, hence, slowing down the progress in malaria control. This work assessed the public-private share and geographical variations of the proportional use of ACT in treatment of uncomplicated P.falciparum infections in children in malaria endemic countries two decades since the recommendation of the policy. Utilizing data from demographic health surveys, hierarchical Bayesian modelling framework were developed and deployed to estimate country-year, sector-specific and subnational distribution of the usage. The models were adjusted for treatment seeking rates, health system, socio-demographic, and environmental factors. Our findings indicate that rural and low-wealth areas have lower uptake of the ACT policy, despite an overall increase in the public sector's share of malaria services from 46.7% in 2001 to 61.8% in 2022. Overtime, use of ACT has significantly improved within both sectors. Over two decades, 79.8% of children treated in public sector received ACT contrary to 67.2% in private sector. Private sector increases in ACT use outpaced public sector increases by 75.6% to 64.5%. Regional, national and subnational variations exist, with the public sector dominating in provision of malaria services in most. SSA countries. In Nigeria, private sector is treating most cases mostly with ACT, however, in the Democratic Republic of Congo, despite public sector treating most almost a third receiving non-ACT.

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SPATIAL AND TEMPORAL VARIATION OF MALARIA CLINICAL INCIDENCE IN CHILDREN UNDER 10 YEARS OF AGE IN KOULIKORO, MALI

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Despite the wide deployment of malaria control interventions during the last decades, we are observing over the last 5 years a plateauing of the number of cases in many endemic countries like Mali. Thus, it is necessary to review and redirect malaria interventions specifically in low and middle-income countries with more malaria. The cost-effectiveness of malaria interventions will depend on the area' level of endemicity and seasonality of transmission. Spatiotemporal analysis of malaria burden variation in Koulikoro health district of Mali was used to determine the variation in malaria indicators such as incidence among children less than ten years of age.A total of 2,916 children were enrolled in July 2021 and followed up to April 2022 (a ten-month period). Households of participants were geolocated at enrolment and for the purpose of spatial analysis, locations were aggregated to 1km2 grid cells to calculate cumulative incidence rates (CIRs) per 100 persons. To assess the temporal variation of malaria both hot spots and cold spots within the study area, we used the Fish Model on SaTScan. To reduce the dimensions of environmental variables and avoid collinearity between environmental factors, we performed a principal component analysis (PCA) in the FactoMiner. Data were collected from all children visiting health care facilities for malaria symptoms using digital tablets. Overall, malaria incidence rate was 4.1 children per month in October and 70% of children had at least one malaria episode during the follow-up period. Peak of malaria incidence was observed in September and November and the maximum number of malaria episodes a child experiences was 4 over 10 months. Recurrent malaria events were frequently observed in villages along the Niger River with a heterogeneous distribution during the transmission season.

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THE VALUE OF END-USE VERIFICATION SURVEYS ON THE AVAILABILITY OF ANTIMALARIAL COMMODITIES IN MADAGASCAR, 2022

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To monitor the availability of quality health commodities in Madagascar, the Malagasy Ministry of Public Health (MOPH) has implemented end-use verification (EUV) surveys—a USAID-funded standardized methodology for assessing the storage conditions and inventory management of antimalarial and other commodities. The USAID Improving Market Partnerships and Access to Commodities Together (IMPACT) project has been supporting the MOPH in conducting the EUV surveys and implementing corrective actions and recommendations in response to survey findings since 2020. EUV surveys are conducted every 6 months in around 100 randomly sampled health facilities: 3% hospitals, 17% district pharmacies (Pha-G-Dis), 64% basic health centers (CSBs) and 15% community health workers in USAID-supported regions with higher malaria incidence. Findings of each assessment are discussed among stakeholders at each administrative level and actions defined to address the challenges. The results of the malaria EUV survey in December 2022 in 109 facilities show that, on the day of the visit, 35% of 23 Pha-G-Dis had an appropriate stock of artemisinin combination therapy (ACTs) for infants, compared to 13% of 18 in May 2022; and 31% of Pha-G-Dis had an appropriate stock of injectable artesunate, compared to 21% in May 2022. From September to November 2022, all 109 structures recorded 0% stock out of ACTs for adolescents compared to 20% in May 2022; 0% stock out of ACTs for adults compared to 14% in May 2022; and 0% stock out of malaria rapid diagnostic tests compared to 7% in May 2022. At the health facility level, 81% of 72 facilities (both CSBs and hospitals) had a formulation of ACTs for children under 5 years old (compared to 76% of 70 facilities in May 2022) and the stock out rate of adult ACTs was 7% (compared to 12% in May 2022). The action plans developed and implemented by regional and district supply chain actors after reviewing EUV survey results have contributed to improvements in subsequent surveys. IMPACT continues to support the Madagascar MOPH in effective use of data for evidence-based decision making.

6218

ENGAGING HEALTH FACILITY TEAMS TO IMPROVE MALARIA DATA QUALITY, USE, AND SERVICE DELIVERY IN AKWA IBOM STATE

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The National Health Management Information System (NHMIS) is one of the six building blocks of health systems that integrates data collection, processing, reporting, and use (WHO, 2010). Data is critical to delivering high-quality malaria services and guides malaria elimination efforts in Nigeria. This study examines the utilization of health facility (HF)-based data quality teams set up in five high-volume HFs in Akwa Ibom state in July 2021. The objective of the data quality teams was to enable HFs to generate and use quality data for improvement of malaria services. The teams were trained and supervised for the first 6 months of implementation and their responsibilities included coordinating facility data validation and triangulation and conducting monthly HF data review meetings. A descriptive quantitative analysis of NHMIS data on the proportion of fever cases tested for malaria and confirmed uncomplicated malaria treated with artemisinin-based combination therapy (ACT) was conducted in the selected HFs for a 3-year period (January 2019 - December 2021). Data availability across the HFs improved from 91% in 2019 to 100% between July-December 2021 when the data quality team meetings were set up and conducting monthly data reviews. The data also showed an improvement in malaria service delivery. In 2019, 72% of data records of fever cases tested for malaria deviated from the national target of 100%; this dropped to 8% between July - December 2021. A similar pattern was reported for the proportion of confirmed uncomplicated malaria cases treated with ACTs, where service delivery gaps reduced from 55% in 2019 to less than 2%. Continuous review of data using HF-based data quality teams presents a sustainable and scalable approach for HFs, fosters continuous use of data to identify gaps, and supports adaptive and improved adherence to standards of care. Implementing this strategy should take into consideration factors that support sustainability and ownership, such as skills transfer from members of the data quality team to all relevant HF staff and continuous on-the-job mentoring from government supervisors to HF teams.

6219

MALARIA MOLECULAR SURVEILLANCE IDENTIFIES CLONAL PARASITE POPULATION STRUCTURE IN DIOURBEL SENEGAL THAT REVEALS TRANSMISSION PATTERNS TO INFORM OPERATIONAL ACTIVITIES

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Ongoing national surveillance of Senegal Plasmodium falciparum infections provides emerging threat detection including drug resistance to inform transmission patterns that can guide intervention use by the Senegal National Malaria Control Program (NMCP). Parasite genetic metrics such as the frequency of clonal and multiple strain (polygenomic) infections, and genetic relatedness are emerging as key indicators for both monitoring transmission trends and identifying transmission patterns for tailoring subnational intervention stratification. We surveyed parasite genetic parameters from Diourbel, a site of moderate transmission (annual incidence ~25 cases/1000/year). Genotyped samples were collected through passive case detection (PCD) at health facilities from 2018 to 2020 (n = 412) and active case detection (ACD) at large residential schools called Daaras in 2020 (n = 120). Based on the PCD samples, infections in Diourbel were unusually clonal and inbred relative to its reported incidence levels. Between 2018 and 2020, we did not observe an increase the frequency of polygenomic infections (0.13 [0.08, 0.20] in 2018 to 0.10 [0.07, 0.15] in 2020). Despite this, infections in Diourbel have become increasingly clonal and inbred over time. The proportion of monogenomic samples infected with a shared clone increased from 0.48 [0.39, 0.58] to 0.83 [0.76, 0.88]) and the relatedness of strains (measured with RH) within polygenomic infections increased from 0.03 [0, 0.08] in 2018 to 0.40 [0.35, 0.46] in 2020. Five persistent clonal parasite lineages were observed across multiple sampling years. This unusual clonal and inbreeding structure was not observed in nearby Touba, which has a similar incidence. Genetic metrics collected through PCD and ACD were similar except for RH, which was 0.10 (0.03, 0.18; compared to 0.40 overall) in the ACD samples collected in 2020. We hypothesize that this unusual population genetic structure represents a unique focal spatial structure in Diourbel and are working with the Senegal NMCP to map the spatial structure of clonal parasite populations to identify transmission sources for intervention targeting.

6220

IMPROVING MALARIA SURVEILLANCE DATA: INSIGHTS FROM SOUTHERN ANGOLA

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Malaria in SADC region has significantly reduced over the last decade. As countries progress towards elimination, it is key to turn surveillance as a core programmatic component not only for first line elimination targeted countries but also for the second line countries which adequate control is essential to sustain elimination goals. In 2020, Angola started to implement aggressive activities focused on improving surveillance for elimination practices in southern border districts with Namibia. Surveillance activities integrated a combined approach that included support to routine collection of monthly reports, on site data quality assessments and on the job supportive supervision. The objective of this work is to highlight the achievements in core surveillance indicators achieved in 3 years of programmatic implementation. Reporting coverage was retrieved from National Health Information System to analyse progress of health facility reporting coverage over time. Information from data quality assessments was extracted from a database and simplified data quality indicators were analysed to understand trends in data quality over time. Results show that none of the 7 border districts targeted for intensive surveillance interventions had an annual reporting coverage above 90% in 2018, 1 in 2020 while all seven targeted districts had reporting coverages above 90% in 2022. Data quality shows that, in 2020, 58% of health facilities had incompletely filled reports whereas in 2022 this proportion dropped to 13%. In 2020 the accuracy of data between the consultation books and monthly reports was 93% but was improved to 99% in 2022. In 2020, 25% of the health facilities visited reported stock out of monthly reporting forms and 39% of consultation books. In 2022, those proportions changed to 5% and 17% respectively. A strong malaria surveillance system is highly dependent on availability and quality of data. Implementation of intense activities focused in improving data accessibility and quality showcase that it is possible to improve the system and sustain those gains over time.

6221

DEFINING PCR-DETECTED PARASITEMIA THRESHOLDS FOR CLINICAL MALARIA FROM ACTIVE AND PASSIVE CASE DETECTION

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Historically, clinical malaria was defined as fever and a blood smear positive for Plasmodium parasites above a defined density threshold. Blood smears have since been replaced by rapid diagnostic tests for diagnosis and more sensitive molecular diagnostic tests for research purposes. Thus, sensitive and specific definitions of clinical malaria using parasite density thresholds based on molecular diagnostics in the absence of blood smears are needed in 1) clinical settings where they must account for community prevalence of infection and 2) community-based surveillance to quantify disease among those not seeking treatment. We calculated the threshold of PCR-detected P. falciparum parasitemia that indicated clinical malaria disease among 1) individuals seeking treatment at health care facilities, and 2) individuals included in active case detection (ACD). Infection was detected by qPCR (18SrRNA) in a cohort of 962 Malawians of all ages who were followed for one year, using monthly active, and continuous passive case detection. ROC curves for the total population and by age were used to identify the qPCR-detection thresholds for 1) clinical care-seeking with fever and positive RDT, and 2) fever measured or reported during ACD. Among 1949 episodes of infection without recent antimalarial treatment, median age was 11y (IQR = 7, 19); median parasitemia was 16.21 parasites/ul (IQR = 2.23, 350.15). There were 283 clinical episodes, with an AUC of 0.89, and the parasitemia threshold identified was 427/ul, with sensitivity and specificity = 0.88 and 0.76. During ACD, there were 487 febrile episodes, with an AUC of 0.72, and the parasitemia threshold was 519/ul, with sensitivity and specificity = 0.88 and 0.51. Thresholds were higher among children under age 5 (634 and 904/ul for the two case definitions, respectively) and significantly lower among individuals over age 15 (40 and 70/ul). Results on predictors of care seeking by age and season will also be presented. While

these thresholds are likely to be specific to our transmission setting, our results highlight the importance of age-specific parasite density cut-offs for clinical disease.

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INTEGRATED AND INNOVATIVE DECENTRALIZED MALARIA RESURGENCE RESPONSES IN THE SOUTH EAST OF MADAGASCAR

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The Ministry of Health (MOH) sub-national team, supported by the National Malaria Control Program (NMCP) and partners conducted a package of response activities to address malaria resurgence in the districts of Farafangana and Vangaindrano in the South East region of Madagascar. The incidence of malaria cases increased from 63 per thousand inhabitants in Farafangana in October-December 2021 to 99.9 per thousand in 2022 in the same period. In Vangaindrano, incidence increased from 188.4 per thousand to 217.4 cases per thousand inhabitants from 2021 to 2022 for the same periods. The response package included: 1) mass behavior change communication; 2) active mass screening and treatment (MSAT); 3) Outreach Training Supportive Supervision (OTSS+) for targeted health facilities;4) in-service training on malaria case management. During the MSAT in Farafangana, 1,808 people of all ages were tested by malaria Rapid Diagnostic Test (RDT). The RDT test positivity rate was 47% and 84% were asymptomatic. In Vangaindrano district, 1,686 were tested by RDT. The RDT test positivity rate was 46.5% and 88% were asymptomatic. Most of these 1808 people tested received sensitizations on the prevention of malaria. In the four health facilities visited in Farafangana, the OTSS+ checklist showed the biggest gaps were register completeness (49%) and simple malaria case management competency (51%). The highest performance was on RDT competency (85%). In the three health facilities visited in Vangaindrano, the biggest gap was simple malaria case management competency (45%). Register completeness (60%) and RDT competency (86%) were slightly higher. Two in service medical training sessions for public and private providers were then conducted and tailored to address the subjects that OTSS+ showed poor performance on. The innovative decentralized response package to the malaria outbreak was accepted by health workers and the population. Malaria services delivery could be evaluated and strengthened through OTSS+. Community level can feasibly conduct mass active response to control malaria transmission in the context of high asymptomatic malaria cases rate.

6223

USING DATA INTEGRATION AND VISUALIZATION TO STRENGTHEN THE MALARIA SURVEILLANCE SYSTEM IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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A robust malaria surveillance system is the backbone of malaria control and elimination. Data integration and visualization are critical components of enabling the use of large volumes of data and answering analytical questions. Integration consolidates data from different sources into a single database. Visualization allows for more intuitive manipulation and interpretation of large and complex datasets. In 2021 in DRC, Bluesquare's open-source data platform, OpenHEXA, was used to create an integrated database using routine data from the National Health Information System's DHIS2, weekly surveillance data from the Integrated Disease Surveillance and Response platform, and environmental data. DRC is now capable of automatically running data integration routines to ensure the most recent version of each data source is used at all times. Analytics dashboards using Tableau software were also developed, allowing an interactive exploration and use of the integrated data. Dashboards include a weekly National Malaria Control Program (NMCP) epidemiological bulletin; analytics down to the health area level to monitor malaria trends, commodities, and data quality; and monitoring of environmental data. Institutionalization of these tools included training Ministry of Health (MoH) staff at all levels of the health system to analyze, interpret, and use malaria data. Changes in data utilization were observed since the introduction of these dashboards at the government stakeholder level, including using dashboards for evidence-based planning of supervision, decision-making on rapid outbreak response, distributing malaria commodities, internal redeployment of malaria commodities between health facilities, identifying data outliers, active monitoring of indicator performance, providing feedback on data quality and on malaria case management data, and reducing data validation violations. Key next steps include integrating entomological data into the data integration and analytics platform, improving spatial granularity down to the health facility level, and improving coverage of trained MoH staff on the NMCP dashboards.

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MODEL-BASED ESTIMATES OF LONG-TERM AND SEASONAL MIGRANTS IN NORTHWESTERN DISTRICTS OF ETHIOPIA

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Human mobility represents a major driver of the spread and persistence in Ethiopia's malaria epidemiology. Large scale movements of seasonal workers between areas of low and high malaria transmission have complicated efforts to reduce disease burden at both ends. In resource-poor farming settings where road transport or mobile-phone based data or large-scale population surveys are lacking, long-term migration patterns correlate with seasonal migration patterns and thus have been suggested for use in quantifying seasonal migration patterns. In this study, we used a five-year (2009-2013), survey-based internal migration dataset covering 78 zones in Ethiopia to develop a spatial-interaction model, and down-scaled estimates of migration to a finer spatial scale, in 816 districts (woredas). We also used the estimates to infer seasonal migration to woredas in northwestern Ethiopia identified as development corridors hosting seasonal workers. Accordingly, there were an estimated 1.53 million (95% CI: 1.51 - 1.56 million) long-term migrants crossing zonal borders annually, while 1.76 million (95 CI: 1.72 - 1.80 million) migrants crossed woreda borders, among them 10.6k (10.2 - 11k) migrated to the northwestern woredas. Based on our association model, this meant 294k (95% CI: 94k - 735k) seasonal migrants arriving at the northwestern woreda annually, which, according to reported prevalence of Plasmodium falciparum among seasonal migrants, translates to 37k (95% CI: 12k - 93k) positive cases returning to their home woredas annually. By applying a previously developed spatial downscaling approach and using secondary data on seasonal migration and prevalence of P. falciparum, our study inferred seasonal migration between a larger set of sources and destinations, thus filling a critical data gap. Results from this study are being used to inform meta-population disease transmission

models crucial in the identification of effective malaria control interventions in the presence of seasonal migration. This work constitutes an important part of the strategic plan aiming at malaria elimination in districts of moderate and low transmission risks.

6225

A SECOND BLOOD MEAL ELEVATES THE PLASMODIUM VIVAX SPOROZOITE LOAD IN ANOPHELES DIRUS SALIVARY GLANDS

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Anopheles mosquitoes become infectious with Plasmodium sporozoites by taking blood from an infected human. The parasites undergo a series of developmental changes in the mosquito and mature to sporozoites capable of infecting the next human. The time duration required by the parasites to develop within the mosquito to become infectious sporozoites, known as the extrinsic incubation period (EIP), is a key determinant of the vectorial capacity of the mosquitoes. During their life span, mosquitoes naturally feed multiple times in order to complete gonotrophic cycles. Previously, our group examined the impact of the second blood meal on P. vivax sporogonic development and observed significantly larger oocysts and shorter EIP in twice-fed mosquitoes. In this study, we further investigated the influence of the second blood meal on the number of salivary gland sporozoites and evaluated the infectivity of these sporozoites. Salivary gland sporozoites were inoculated to a hepatocyte-derived cell line, HC-04, then the number of the liver stage parasites were counted at day 4 and day 7 post inoculation. With the same number of sporozoites per well, there was no significant difference in the number of infected hepatocytes between single and twice fed mosquitoes. From these results, we conclude that the additional blood meal not only accelerates the sporogonic development of the parasite within the mosquito, but also led to a higher number of sporozoites with unaltered hepatocyte infectivity.

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CLONAL TRANSMISSIBILITY AND FACTORS INFLUENCING HUMAN-TO-MOSQUITO TRANSMISSION OF ASYMPTOMATIC PLASMODIUM FALCIPARUM INFECTIONS OVER THE COURSE OF ARTEMISININ-BASED COMBINATION THERAPIES IN MALI

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Plasmodium falciparum malaria infections in high-transmission areas often consist of several distinct parasite clones. Few studies have directly investigated the complexity of Plasmodium falciparum malaria infections in both humans and the mosquitoes they infect. Molecularly undetectable circulating parasite clones were previously found to transmit to mosquitoes, leading to a high complexity of infection in mosquitoes post-feeding. This is likely due to asexual parasite clones being more abundant in peripheral blood than gametocyte clones, the parasite stages responsible for human-to-mosquito transmission. Artemisinin-based combination therapies (ACTs) are the first-line treatment for uncomplicated P. falciparum malaria and eliminate asexual parasites rapidly but have limited activity against mature gametocytes. It is unclear whether certain gametocyte clones persist longer than others post-ACT and whether there are any genetic characteristics that may influence their transmissibility. Using next-generation multiplex amplicon sequencing targeting heterozygous regions in Pfcsp and Pftrap, we analysed complexity of infection in human blood samples at six timepoints over the course of an ACT and in the midguts of the mosquitoes that became infected in membrane feeding experiments using the same blood material at these different timepoints. We found that after the elimination of asexual parasites by the ACT, parasite clones in human blood and cognate mosquito midguts largely match, although there is still some transmission of molecularly undetected circulating clones. In addition, data will be presented on genetic factors that may influence the level of transmission, such as molecular markers of drug resistance in Pfcrt, Pfmdr1, Pfdhps, Pfdhfr and PfK13 and genetic variability in the P. falciparum surface protein Pfs47 and the Pfs47 midgut receptor, by which parasites that express a compatible Pfs47 haplotype can evade the mosquito immune system.

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STUDY OF AN IMPORTANT GENE FOR SEXUAL REPRODUCTION OF PLASMODIUM BERGHEI AS A POTENTIAL TARGET FOR BLOCKING MALARIA TRANSMISSION

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Through advances in genomics, proteomics and transcriptomics, currently studies analyzing these tools in search of new targets for potential drugs and vaccines are increasingly present in academia. Important targets to be studied are proteins involved in the life cycle of the protozoan Plasmodium, the malaria-causing agent, for potential vaccine formulations, such as vaccines with the transmission-blocking strategy. Recently, our research group identified a group of genes from P. berghei, conserved in different Plasmodium species, as essentials for the fertilization of the protozoan during its sexual reproduction phase. This project aims to deepen the studies on one of these genes and the protein it encodes, producing it recombinantly for antibody production, with the purpose of studying whether these antibodies would be able to inhibit protozoan fertilization, thus characterizing the protein as a potential candidate for the development of a transmission-blocking vaccine. Previously, a P. berghei ANKA knockout parasite was constructed for the studied gene. This knockout was carried out in a parasite previously constructed in the laboratory that has the luciferase gene linked to its ookinete formation process (PbOokluc). After obtaining the knockout, the characterization of the parasite phenotype was carried out through tests of parasitemia and gametocythemia curves, ookinete conversion and exflagellation assays. After these results, it was observed that the knockout parasite has a lower ookinete formation rate when compared to the Ookluc parasite. To obtain the recombinant protein for antibody production in mice, protein expression was performed in cultures of E. coli BL21 bacteria, and the protein is currently being purified so that it can be inoculated in mice for antibody production. After this step, it is expected to use these antibodies in P. berghei Ookluc parasites submitted to conversion assays to observe whether these antibodies are capable of inhibiting the sexual reproduction of the parasites.

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EVALUATION OF THE ACTIVITY OF ESSENTIAL OILS OF HYPTIS SPICIGERA LAM. AND OCIMUM AMERICANUM L. IN THE MALARIA TRANSMISSION BLOCKING

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Medicinal plants are widely used, and many of them have already proven their therapeutic effects through scientific studies. African populations in developing countries rely greatly on medicinal plants for their healthcare. Malaria remains a global public health concern, with 247 million cases registered in the world in 2022 and 95% of which occurred in Africa (WHO, 2022). Control methods are developed continuously because of resistances observed with antimalarial drugs and insecticides. In the present study, we

assessed the antimalarial activity of essential oils from two medicinal plants of Burkina Faso.Hydrodistillation was performed on fresh leaves of Hyptis spicigera Lam. and Ocimum americanum L. collected in the Hauts-Bassins region of Burkina Faso. In a Direct Membrane Feeding Assay, lab-reared mosquitoes were fed with gametocytemic blood supplemented with the essential oils; control group only received plain gametocytemic blood. Seven days later dissection was performed, and oocysts prevalence and density were determined. H. spicigera had a density of 1 and a prevalence of 1.42%. O. Americanum had a density of 0.72 and a prevalence of 3.13%. As for the control group, density was 33.8 and prevalence was 54.5%. The transmission blocking activity was 97.17% and 92.22% for H. spicigera and O. americanum respectively.These results confirm the potential of medicinal plants in malaria control.

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MALARIA VECTOR NUTRITION PREDICTS RATE OF PLASMODIUM FALCIPARUM DEVELOPMENT AND INFECTIVITY

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The malaria parasite Plasmodium falciparum must complete an intricate series of cell traversal and differentiation steps within the mosquito to enable transmission to the human host. This complex journey from the mosquito midgut to the salivary glands involves multiple parasite developmental stages and is fueled by mosquito nutritional resources that vary by environment. The rate of parasite development in the mosquito is a key determinant of malaria transmission because mosquito lifespan is short. Here we used single-cell RNA sequencing and in vitro hepatocyte infection to evaluate developmental progress of salivary gland sporozoites as a function of adult mosquito nutrition. Salivary gland sporozoites represent the final stage of parasite transcriptional and translational preparation for human liver infection. We specifically compared parasites developing in Anopheles gambiae mosquitoes provided with a single infectious blood feed (1BF) vs. an additional non-infectious blood feed 3 days post-infection (2BF). These treatments mimic natural mosquito gonotrophic variation. Our results demonstrate that transcriptional states of salivary gland sporozoites vary within and across treatments at 11 days post-infection. A marked transcriptional transition is observed during occupancy of the glands, and progress across this transition is significantly advanced in the 2BF treatment. 2BF sporozoites show significantly higher expression of genes associated with human infection whereas 1BF sporozoites show significantly higher expression of genes associated with earlier sporozoite functions. 2BF sporozoites also show upregulation of genes involved in lipid and fatty acid metabolism. Importantly, 2BF sporozoites show significantly higher rates of hepatocyte infection (1.9x rate of 1BF). Together, these results suggest that malaria parasites are not maximally effective at hepatocyte invasion upon initial arrival to the mosquito salivary glands, but undergo an additional maturation phase. Time to final parasite maturity also appears sensitive to mosquito feeding variability common to many malaria settings.

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PLASMODIUM FEMALE GAMETE SURFACE HSP90 IS A KEY DETERMINANT FOR MOSQUITO INFECTION

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Plasmodium female gamete surface HSP90 is a key determinant for mosquito infection Sung-Jae Cha1, Dingyin Tao1,2, Heather M. Kudyba3, Marcelo Jacobs-Lorena1, and Joel Vega-Rodriguez31 Johns Hopkins Bloomberg School of Public Health, Department of Molecular Microbiology and Immunology and Malaria Research Institute, 615 N. Wolfe St., Baltimore, MD, 21205, USA 2 Current address: National Center for Advancing Translational Sciences, National Institutes of Health, 9800 Medical Center Drive, Rockville, Maryland 20850, United States.3 Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD 20852, USA Abstract

Plasmodium fertilization is required for the development of the malaria parasite in the mosquito and is considered a prime target for strategies to block malaria transmission. Using phage peptide display screening we identified MG1, a peptide that binds to male gametes and inhibits mosquito infection, presumably blocking fertilization by competing with a female gamete ligand. Anti-MG1 antibodies bind to the female gamete surface and by doing so, inhibit oocyst formation in the mosquito. We determined that this antibody specifically recognizes HSP90 on the surface of Plasmodium female gametes. Our findings establish Plasmodium HSP90 as a potential target for the development of a transmission-blocking vaccine.

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INVASION OF RED BLOOD CELLS BY PLASMODIUM MALARIAE: UNRAVELING INTRA-ERYTHROCYTE DEVELOPMENT AND MOLECULAR MECHANISMS

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The frequent low parasitemia in Plasmodium malariae natural infections, the common occurrence of co-infections with mainly P. falciparum, and the impossibility of long-term in vitro culture has limited the information available for this species. In particular, but not limited to, there are large gaps of knowledge on specific molecular mechanisms of red blood cell (RBC) invasion and on host-cell preference of differentially mature RBCs present in circulation. In this study we aim to address some of these issues using P. malariae parasites collected from infected individuals aged 1-14 years in Mali. Host cell preference was measured taking advantage of a fluorescently labelled anti-CD71 antibody and, both, a DNA and a mitochondrial dye. A robust assay that allows quantification of new invasions in vitro, permitted to characterize invasion phenotypes using enzymes, which differentially cleave receptors from the RBC surface, and also the blocking effect of antibodies against known essential and non-essential RBCs receptors in other Plasmodium spp (Basigin, CD55, Duffy Antigen, CD71, Band 3 and Glycophorin A, CR1 and Sema7A). Our results show this parasite displayed a clear preference for reticulocytes, opposite to current knowledge. Also, treatment of RBCs with different enzymes (i.e. neuraminidase, trypsin and chymotrypsin) showed a significant but not complete reduction in invasion with all enzymes tested. None of the three antibodies tested, some with known blocking effects in other Plasmodium spp, hampered RBC invasion.

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THE ROLE OF THE PLASMODIUM FALCIPARUM ACETYL-COA SYNTHETASE IN GAMETOCYTOGENESIS AND TRANSMISSION

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Acetyl-CoA synthetase (PfAcAS) catalyzes the synthesis of acetyl-CoA, a key metabolite and histone acetylation donor in Plasmodium falciparum, the most lethal malaria parasite. Previous studies have shown that PfAcAS is essential for blood-stage growth and survival, and that specific

inhibitors of PfAcAS prevent growth by depleting cellular acetyl-CoA and disrupting histone acetylation. However, the role of PfAcAS in other parasite stages remains unknown. Here we investigated the function of PfAcAS in gametocyte and transmission stages using genetic manipulation, chemical inhibition, and functional assays. Using the NF54-iGP2 inducible gametocyte producing line, we generated highly synchronous gametocyte cultures to profile how PfAcAS inhibitors affect parasite viability and histone acetylation throughout gametocytogenesis. We found that inhibition of PfAcAS disrupted the development of early and late-stage gametocytes, and that histone acetylation was reduced in early gametocyte stages, consistent with previous observations in asexual-stage parasites. Using DDD9309, an optimized analogue of the PfAcAS inhibitor MMV019721 with improved biochemical and cellular potency (PfAcAS enzyme IC50 16 nM; 3D7 EC50 40 nM), we selected for resistance in the NF54-iGP2 line, and identified a novel T648A mutation in PfAcAS that conferred high level resistance to multiple PfAcAS inhibitors. We further characterized the ability of PfAcAS-T648A parasites to produce viable gametocytes and undergo transmission through mosquito stages of the parasite's lifecycle. Immunofluorescence assays showed that PfAcAS has a dynamic localization, changing from predominantly nuclear to cytosolic and back during gametocyte maturation, indicating that PfAcAS may perform multiple functions in gametocytes. Our study suggests that PfAcAS plays a role in the epigenetic regulation of gametocyte development, and reveals the essential role of PfAcAS in malaria parasite transmission stages. We propose that targeting acetyl-CoA biosynthesis could be a novel strategy to block malaria transmission.

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MOUSE ERYTHROCYTE BASIGIN INTERACTS WITH PLASMODIUM YOELII ERYTHROCYTE BINDING LIKE PROTEIN

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Malaria merozoites invade host erythrocytes through multiple interactions between parasite and erythrocyte surface proteins. Erythrocyte-binding-like (EBL) proteins, type I integral transmembrane proteins released from the merozoite micronemes, are known to play an important role in the formation of tight junctions between the merozoite and the erythrocyte surface. In human malaria, Plasmodium falciparum encodes 4 EBLs (PfEBA175, PfEBA140, PfEBA181, and PfEBL1) and P. vivax 2 EBLs (PvDBP, PvEBP2). Therefore, it is difficult to elucidate the functions by the loss-of-function approach because they may compensate each other. In contrast, P. yoelii encodes only a single EBL protein, PyEBL, and a single amino acid substitution (C351Y) in the N-terminal cysteine-rich Duffy binding-like region 2 (R2) of PyEBL drastically changed the virulence of P. yoelii parasites suggesting the usefulness of P. yoelii for the functional discovery of EBL proteins. In this study, we sought to elucidate the erythrocyte receptor of PyEBL that mediates its role as an invasion ligand. First, using the eukaryotic wheat germ cell-free system, we developed a protein library consisting of 237 mouse erythrocyte surface proteins and screened the library with native PyEBL protein as a ligand using AlphaScreen technology. We found that PyEBL interacts with mouse basigin, an erythrocyte surface protein. Using surface plasmon resonance, we further confirmed that PyEBL-R2 is the binding region with basigin, and the C351Y mutation did not affect the binding capability. These results are consistent with previous results that the R2 of P. vivax and P. falciparum EBLs interact with their erythrocyte receptors. The identification of basigin as the putative PyEBL receptor offers new insights into the role of this molecule and provides an important base for in-depth studies toward developing novel interventions against malaria.

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TRANSMISSIBILITY OF PRIMARY AND RECURRENT PLASMODIUM VIVAX INFECTIONS AND THE ROLE OF TRANSMISSION MODULATING IMMUNITY IN ETHIOPIA

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The prevalence of antibodies against sexual stage Plasmodium vivax parasites determines the success of transmission to mosquitoes, but their dynamics is not well characterized in homologous and heterologous recurrent infections. We evaluated the kinetics of transmissibility to mosquitoes and level of transmission blocking and enhancing antibodies among P. vivax infected patients (n=155) using direct membrane feeding assays (DMFAs) in 12 months follow up in Ethiopia. Of the 399 DMFAs done using 47,880 mosquitoes, 68% feeds were infectious with no difference between recruitment (67%, 169/252) and recurrent (70.7%, 104/147) infections. Of the feeds that involved serum replacement (n=146) using 23,993 mosquitoes, more feeds were infectious when naïve sera were used (80%) than feeds with patient's own sera (73%). Transmission reducing activity (TRA) >80% was observed in 16% (24/146) of these feeds. The mean oocyst density was higher in infected mosquitoes fed on naïve serum (42; 1-321) compared to autologous sera (21; 1-272; $p<0.001$). The proportion of infected mosquitoes associated with total (18S based qPCR) parasite ($\rho=0.32$; $p<0.001$) and gametocyte (sex specific RT-qPCR) densities ($\rho= 0.35$; $p=0.001$). Antibody responses against a panel of P. vivax gametocyte antigens are being quantified using ELISA. From a preliminary observation, antibodies against Pvs47, Pvs230 and Pvs25 were associated with reductions in mosquito infections and PvsHAP2 or Pvs47 antibodies were produced more likely in samples with TRA. The very high transmissibility of recurrent infections strengthens the need to implement radical cure strategies in P. vivax endemic settings. The sustained transmission blocking activity in recurrent infections hints the additional benefit transmission blocking interventions could add. Samples from patients at recruitment and recurrence were sequenced using short amplicon Next Generation Sequencing (NGS) using a panel of 100 P. vivax microhaplotype. We will apply a modelling framework that uses genotyping to determine the likelihood that recurrent infections derive from new (reinfection), recrudescent or relapse.

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A TWO PATCH MODEL FOR MUTASA AND NYANGA DISTRICTS IN MANICALAND PROVINCE ZIMBABWE INCORPORATING CLIMATIC CONDITIONS

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In Zimbabwe more than 50% of malaria cases are concentrated in Manicaland province, where seasonal malaria epidemics occur despite intensified control strategies. Understanding the local epidemiology of malaria, particularly diverseness across time and space is crucial to achieving control and elimination. Elimination and control efforts need to take cognisance of mobility patterns as well as climatic conditions as these can significantly influence prevalence and transmission of malaria. A two-patch model of non-linear differential equations for Mutasa and Nyanga district within Manicaland province is formulated and used to assess how variability in temperature and rainfall as well as mobility patterns affect the transmission dynamics of malaria in a population. The model is fitted using number of malaria cases, mean monthly temperature and rainfall data for the period 2005-2020. Sensitivity analysis using temperature and rainfall data highlighted that mosquito carrying capacity, and transmission

probability per contact for susceptible mosquitoes influence malaria transmission dynamics in the patches. The malaria burden within the two districts increases with increases in mean monthly temperature and mean monthly rainfall (|17-250C| and |32-110mm|) respectively. Numerical simulations reveal that mobility accounts for endemicity of the disease in both patches, in particular if biting intensity of the mosquitoes is high then infection prevalence increases with mobility. Incorporating variability in climatic conditions and mobility in the patch model helps forecast malaria transmission patterns and highlights which areas need interventions. The numerical simulations highlighted that perturbations as a result of major climatic changes also affect mobility patterns, therefore there is need to continually monitor and evaluate the implications of these changes.

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DESCRIPTION OF PLASMODIUM FALCIPARUM TRANSMISSION ASSOCIATED HAPLOTYPES

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Malaria is the deadliest mosquito-borne parasitic infection worldwide, with one parasite, Plasmodium falciparum (Pf), accounting for the majority of deaths, especially in Africa and Asia. Despite its tremendous impact on public health, much remains to be characterized in global populations of Pf, including existing structural variation among Pf genomes. Recent observations, based on whole genome sequencing data from Pf samples from Africa and Southeast Asia (SEA), suggest that the vector may have an underappreciated impact on Pf evolution. In particular, we have identified (nearly) fixed nonsynonymous SNPs in loci preferentially expressed during transmission-related stages of the life cycle. Now, based on whole genome assemblies for 19 Pf samples from countries in Africa and SEA, we have also identified fixed structural differences between African and SEAn Pf populations. AP2-G, a key transcription regulator of sexual stage commitment, harbors a 200 bp deletion at the 3' end of the gene in all African Pf samples, including the reference Pf3D7. This deletion spans the in-frame stop codon found in SEAn Pf strains, as well in outgroup Plasmodium species, resulting in a longer and quite different C-terminal AP2-G sequence in African strains. Here, we investigated if there are other genomic variants in allelic association with the AP2-G deletion, which could contribute to modulate its function. In addition to 4 additional genes containing fixed structural variants, there are 28 nonsynonymous SNPs, identified among 12 genes, in strong linkage disequilibrium (r2 >= 0.7) with the observed AP2-G deletion. These genes are enriched in biological processes such as responses to defenses of host. Most of these genes are primarily expressed in Pf sexual life-cycle stages. We are investigating possible interactions between these genes and AP2-G. Finally, several of these genes are transmission-associated loci targeted by vaccines currently in the developmental pipeline, including Pfs47 and the gene encoding TRP1, providing region-specific Pf transmission-associated haplotypes, which may be important to consider in vaccine formulations.

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DYNEIN HEAVY CHAINS IN PLASMODIUM FALCIPARUM DURING GAMETOCYTES DEVELOPMENT

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Plasmodium falciparum is the deadliest among the malaria causing parasites. The sexual conversion into the gametocyte and development (gametocytogenesis) is crucial step for the successful transmission of parasite in the mosquitos. Further, the gametocytogenesis is a response of the parasite to cope up with the continuous stresses that it faces during the asexual intra-erythrocytic development cycle (IDC) in the human host. In our previous genetic phenotype piggyBac mutagenesis screen we found that one of the Dynein Heavy Chains gene (DHC) Pf3D7_1122900, a microtubule associated protein, manifests the increased sensitivity to stress response pathways during IDC upon heat shock and Dihydroartemisinin (DHA) stress. Orthologs of these proteins known to act as the ATP dependent motor proteins on the microtubules for the cellular transportation of the cargos, positioning of the organelles and the structural integrity of the cells. However, these genes remain uncharacterized in the P. falciparum. Here we report the piggyBac screening for the gametocytogenesis and found that several piggyBac DHC mutants are involved in the induction of gametocyte conversion and the development. In order to characterize their functions, we used Lox-Pint mutagenesis and generated conditional Knock-out mutants for these genes. Dynein heavy chains and their associated proteins play an important role in the transport and structural integrity of the cells that is also an essential mechanism for the gametocytes to attain their specific falciform shape in order to get transmitted successfully. Therefore, functional characterization of this family would provide new drug targets to mitigate the malaria pathogenesis by inhibiting the transmission of parasite from human to mosquitos through breaking the survival chain of the parasite.

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LOSS OF FUNCTION OF THE PLASMODIUM FALCIPARUM PROLINE TRANSPORTER MFR4 MEDIATES HALOFUGINONE RESISTANCE BUT RESULTS IN OOCYST DEVELOPMENTAL DYSFUNCTION.

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Halofuginone (HFG) is a potent antimalarial targeting the cytoplasmic proline-tRNA synthase of Plasmodium falciparum. We have previously demonstrated that resistance to HFG can be mediated through two distinct mechanisms: the Adaptive Proline Response (APR) and mutations in the active site of the target gene. In asexual parasites, the APR is characterized by accumulation of cytoplasmic proline that confers low level (20-fold) resistance to HFG by competing for binding the target protein. Whole genome sequencing identified frameshift and nonsense mutations in the major facilitator superfamily related protein 4 gene (pfmfr4, also known as ApiAT2) associated with the APR phenotype. Metabolic labelling experiments were used to demonstrate that during asexual blood-stages, MFR4 functions to export proline derived from hemoglobin degradation and biosynthesis from arginine. To understand whether HFG resistant parasites are transmissible, infectious bloodmeals containing drug-selected ΔMFR4 parasites were fed to Anopheles gambiae mosquitoes. ΔMFR4 parasites show no defect in infectivity to mosquitoes, but are dysfunctional in their development as oocysts. While ΔMFR4 parasites cannot complete development to sporozoites, a subset of the oocyst population demonstrates growth at a reduced rate. Previous work in the Plasmodium

berghei/Anopheles stephensi experimental system pointed to an essential role of MFR4 in transmission. Our data suggest that proline transport and metabolism play a critical, yet unknown role in the transmission stages of P. falciparum development, revealing a novel target for mosquito-based transmission blocking interventions.

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A SINGLE FULL-LENGTH VAR2CSA ECTODOMAIN ELICITS HETEROLOGOUS FUNCTIONAL ANTIBODIES IN AOTUS NANCYMAAE

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Malaria caused by Plasmodium falciparum continues to be a global problem with devastating consequences. Pregnancy malaria is associated with poor outcomes including stillbirth, preterm delivery, and low birth weight. Placental malaria (PM) is caused by P. falciparum-infected erythrocytes that bind to the placental receptor chondroitin sulfate A (CSA) and sequester in maternal intervillous spaces. In first-time mothers, parasite sequestration in the placenta often induces a macrophage-rich inflammatory infiltrate associated with poor pregnancy outcomes. Women become resistant to pregnancy malaria as they acquire antibodies that target surface proteins expressed by placental parasites. VAR2CSA, a member of the PfEMP1 variant antigen family, is a surface protein of infected erythrocytes (IE) that mediates adhesion to CSA and is the leading target antigen for a vaccine to prevent PM. Here, we assessed the functional activity of antibodies raised against a recombinant full-length VAR2CSA ectodomain (NF54 variant). Plasma samples from Aotus (N=4) immunized with full-length VAR2CSA were tested in binding-inhibition assays that used freshly collected IE from 15 pregnant women in Ouelessebougou, Mali. All plasma samples inhibited IE binding to CSA (i.e., reduced the number of parasites bound >50%) in most isolates (range, 53-73% of isolates). These results suggest that a VAR2CSA vaccine using a single or limited VAR2CSA alleles can elicit broad heterologous functional activity.

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INITIAL EVALUATION OF THE PVS230D1-EPA CONJUGATE VACCINE CANDIDATE

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Pvs230, a pre-fertilization gametocyte/gamete antigen of Plasmodium vivax, is a promising malaria transmission-blocking vaccine (TBV) candidate. Pvs230 is expressed by parasite gametocytes in the human host and displayed on the surface of gametes in the mosquito host. To increase immunogenicity, the recombinant, Pichia pastoris-expressed domain 1 of Pvs230 (Pvs230D1M) was conjugated to the recombinant, non-toxic Pseudomonas aeruginosa ExoProtein A (rEPA) in conformance with current good manufacturing practices (cGMP). In order to meet regulatory requirements prior to clinical trials, extensive evaluations of the conjugate must be conducted. In this study, the cGMP Drug Product Intermediate (DPI) Pvs230D1-EPA conjugate was evaluated by the following analyses: purity by visual inspection (appearance); limulus amebocyte lysate (LAL) for endotoxin; microbial enumeration tests for bioburden; general safety and rabbit pyrogenicity test; strength (protein content) by UV spectrum (A280) and BCA protein assay; identity by amino acid composition; pH; SDS-PAGE with Coomassie blue staining (migration pattern); Western blot using conformation-dependent monoclonal antibody 1H3 and an anti-exotoxin A polyclonal antibody; and integrity by SDS-PAGE, reverse phase ultra-performance liquid chromatography (RP-UPLC), size-exclusion ultra-performance liquid chromatography (SEC-UPLC) and size exclusion chromatography with inline multi-angle light scattering (SEC-MALS). Our results indicate the cGMP grade Pvs230D1-EPA meets regulatory requirements and is suitable for use in human clinical trials.

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SYSTEMS SEROLOGY OF PFSPZ VACCINE REVEALS IMPORTANCE OF NON-PFCSP ANTIBODY IMMUNITY IN LONG-LASTING PROTECTION

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Malaria remains a major cause of morbidity and mortality across Sub-Saharan Africa as well as globally. PfSPZ Vaccine is a whole cell radiation attenuated Plasmodium falciparum (Pf) sporozoite (SPZ) vaccine that has demonstrated promising efficacy in multiple clinical trials. Previous work has suggested that liver resident CD8+ T cells are essential for long-last PfSPZ-mediated protection. Here we have applied high-dimensional antibody profiling to identify humoral correlates of long-lasting protection. Though Anti-PfCSP Ab titers and antibody-dependent complement deposition (ADCD) increase with PfSPZ vaccination and are associated with protection early on, their responses wane and are not central to long lasting-protection. Our machine learning and statistical methods showed a new role for non-PfCSP non-IgG and complement activity in PfSPZ-mediated long lasting protection and point to the importance of non-PfCSP functional antibody responses in pre-erythrocytic vaccine-mediated immunity.

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CHARACTERIZATION OF KENYAN PLASMODIUM FALCIPARUM FIELD ISOLATES FOR USE IN CONTROLLED HUMAN MALARIA INFECTION

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Controlled human malaria infection (CHMI) is a critical tool for evaluating drug and vaccine efficacy in a controlled setting. However, CHMI studies have been conducted with limited number of parasite strains isolated from human more than 40 years ago. This could lead to false inferences due to lack of parasite diversity inherent in present-day natural infections. Only two unique cloned strains are available for use (NF54/3D7 from Africa and 7G8 from Brazil). To fill this gap this study is designed to identify, down select parasites sensitive to chloroquine (CQ), quinine (QN), atovaquone (AV), primaquine (PQ), artemether (AR), artesunic acid (AS), amodiaquine (AMQ), artemisinin (ART), halofantrine (HAL), and tafenoquine (TAF). Isolates should produce infective gametocytes and genetically diverse. A total of 56 individuals from WRAIRs 2454 protocol presenting symptoms of uncomplicated malaria were screened for blood borne pathogens before enrollment, and a total of 40 individuals were excluded. Immediate ex vivo

analysis was done for sensitivity testing and molecular analyses to confirm species composition, genotypes, gametocytes and drug resistance marker profile. Serum and plasma for n (16) was processed and sent to WRAIR for blood borne pathogen confirmatory testing. Of n=16, 10 were tested and had the following median drug concentration (IC50s) 14 ng/ml (7.946-14.78) for chloroquine, 29.04 ng/ml (21.71-57.17) for quinine, 4.955 ng/ml (3.631-6.173) for atovaquone, 870 ng/ml (622.6-900.1) for primaquine, 3824 ng/ml (1527-6569) for doxycycline, 5.796 ng/ml(3.941-8.531) for artemether, 3.627 ng/ml (3.299-6.829) for artesunic acid, 1.457 ng/ml (0.9395-1.666) for amodiaquine, 5.796 ng/ml (3.941-8.531) for artemisinin, 19.69 ng/ml (16.45-27.74) for halofantrine and 423.4 ng/ml (141.2-859.4) for tafenoquine. Of the 16 samples, 87.5% harbored gametocytes, 68.75% had falciparum only, and 12.5% had co-infection of either P. falciparum with P. malariae or P. falciparum with P. o.wallikeri respectively. These findings prequalify and support the identification of new isolates for consideration in future CHMI studies.

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CROSS-SECTIONAL ASSESSMENT OF FACTORS DRIVING PARTIAL VERSUS FULL UPTAKE OF RTS,SAS01 MALARIA VACCINE AMONG CHILDREN IN RARIEDA SUB-COUNTY, WESTERN KENYA, 2021 TO 2022

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Following the 2015 World Health Organization (WHO) recommendation, pilot implementation of the 4-dose RTS,S/AS01 (RTS,S) malaria vaccine began in western Kenya in September 2019 as part of the routine childhood immunization schedule at 6, 7, 9, and 24 months of age. We used data from a continuous Malaria Indicator Survey (cMIS), a cross-sectional survey conducted from November 2021-July 2022 in 847 households, to assess RTS,S coverage and uptake 2 years post-introduction in Rarieda sub-county. Of 148 children, 71 aged 12-23 mo and 77 aged 27-38 mo, 66% had a home-based vaccination record documenting vaccination status (12-23 mo: 72% and 27-38 mo: 60%). RTS,S1, RTS,S2, RTS,S3, and RTS,S4 coverage was 90.2% (95% CI: 78.5-96.7), 84.3% (95% CI: 71.4-93.0), 80.4% (95% CI: 66.9-90.2), and 26.1% (95% CI: 14.3-41.1), respectively. Corresponding mean age at vaccination was 6.6 (95% CI: 6.0-7.1), 7.7 (95% CI: 6.9-8.6), 9.9 (95% CI: 9.3-10.6), and 23.3 months (95% CI: 19.4-27.1). Benchmark measles vaccine coverage (dose 1 - RTS,S3; dose 2 - RTS,S4) was 88.2% (95% CI: 76.1-95.6) and 56.5% (95% CI: 41.1-71.0). Odds of being fully vs. partially RTS,S vaccinated (<3 doses by 23 mo and primary series only by 38 mo) did not differ significantly by gender, household wealth, caregiver education, or bednet use. Of children 12-23 mo, those who were the only child under 5yrs in the household were 9.6 times (95% CI: 1.5-190.9) more likely to have received all 3 RTS,S doses compared to those in households with more than 1 under 5 yrs. Of children 27-38 mo, those with measles dose 2 were 9.9 times (95% CI: 1.5-199.9) more likely to be fully vaccinated with 4 RTS,S doses vs. those without the 2nd dose. While not significant, those who were fully vaccinated with core EPI vaccines per WHO guidelines were more likely to be fully vaccinated with RTS,S (OR: 1.8 [95% CI: 0.2-10.6]). Our study found high uptake and moderate dropout for the primary series. RTS,S4 may face similar uptake barriers as other second-year of life vaccines. If RTS,S vaccination schedules are revised, understanding populations at greater risk for dropout can guide vaccination roll-out strategy to ensure optimal coverage.

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FEASIBILITY EVALUATION OF RTS,S/AS01 MALARIA VACCINE PILOT INTRODUCTION IN WESTERN KENYA: COVERAGE SURVEY RESULTS 30 MONTHS POST-INTRODUCTION

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RTS,S/AS01 (RTS,S) malaria vaccine was introduced in western Kenya in September 2019 through the World Health Organization-initiated pilot to evaluate the safety, impact, and feasibility of integrating the 4-dose schedule (at ages 6, 7, 9, and 24 months) into routine immunizations. Three large household surveys assessed RTS,S uptake of doses 1-3 among children aged 12-23 months, and dose 4 in children 27-38 months in 46 pilot sub-counties before (HHS1, July-October 2019), and 18 (HHS2, May-July 2021) and 30 (HHS3, April-June 2022) months post RTS,S introduction. RTS,S coverage was measured by vaccination cards, available for 86%, 88%, and 89% of children in HHS1, HHS2, and HHS3, respectively; or caregiver recall for those with no cards. In HHS3, the coverage for RTS,S doses 1-3 was 82.7% (95%CI 78.6-86.1), 78.1% (95%CI 73.7-81.9), and 68.9% (95%CI 63.9-73.6), respectively, with an improvement from HHS2 in coverage (dose 1-3: 78.6%, 71.4%, and 62.3%) and dropout rates (9.2% to 6.0% dose 1 to 2; 20.7% to 16.9% dose 1 to 3). RTS,S dose 4 coverage was 32.7% (95%CI 27.9-37.9), with 52.2% dose 3 to 4 dropout, and lower uptake than measles dose 2 (58.9% (95%CI 55.3-62.4)) given 6 months earlier. RTS,S coverage was lower among children not sleeping under a bednet the night before, compared to those who did (dose 1: 57.6% vs. 84.2%; dose 2: 55.1% vs 79.4%; dose 3: 46.9% vs. 70.2%; $p<0.05$); and in areas with indoor residual spraying (IRS), than areas without IRS (dose 3: 55.1% vs. 73.3%; dose 4: 10.6% vs. 40.1%; $p<0.05$). No differences in RTS,S uptake were noted by sex, caregiver's age or parity, or residence (urban vs. rural). Caregivers with secondary or higher education were 2.1 times (95%CI 1.5-3.1) more likely to bring their child for all 4 RTS,S doses than those with primary education only, and uptake increased with wealth. No negative impact of RTS,S introduction on other malaria (bednet use) and childhood interventions (vitamin A supplements, deworming), or uptake of other vaccines was observed 30 months into the pilot. Our study found that coverage of the first 3 RTS,S doses and the dropout rates improved over time, while low uptake of the fourth dose remains a challenge.

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THE ADDITIVE VALUE OF RTS, S,AS01 MALARIA VACCINE IN REDUCING MALARIA INFECTION AMONG UNDER FIVE CHILDREN IN MALAWI

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The RTS, S/AS01 malaria vaccine was recently recommended by World Health Organization (WHO) for widespread use among under-five children in areas with moderate to high Plasmodium falciparum malaria transmission. As part of the Malaria Vaccine Implementation Program (MVIP), we estimated the additive value of RTS, S/AS01 in preventing malaria infection. We assessed prevalence of malaria in areas deploying: i) traditional mosquito nets, ii) Pyrethroid-piperonyl butoxide (PBO) or Interceptor G2 (IG2) nets only, iii) indoor residual spraying (IRS) only, vi) RTS, S/AS01 only, v) PBO/IG2 nets + RTS, S/AS01, vi) IRS + RTS, S/AS01. A total of 4,909 children aged 5-48 months were recruited for the survey. The mean age was 25 months (SD=11) and 2,456 (50.0%) were females. Out of the

enrolled children, 638 (13.0%), 1,256 (25.6%), 556 (11.3%), 323 (6.6%), 1,375 (28.0%) and 760 (15.5%) were from areas deploying traditional nets, with PBO/IG2 nets only, IRS only, RTS, S/AS01 only, PBO/IG2 nets + RTS, S/AS01 and IRS + RTS, S/AS01 respectively. Malaria prevalence was lowest in areas implementing PBO/IG2 nets + RTS, S/AS01 [4.8% (95% CI: 3.6%, 6.3%)], followed by PBO or IG2 nets only [5.4% (95% CI: 3.8%, 6.7%)], IRS + RTS, S/AS01 [13.8% (95% CI: 8.6%, 21.4%)], RTS, S/AS01 only [14.4% (95% CI: 4.6%, 37.2%)] then IRS only [23.2% (95% CI: 17.3%, 30.2%)] and highest in areas deploying traditional nets [25.2% (95% CI: 18.6%, 33.2%)]. To conclude, this survey has demonstrated that RTS, S/AS01 has substantial added value in reducing malaria infections when combined with existing standard vector control interventions such as the ITNs use or IRS. As malaria endemic countries are rolling out the RTS, S/AS01 malaria vaccine, policy makers and programmers should focus on promoting use of combined delivery of vector control interventions to rapidly reduce burden of malaria among children.

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RTS,S MALARIA VACCINE COMBINED WITH PYRETHROID-PIPERONYL BUTOXIDE-LONG-LASTING INSECTICIDAL NETS (PBO-LLIN) PROVIDES ADDED PROTECTION AGAINST PLASMODIUM FALCIPARUM INFECTION COMPARED WITH PBO-LLIN ALONE

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Both PBO nets and RTS,S vaccine have been shown to be independently effective against malaria in areas of high prevalence. However, the combined effects of these interventions have not yet been explored. The current study aimed to examine whether adding RTS,S to PBO nets is more effective in preventing Plasmodium falciparum infection compared with PBO nets alone. We analyzed data from 776 children aged 7 months to 10 years from a prospective community-based longitudinal study in Malawi. Index children aged 7-18 months received 3 doses of RTS,S, and PBO nets, while those aged 19 months to 10 years (siblings) received PBO nets only. Capillary blood samples were collected at enrollment (month 0), and at 2, 4, and 6 months thereafter, for detection and quantification of P. falciparum using qPCR targeting the 18s rRNA gene. The effect of adding RTSS+PBO nets compared to PBO nets only was estimated using multivariable generalized estimating equation models after adjusting for predictors including age. In total, 60% (469/776) of children received both PBO nets and RTS,S whilst 40% (307/776) received only PBO nets. In this analysis, all children contributed to 325 person-years of follow-up. There were 376 infection events/100 person-years at risk in the PBO nets alone group against 157 events/100 person-years at risk in the RTS,S+ PBO nets group. The adjusted incidence rate ratio (IRR) in children who had received only PBO nets was twice that of children who had received RTS,S+PBO nets (IRR: 2.11; 95% CI: 1.62-2.75). These results suggest that adding RTS,S vaccination to PBO nets intervention might be used to further reduce P. falciparum transmission and infection in areas where malaria is perennial.

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IMPACT OF RTS, S/AS01E VACCINATION ON PLASMODIUM SPECIES COMPOSITION IN INDIVIDUALS ENROLLED FOR AT BASELINE AND DURING THE SUBSEQUENT FOLLOW-UP PERIOD IN MALARIA ENDEMIC REGIONS OF WESTERN KENYA IN KISUMU COUNTY

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RTS, S/AS01E is a recombinant protein-based malaria vaccine that elicits the production of antibodies against the Plasmodium falciparum (Pf) circumsporozoites, thereby blocking the establishment of the infection in the liver cells. In 2014, a phase 3 trial showed that RTS, S had high efficacy in infants and young children, and based on this, the World Health Organization recommended the vaccine roll-out of in selected regions of Africa. However, information on the potential of the vaccine to protect against the acquisition of non-Pf species, such as P. malariae (Pm), P. ovale curtisi (Poc), and P. ovale wallikeri (Pow), is limited despite the rising frequency of non-Pf species infections, which account for 25% of imported malaria cases worldwide.A total of 125 samples from African adults with sub-clinical PCR positive parasitemia in Kombewa, Kenya participating in a RTS, S vaccine efficacy study were characterized for Plasmodium species composition at enrolment versus subsequent follow up time-points. Concurrently, 153 samples were obtained from symptomatic individuals visiting Kombewa Sub County Hospital within the same catchment and characterized for species composition of the infections was established using rt-PCR at enrolment as well as upon subsequent infection detection. Infections containing Pf were most frequent among the symptomatic individuals enrolled from the same catchment, with 76.19% followed by P. malariae, with 27.38%, P. ovale wallikeri, 17.86% while P. ovale curtisi was least prevalent at 10.0%. Analysis of species composition for the samples from individuals who received vaccines at the initial timepoint and at subsequent time-points during follow-up visits is underway

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EFFICACY OF THE RTS, S/AS01E MALARIA VACCINE ADMINISTERED ACCORDING TO DOSAGE REGIMEN UNDER CONDITIONS OF NATURAL EXPOSURE IN AFRICAN CHILDREN AGED 5-17 MONTHS: INSIGHTS FROM EXTENDED GENOTYPING-BASED ENDPOINT RESULTS AND MALARIA INFECTION STATUS AT FIRST VACCINATION FROM A PHASE 2B RANDOMIZED CONTROLLED TRIAL

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A phase 3 trial showed moderate vaccine efficacy (VE) of RTS,S/AS01E against clinical malaria in African children when administered according to a 0, 1, 2-month (M) primary schedule (M012) with a 4th dose given at M20. We present initial results deriving from PCR-based genotyping endpoints of an ongoing phase 2b open-label, randomized, controlled trial (NCT03276962) evaluating efficacy of RTS,S in multiple full vs fractional (Fx) dose regimens under conditions of natural exposure. A total of 1500 children aged 5-17M were randomized (1:1:1:1:1) to receive RTS,S (2 full-dose and 2 Fx dose regimens) or a rabies control vaccine (M012). We evaluated two molecular endpoints: the time to the first new molecular infection, and the total number of new molecular infections, each during 32 months post-dose-1 and 24 months starting at 14 days post-dose-3, using Illumina-based amplicon sequencing of the CS C-terminus and a control antigen. As in a previous analysis with shorter follow-up periods, we observed significant VE, in the 26%-42% range (95% CI union, 11%-53%), against the first molecular infection for all 4 RTS,S regimens vs. control across both follow-up periods. VE against the first molecular infection was similar across the 4 RTS,S regimens, with no significant differences. Each RTS,S regimen significantly reduced the number of new

molecular infections. We also tested the hypothesis that VE of RTS,S might be reduced in participants with evidence of existing baseline infections at the time of first vaccination from microscopy and/or PCR amplicon data. Contrary to expectation, VE of RTS,S against the first infection was significantly higher (P=0.0015) in participants who were malaria-infected (67.8%; CI 50.5-79.0%) vs. uninfected (31.3%; CI 17.5-42.9%) at the first vaccination. Higher VE in baseline-infected participants could suggest new strategies for highly efficacious malaria vaccine development or implementation.

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THE EFFECT OF RTS,S, AND SEASONAL MALARIA CHEMOPROPHYLAXIS (SMC) ALONE OR COMBINED ON ANTIMALARIAL ANTIBODY RESPONSES

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The combination of the malaria vaccine RTS,S and seasonal malaria chemoprophylaxis (SMC) has been shown to have a significant reduction in malaria incidence in children up to 5 years old compared with either intervention delivered alone. However, it is likely interventions will effect the development of naturally acquired immunity to malaria; understanding this effect may help predict and mitigate any post intervention effects on incidence in children as they age. Dried blood spots were collected in November, the peak transmission season, in 2019 and 2020 from study children who had received the combination of RTS,S and SMC together or separately in Mali and Burkina Faso. Samples were assayed against ~ 30 malaria specific antigens classified into representing historical & recent exposure and protection associated. Continuous antibody responses were analysed using principal components analysis (PCA). As expected, responses to the RTS,S vaccine components were significantly higher in those that received the vaccine (linear regression coefficient 1.97 for RTS,S alone vs SMC P<0.001 & 0.00 RTS,S/SMC vs RTS,S alone p=0.99).This included antibody responses to MSP5 an 'off target' antigen response that has previously been associated with RTS,S vaccination. For other antigen groups, responses were typically higher in participants from Burkina Faso than those from Mali reflecting differences in malaria transmission intensity. Overall, responses showed broadly similar patterns: lowest in children receiving the combined intervention and highest responses in those that received the vaccine alone (e.g protective associated - linear regression coefficient 0.03 for RTS,S alone vs SMC P0.05 & -0.09 RTS,S/SMC vs RTS,S alone p<0.001). This most likely reflects the mode of action of the different study interventions. Preliminary data on antibody avidity suggest antigen specific differences that may be linked to the development of protective immunity. How meaningful these antibody responses will be determined by the ability of children in each arm to be naturally protected from malaria in an ongoing prospective study.

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ESTABLISHING RTS,S/AS01 AS A BENCHMARK COMPARATOR FOR NEXT-GENERATION MALARIA VACCINES IN THE TGPB-PFCSP MOUSE CHALLENGE MODEL

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Mouse models using transgenic Plasmodium berghei sporozoite tgPb-PfCSP containing full-length P. falciparum CSP allow two assessments of efficacy: reduction in liver infection following IV challenge, and sterile protection against blood-stage infection following mosquito bite challenge. We introduce a clinically relevant benchmark for comparison of next-generation PfCSP targeted vaccines to the RTS,S/AS01E vaccine. We focus on reproducibility of antibody responses and functional activity in conjunction with robust statistical analyses. A 200-fold range of RTS,S was tested in a constant amount of AS01E adjuvant. Two or three doses were given intramuscularly at three-week intervals, with challenge two weeks after the last vaccination. Protection was highest with the three-dose schedule, but levels remained lower than those seen when potent anti-CSP mAbs, such as mAb317, are administered, indicating the range of this model is suitable for screening more potent vaccines. Induced sera anti-CSP antibody concentrations were also associated with activity: 141 µg/mL reduced liver infection by 50% relative to controls, whereas 300-350 µg/mL is required for 50% protection against blood-stage infection in the parasitemia model. These results provide guidance on using a mouse model of infection to compare vaccines against the only approved malaria vaccine to date. Accounting for assay variability, liver infection experiments are powered (80%) to detect a three-fold change in liver burden using at least eight mice per group and parasitemia studies are powered to detect a 35-40% improvement over three doses of RTS,S/AS01E using ten mice per group. With reasonable sample sizes, inter- and intra-assay variability remain within acceptable bounds for detecting improvement in vaccine function whether the result of greater levels or potency of the induced responses. This ability to compare advanced preclinical and clinical-stage CS-based vaccines to RTS,S/AS01 is now available to the broader malaria vaccine community.

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GENETIC PHYLOGENY OF DIARRHEAGENIC ESCHERICHIA COLI ISOLATED IN CHILDREN BELOW FIVE YEARS LIVING IN CLOSE CONTACT WITH FOOD ANIMALS, KISUMU COUNTY

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Diarrheagenic Escherichia coli strains they cause diarrhea infection in children below five years and food animals. Focus of the study; understand the genetic phylogeny of diarrheagenic E.coli isolated in children below five years and that isolated from food animals in Kisumu County, to establish possibility of zoonotic transmission, and determine their antibiotic resistance patterns. Two hundred children samples and animal samples were collected and processed using traditional culture methods. The molecular identification of pathotypes was assayed using primer-specific polymerase chain reaction (PCR) targeting three virulence genes (lt, st, bfpA, eae, aatA and aaiC) related to three DEC pathotypes (EPEC, EAEC and ETEC). The antimicrobial susceptibility testing was carried out using the Kirby-Bauer disk diffusion method. Colonies from 156 study subjects (100 diarrhea children and 56 diarrhea food animals) were positive for E. coli isolates. Subsequent PCR detection discovered that 26% of children and 10.7% of diarrhea food animals' isolates were positive for one or more virulence genes typical of particular strains. Among those EAEC [(11%), (2%)] ETEC,

[(4%), (0%)] and EPEC [(3%), (8.9%) Of the identified E. coli isolates, about (4%%) were found to be mixed infections. ETEC/EAEC (2%) and EAEC/EPEC (2%) strains this were better detected in children with close contact with diarrhea food animals than children with no contacts. Most antibiotic resistances were obtained towards trimethoprim sulfamethoxazole (95.8%), tetracycline (91.7%), and ampicillin (91.6%). ninety percent of isolates were resistant to a minimum of three categories of antibiotics. Diarrheagenic E.coli is the key contributor of diarrhea in children below five years, there is risk of severe diarrhea from known pathogenic strains hence emergence of resistance narrows options of treatment. Sequencing of isolates is ongoing.

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CHANGES IN GROWTH OBSERVED IN DIFFERENT ANTHROPOMETRIC INDICES AT 90-DAY POST-DISCHARGE FOLLOW-UP AMONG CHILDREN AGED 2-23 MONTHS REQUIRING READMISSION COMPARED TO THOSE WHO DID NOT REQUIRE READMISSION

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Due to availability of limited information on post-discharge growth follow-up among children requiring readmission, we sought to investigate whether post-discharge readmission at day-90 follow-up had any impact on growth in children aged 2 to 23 months. We conducted a case-control study and data extracted from “Antibiotic for Children with Diarrhea (ABCD)” trial which was a seven-country double-blind, randomized, placebo-controlled clinical trial. The Bangladesh site enrolled 1431 children aged 2 to 23 months who were dehydrated or severe stunted or moderately wasted or any combination of these. Among them, 145 children were readmitted to hospital (cases) within a 90-day post-discharge follow-up. Each cases were matched by age and sex to three controls (n = 435). Anthropometry of all children were measured at the time of enrolment and on the 90-day follow-up. The data were analysed using multivariate linear regression to assess the changes in growth at day-90 post-discharge follow-up. At 90 days of post-discharge follow-ups, the mean changes in growth among the cases using four anthropometric indices were found to be significantly reduced compared to the controls ($p<0.05$). After adjusting the potential factors, the anthropometric outcomes Δhaz (coef.-0.10, 95% CI -0.19, -0.01, p-0.036), Δwaz (coef.-0.22, 95% CI -0.32, -0.12, p-<0.001), Δwhz (coef.-0.21, 95% CI -0.35, -0.08, p-0.002) and Δmuac (coef.-0.15, 95% CI -0.28, -0.03, p-0.014) were found to have significant reduction of growth among the readmitted cases compared to their counterpart. In conclusion, the present study prevailed there was a significant reduction of growth in all anthropometric indices at day-90 post-discharge follow-up among children requiring readmission compared with those who didn`t require readmission. This finding underscores the importance of investigating the clinical and social risk factors of readmission that may help to design a post-discharge intervention that may further help to reduce the growth faltering by reducing post-discharge readmission.

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CLINICAL, SOCIO-ECONOMIC AND PATHOGENIC FACTORS OF WASTED AND OVERWEIGHT/OBESE UNDER-FIVE CHILDREN WITH DIARRHOEA: EXPERIENCE FROM AN URBAN HOSPITAL IN BANGLADESH

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Wasting (weight-for-height z score <-2 SD) and overweight/obese (weight-for-height z score >+2 SD) are two critical indicators of malnutrition. In recent years the burden of overweight (39 million) is increasing alongside a continuing problem of wasting, creating a “double burden” of nutrition-related health issues. Data are limited concerning the comparison of these two groups of under-five children with diarrhoea. Therefore, we aimed to compare the associated factors and outcomes of wasted children with overweight/obese children with diarrhea admitted to Dhaka hospital, icddr,b. Data from 15,795 children aged <5 years were extracted from the surveillance system of Dhaka Hospital between January 2012 and December 2021. After excluding the non-desired population (n=13,074), 2296 wasted and 425 overweight/obese children were analyzed. After adjusting age and sex, fever (aOR: 1.574, 95% CI:1.26,1.96, P<0.001), dehydration (aOR: 3.078, 95% CI:2.40,3.95, P<0.001), and use of IV fluid (aOR: 2.551, 95% CI:1.49,4.37, P=0.001) was more likely associated with wasted children compared to overweight/obese children. On the contrary father’s education (aOR:0.231, 95% CI:0.15,0.35, P<0.001), mother’s education (aOR: 0.260, 95% CI:0.16,0.42, P<0.001), antibiotic use before admission (aOR:0.520, 95% CI:0.39,0.69, P<0.001), use of sanitary latrine (aOR: 0.633, 95%CI:0.45,0.89, P=0.008), water purification (aOR: 0.737, 95% CI:0.60,0.91, P=0.004) were less likely associated with wasted children compared to their counterparts. Exposure to enterotoxigenic Escherichia coli (ETEC) (aOR: 2.603, 95% CI:1.12,6.04, P=0.026) was significantly associated with wasted children whilst rotavirus (aOR: 0.554,95% CI:0.37,0.83, P=0.004) exposure showed an opposite trend after adjusting age and sex. Clinical and microbiological presentations are different in these two nutritional groups of children with diarrhoea. This study may help the policy maker to establish better identification and management strategy for these vulnerable populations.

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TITLE: SOCIODEMOGRAPHIC AND CLINICAL DETERMINANTS OF DIARRHEA AFFECTED CHILDREN TREATED WITH ANTIBIOTICS EMPIRICALLY PRIOR COMING TO HEALTH CARE FACILITIES IN DEVELOPING COUNTRIES LIKE BANGLADESH

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Scarcity of evidence, children are receiving antibiotics empirically in acute watery diarrhea. This study explores the sociodemographic and clinical determinants of children who received antibiotics in acute watery diarrhea. Secondary Data were extracted from the” Antibiotic for children with diarrhea” trial, Bangladesh site database. ABCD study was a randomized multi-country, multi-site, double- blinded, placebo -controlled trial, conducted on seven countries from 1st July 2017 to 10th July 2019 among the 2-23-month-old children. Among 35137 screened participants, total 13630 children received antibiotics prior seeking treatment in health facility. The prevalence of using antibiotics (52%) by literature review, 384 are randomly taken who received antibiotics as case. Control was selected 2 times more, matched with age and sex. Children treated with antibiotics has 3- 5 times/day,6.77%, less dehydration 0.8% than control, 10.6% and 3.4% respectively and also has higher proportion of no sign of dehydration (99%) rather than control (96%), showing statistically significant. Mother’s aged ≥30 Years, well-educated and having one parity treated their children with antibiotics more likely (57%, 88.54% and 87.24%) than Control (50.13%, 80.8% and 79.9%). Logistic regression summarized that the odds of case [aOR:3.5, (95%CI:1.23,9.96); p-value: 0.019] were more likely severely stunted. children passing stool > 10 in a day has more in case [aOR:1.67, (95%CI:1.01,2.76); p-value: 0.044.]. mother’s age ≥30 Years and well educated has strong association with case [aOR:2.12, (95%CI:1.39,3.23); p-value:<0.001], [aOR:2.79, (95%CI:1.63,4.79); p-value: <0.001.]. Mothers having two parity [aOR:0.62, (95%CI:0.43,0.90); p-value: 0.012.] were less likely treated their child with antibiotics. After adjusting all covariates, by logistic regression we found that case had hospitalized more [aOR:1.17, (95%CI:0.40,3.43); p-value: 0.772.] than control. Despite

well education and less parity of mother, they treated their young child with antibiotics without considering its severity, needs awareness at community specially caregivers.

6255

DIARRHEA IN A MILITARY SETTING: EPIDEMIOLOGY, ETIOLOGIES AND IMPACT OF THE DISEASE IN MILITARY PERSONNEL DEPLOYED AT CAMP LEMONNIER, DJIBOUTI

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Diarrhea has immense impact on military operational readiness. Overseas military personnel are at increased risk of exposure to enteric infections. We studied the epidemiology of diarrhea among US military personnel stationed at Camp Lemonnier, Djibouti, the primary US base of operations in the Horn of Africa. From May 2021 to March 2023, 201 diarrhea cases were enrolled, answered a questionnaire, and provided a stool sample. Samples were tested using FilmArray (FA) GI panel. For comparative purposes, a subset of 109 samples was evaluated using published qPCR assays for the detection of pathogenic E. coli, Salmonella, Shigella, Campylobacter, and norovirus. The majority (79%) of the 201 enrollees were males. Participants were Reserve (34%), Active Duty (33%), or National Guard (28%). Acute diarrheal episodes ranged between 1 to 13 days with an average of 4.2 days and a median of three days. Most reported symptoms were abdominal pain/cramps (87%), fatigue (76%), and malaise (73%). Signs of dehydration were observed in about one third, while impact on work performance was reported by 55% and ranged between reduced performance (48%) and loss of duty days (7%). FA identified at least one pathogen in 84% of cases and co-infections, up to 5 pathogens, in 56%. ETEC (54%), EAEC (47%), EPEC (29%), and STEC (24%), had the highest infection rates. Other pathogens ranged between 0.5% to 13% with V. cholerae in 3%. In the 109 samples tested by both techniques, 10 (67%) of 15 Shigella positive cases by qPCR were missed by FA; confirmation of qPCR data was performed using multiple assays targeting ipaH, virB, wbgZ, rfpB, and rfc genes. Of 29 STEC positive by FA, 21 (72%) were not O157 and were not detected by qPCR assays. For ETEC positives, CS1 (59%), CS6 (56%) and CS21 (53%) were the most identified colonization factors; CS1CS3CS21 was the common combination. The existence of multiple pathogens in more than half of the cases is a barrier against administration of successful treatment and prevention strategies. Also, data describes the epidemiology of diarrhea and its significant impact on work performance in a military setting.

6256

ASSOCIATION BETWEEN ENTEROPATHOGENS, THE GUT MICROBIOTA AND BIOMARKERS OF ENVIRONMENTAL ENTERIC DYSFUNCTION IN RURAL MALAWIAN CHILDREN

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Environmental Enteric Dysfunction (EED) is a subclinical condition of the gut that is characterized by changes in gut morphology and function due to chronic inflammation triggered by exposure to toxins and enteropathogens. There is limited data examining the link between exposure to enteric infections and EED. We aimed to estimate the prevalence of enteropathogens in rural Malawian children with signs of EED and examine associations with gut microbiota diversity. We used archival total genomic DNA samples extracted from stool, and corresponding demographic data from a nested cohort study conducted within the framework of a randomized controlled trial (NCT02047981). We analysed 102 baseline samples from children aged 1-59 months. We used 16S rRNA gene sequencing to generate data on gut microbiota and enzyme-linked immunosorbent assay to quantify selected fecal biomarkers of EED (myeloperoxidase, neopterin, and alpha-1 antitrypsin). Additionally, we customized an enteropathogen Taqman array card that could test for 20 different enteropathogens simultaneously, including viruses, bacteria, helminths, and protozoa. Out of the 20 enteropathogens tested, 11 were detected, with Giardia (45%) and adenovirus (24%) being the most common. Giardia carriage was highest in children between the age of 13-24 months. We found no significant differences in fecal levels of biomarkers of EED between children who tested positive and negative for any of the enteropathogens. Similarly, the microbiota alpha diversity index did not differ between the two groups of children. Our findings suggest that Giardia and adenovirus are prevalent enteropathogens in rural Malawian children and they may represent regular exposures in EED. However, despite their prevalence, we did not find any associations between the carriage of these enteropathogens and either gut microbiota diversity or biomarkers of EED. Given the potential health implications of these enteropathogens, it is critical to conduct more comprehensive studies to investigate the long-term consequences of their fecal levels on the gut microbiota and EED biomarkers.

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HYPERGLYCEMIA IN DIARRHEAL CHILDREN; CAN WE PREDICT CLINICAL STATUS?

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A high blood sugar level is indicative of various clinical disorders and has crucial implications. Our objective was to determine the relationship between clinical and laboratory alterations and hyperglycemia in diarrheal children under the age of five. This is a retrospective study using the electronic data system of Dhaka Hospital, icddr,b from March 2019 to December 2021. Out of 10828 diarrheal children under age five, 2167 were hyperglycemic (RBS >7.0 mmol/L), and 8661 (RBS 2.5 mmol/L–6.9 mmol/L) were normoglycemic children on admission. We analyzed two groups of children using STATA software. After adjusting age, sex and dehydration status, hyperglycemia was significantly associated with fever on admission [aOR = 1.16 (95% CI: 1.04, 1.29); p=0.006], anemia [aOR = 1.16 (95% CI: 1.01, 1.33); p=0.036], leukocytosis [aOR = 1.49 (95% CI: 1.27, 1.75); p<0.001], thrombocytosis [aOR = 1.39 (95% CI: 1.12, 1.73); p=0.003], hypernatremia [aOR = 3.48 (95% CI: 2.89, 4.18); p<0.001], hypokalemia[aOR = 1.85 (95% CI: 1.58, 2.18); p<0.001], raised creatinine [aOR = 2.69 (95% CI: 2.20, 3.30); p<0.001]. Death was more than three times higher among hyperglycemic cases than normoglycemic cases. Hyperglycemic children were less likely to be breastfed [aOR = 0.88 (95% CI: 0.78, 0.98); p=0.021], severely malnourished [aOR = 0.82 (95% CI: 0.71, 0.93); p=0.003]. Our examination demonstrated that hyperglycemia can be a significant risk factor for critical illness and aberrant electrolyte imbalances upon admission. Diarrheal children with hyperglycemia should have a proper evaluation and an intense monitoring system to avoid a fatal outcome.

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EPIDEMIOLOGICAL AND LABORATORY INVESTIGATION TO IDENTIFY SOURCES OF A COMMUNITY OUTBREAK OF CHOLERA

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An outbreak of cholera with 76 microbiologically confirmed cases were reported between June and September 2022, from Kathmandu, Nepal. Identification of risk factors are crucial for control and prevention of cholera.

We conducted an outbreak investigation utilizing both epidemiological and laboratory methods to identify potential sources. A descriptive epidemiological study was followed by an analytical study. A semi-structured questionnaire was used to capture hygiene behavior, education level, water source, latrine use, and environmental conditions of the cases. Water samples from community sources consumed by the cases were collected, filtered, and tested for the presence of Vibrio cholerae. Inspection of drinking water storage, decontamination and treatment methods, and waste management was conducted. To find asymptomatic V. cholerae carriers, stool samples from patient's immediate household members were collected and tested using rapid diagnostic test (RDT) and culture techniques using selective media. Total 283 water samples (262 household water, 21 river water) were collected for environmental assessment. Presumptive V. cholerae were isolated from 14 household water samples (7 tap, 5 well, 2 jar) of confirmed cases whereas none were isolated from river water samples and stool samples of family members. In household surveys, 27.3% reported recent diarrhea among family members, while 18.2% reported illness resembling cholera. Most of the affected individuals (70.8%) had consumed raw fruits within 5 days before illness. Common symptoms included body ache (29.7%), headache (25.2%) and nausea (15.3%). Only 38% households reported treating water before use (boiled 58%, filtered 26%). Hand hygiene using soap and water after toilet use was reported by 95.5%. Most households disposed of waste through waste collectors (75%), burnt (12%), or dumped in river (4.5%). Most households had private toilets (69%). In conclusion, environmental contamination of water source and untreated drinking water are the likely causes of this cholera outbreak.

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CHARACTERISTICS OF 2-23 MONTHS OLD CHILDREN WITH PROLONGED DIARRHEA COMPARED TO THOSE WITH ACUTE DIARRHEA AND THEIR IMPACT DURING POST-DISCHARGE FOLLOW-UP AT DAY 90

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It is estimated that in 2019, about half a million under-5 children die annually due to causes attributed directly to diarrhea. A prolonged episode of acute diarrhea, defined as diarrhea lasting for 7–13 days, accounts for around 12 percent of all diarrheal episodes and over two-thirds of deaths associated with diarrhea. Here, we have compared the background characteristics of young children aged 2–23 months with acute diarrhea and prolonged diarrhea and also their impact at post-discharge follow-up at day 90. For this descriptive analysis, relevant data were extracted from the Antibiotics for Children with Diarrhea (ABCD) trial, which was a randomized, multi-country, multi-site, double-blind, placebo-controlled clinical trial. A linear regression model was used to compare the mean of the anthropometric outcome (ΔWLZ) across the two groups (prolonged diarrhea vs. acute diarrhea) in surviving children after adjusting for relevant covariates. A total of 8266 children were analyzed, of whom 756 had prolonged diarrhea and 7510 had acute watery diarrhea of <7 days duration. The overall prevalence of prolonged diarrhea was 9.15%. However, the highest prevalence was 15.7% in Pakistan, and the lowest was 1% in Tanzania. We observed that children aged 2–11 months who have more than three children under the age of 5 in their families and maternal illiteracy are at increased risk of developing prolonged diarrhea. At Day-90 follow-up, the children with prolonged diarrhea were found to have significantly lower weight for age Z score compared to those who suffered from acute diarrhea of <7 days duration, though their anthropometric indices were comparable at baseline. The mean± SD change in length-for-age z score from day 1 to day 90 was –0.09± 0.61 in the prolonged diarrhea group and –0.18± 0.60 in the acute diarrhea group ($p < 0.001$). There were 46 (6.1%) hospitalizations by day 90 in the prolonged diarrhea group compared with 335 (4.5%) hospitalizations in the acute diarrhea group ($p = 0.04$). Studies assessing the causes of prolonged diarrhea may be useful to predict children at risk and avert the long-term sequelae involving childhood growth.

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CLINICAL AND ENVIRONMENTAL EPIDEMIOLOGY OF VIBRIO CHOLERAE IN EASTERN DEMOCRATIC REPUBLIC OF THE CONGO, 2020-2022 (PICHA7 PROGRAM)

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Globally, there are an estimated 2.9 million cholera cases annually in cholera-endemic countries, which result in 95,000 deaths. The Democratic Republic of the Congo (DRC) is estimated to have 189,000 cholera cases each year, resulting in 7,100 deaths. The majority of cholera cases are found in cholera "hotspots", such as eastern DRC in the Great Lakes Region. However, there is limited longitudinal surveillance of cholera epidemiology in this region with most studies focusing on surveillance of suspected cholera cases rather than cases confirmed by bacterial culture. The objective of the Preventive Intervention for Cholera for 7 Days (PICHA7) program is to develop evidence-based water, sanitation, and hygiene interventions to reduce cholera in Eastern DRC. From March 2020 to December 2022, the PICHA7 program screened 644 diarrhea patients admitted to health facilities for cholera in urban Bukavu in South Kivu province of Eastern DRC. Diarrhea patient stool samples were collected within 24 hours of patient admission, and were analyzed by both rapid dipstick testing (RDT) using direct testing by the Crystal VC kit, and by bacterial culture for Vibrio cholerae. Both source and stored water samples were collected within 48 hours of patient admission for those patients confirmed to have cholera by RDT. Twenty six percent of diarrhea patients (166/644) had stool samples positive for cholera by RDT, and 21% (136/644) had stool samples positive for Vibrio cholerae by bacterial culture. The Crystal VC RDT by direct testing had moderate specificity and sensitivity compared to bacterial culture, 91% and 89% respectively. Nine percent of stored water samples (6/66) had detectable Vibrio cholerae by bacterial culture and 5% (3/64) of source water samples. These findings show a high prevalence of cholera among diarrhea patients presenting for treatment at health facilities in this cholera endemic setting in Eastern DRC and suggest that water is a transmission route for cholera infections in this setting.

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ACUTE FEBRILE ILLNESS IN PAKISTAN: ASSESSING CO-INFECTION OF MALARIA AND TYPHOID FEVER IN TERTIARY CARE FACILITIES IN KARACHI

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Acute Febrile Illness remains a major global public health threat. Historically, scholars have focused research on single disease etiologies, or exclude malaria-positive patients from further examination. To our knowledge, there have been few studies that investigated the co-infection of malaria and typhoid fever, and any related socio-demographic factors that might contribute to risk, in Pakistan. Furthermore, current diagnostic methods may represent a challenge in determining the exact etiology of acute febrile illness and can lead to misdiagnosis or improper differential laboratory diagnosis of these condition. Here, we present the result of a prospective cross-sectional study that evaluated the burden of malaria and typhoid fever single and co-infection. We also explored socio-demographic and cultural risk factors related to the occurrence of these two diseases. Overall, 550 participants (male:54%, female: 46%) aged from 2 to 80 years participated in our study and were screened using rapid diagnostic tests for typhoid and malaria. Among the study participants, 27.82% (153/550) were

typhoid positive (65 IgG and 153 IgM positive), P= 0.278, 95% CI [0.24-0.33]; and 4.91% (27/550), P=0.049, 95%CI [0.032-0.071] were malaria positive, constituting 6 cases of Plasmodium falciparum and 24 cases of P. vivax. The estimated co-infection rate for malaria and typhoid was 2.36% (13/550), P=0.24 95%CI [0.13-0.40]. Blood culture confirmed 49 typhoid cases (out of the 153 rapid test positives), of which 46 were identified as either extra- or multidrug resistant. The high prevalence of typhoid fever, and particularly drug resistant phenotypes, suggests the need for more research about risk factors contributing to typhoid transmission, and corresponding prevention strategies, in Pakistan. We observed a number of co-infections, highlighting the importance of comprehensive diagnostic testing to address multiple potential disease etiologies. We are conducting PCR testing and sequencing as next steps, which may help shed further light on risk factors and transmission dynamics.

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SIGNATURE OF EUKARYOTIC AND PROKARYOTIC GUT-MICROBIOME AMONG PATIENTS WITH GUT DISORDERS, SAUDI ARABIA

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Gut disorders are important health problems globally and in Saudi Arabia. They include irritable bowel syndrome (IBS), gut immune-mediated inflammatory diseases (IMID) and non-IBS/IMID diseases. Gut microbiota includes prokaryotic microbiota (bacteria and viruses) and eukaryotic microbiota (one-cell animals, including protozoa, and fungi). Variations in gut microbiota have several outcomes which are linked to gut health and disease.Stool specimens were collected from 2109 patients attending the KFHU. Stool specimens were microscopically examined for the parasites and their genomic DNA was extracted. Protozoal DNAs were amplified using PCR assays and PCR products were cut by restrictive enzymes and sequenced to determine genotypes and subtypes. Amplicon sequencing of extracted DNA for gut bacteria (targeting the 16S rRNA gene) and gut eukaryotes (fungi) (targeting the internal transcribed spacer (ITS) sequence) was done for bacterial and eukaryotic profiling, through analysis of BION data. Bacterial and eukaryotic diversity was measured in correlation with patient-related data.There is an unclear increase in the IMID in studies individuals. There is a clear signature of gut eukaryotes and prokaryotes profile that was linked to IBS, IMID and non-IBS/IMID gut disorders. Other than Blastocystis, parasitic infections were very rare among the study population. Gut eukaryotes, mainly Blastocystis were much less prevalent in IMIDs patients and very rare in patients with bacterial colonization. Bacterial diversity was higher in asymptomatic patients. Gut microbiota showed a pattern of distribution among different age groups and sex. The Saudi community share a unique lifestyle, genetic exposure and ethnic background which may influence the correlation between gut microbiota and gastrointestinal disorders. Gut-associated eukaryotes may reshape bacterial diversity and virulence/outcome of gut pathogens, by influencing both gut health and gut disorders.

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USE OF BIOMARKERS TO MONITOR TRACHOMA PREVALENCE AFTER IMPLEMENTATION OF MORE FREQUENT THAN ANNUAL MDA IN MAASAI COMMUNITIES IN NORTHERN TANZANIA

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Through implementation of mass drug administration (MDA), Tanzania reduced prevalence of trachomatous inflammation - follicular (TF) and met the criteria to stop MDA in 60/69 endemic councils. The remaining 9 endemic councils have persistent or recrudescent TF. Four of these councils - Longido, Ngorongoro, Monduli, Simanjiro - are located in remote geographies and largely inhabited by migrant populations. These characteristics contribute to low MDA coverage and continued trachoma transmission. As such, Tanzania is implementing strategies to better reach these districts, including more frequent than annual (MFTA) MDA. To monitor TF during MFTA MDA and understand the impact of seasonal population movement on trachoma transmission, we implemented trachoma sentinel site monitoring (SSM) in two districts receiving MFTA MDA (Longido and Ngorongoro) and two receiving annual MDA (Monduli and Simanjiro). We surveyed 10 sites per district before each MDA, randomly selecting 50 children, 1-9 years per site. We conducted clinical grading for TF and collected ocular swabs to detect Chlamydia trachomatis (Ct) infection and dried blood spots (DBS) to detect antibodies to the pgp3 antigen. Quesionnaires were completed to measure acceptability of sample collection, household occupation, household migratory patterns, and water and sanitation access. After, samples were transported to Muhimbili Hospital for processing, using rapid real-time PCR nucleic acid amplified test and pgp3 lateral flow assay. Preliminary results prior to and following the first round of MDA showed TF prevalence for Longido and Ngorongoro changed from 23.0% to 10.8% and 14.7% to 17.0% respectively and TF prevalence for Monduli and Simanjiro changed from 19.2% to 33.0% and 3.7% to 0.4%. We will present prevalence of Ct infection and pgp3 antibodies across all three rounds at ASTMH. We will draw conclusions on TF prevalence at three points in a ~12-month period in districts receiving MFTA MDA verses annual MDA. We will provide evidence on the usefulness of alternative surveillance approaches in trachoma endgame districts where population migration may be affecting programming.

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QUALITY OF TRACHOMATOUS TRICHIASIS SURGERY IN 25 DISTRICTS OF SOUTHERN NATIONS NATIONALITIES AND PEOPLE'S AND SOUTHWEST ETHIOPIA REGIONS: SUMMARY FINDINGS OF 31 SURGICAL AUDITS IN 2022

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The success of trachomatous trichiasis (TT) surgery in preventing blindness depends on maintaining quality surgical outcome in the operated eyelids. Unfortunately, surgical failure of TT after surgery cannot be zero. World Health Organization suggests Integrated Eye Care Workers (IECWs) aim for a surgical failure of trachomatous trichiasis rate less than 10% at 3-6 month follow up. The main objective of TT surgical audit was to measure actual surgical outcomes and compares them to a desired quality standard and to determine the post-operative trachomatous trichiasis (PTT) rate for the selected IECWs at 3-6 months period. The TT surgical audit was carried out in 25 districts of Southern Nations Nationalities and People's and Southwest Ethiopia regions in 2022. It was conducted by experienced eye care workers from Secondary Eye Care and Tertiary Eye Care Units. Purposeful sampling technique and systematic sampling were used to select IECWs and operated TT cases for those IECWs who had greater than 40 cases at 3-6 months period respectively. For IECWs who had less than 40 cases, all the operated cases were included into the surgical audit. A total of 31 IECWs were audited. A minimum of 26 eyelids and a maximum of 50 eyelids were audited per IECW. A total of 1,207 eyelids (on average, 39 eyelids were audited per IECW) were audited, and of these, 50 eyelids had post op TT which makes the overall PTT rate 4.1%. However, the PTT rate ranges from 0% to 10.0%. In conclusion, all the audited IECWs had low PTT rate at 3-6 months post op period compared to the WHO standard. Overall, only 50 (4.1%) eyelids had post op TT at 3-6 months which remarkably met the WHO quality standard for TT surgical outcome.

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UTILIZING MOLECULAR DIAGNOSTICS TO SUPPORT THE TRACHOMA CONTROL PROGRAM IN NAURU

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Trachoma is the world's leading infectious cause of preventable blindness, caused by the Chlamydia trachomatis bacteria. WHO simplified trachoma grading criteria are used to diagnose cases of trachomatous inflammation—follicular (TF) for field assessments of trachoma, including surveys to monitor progress toward elimination as a public health problem. Control of trachoma is through the SAFE strategy of surgery for trichiasis, antibiotic treatment for trachoma, promotion of facial cleanliness and implementation of environmental improvements. Recent reports of high TF in the absence of trichiasis, particularly in the Pacific region, suggest that TF presentations may be caused by infections other than C. trachomatis. Therefore, molecular diagnostic tools are required to confirm C. trachomatis infection to monitor the progress of eliminating trachoma as a public health problem. A baseline prevalence survey undertaken in 2019 found hyperendemic levels of trachoma in Nauru and 34.9% positive for C. trachomatis. Two rounds of MDA have been delivered, with the most recent survey reporting trachoma prevalence (TF) of 6.2%. In late 2022, the Nauru Ministry of Health, with the support of the Fred Hollows Foundation, Tropical Data and The Kirby Institute, undertook a trachoma impact study utilising the Tropical Data methodology. All consenting participants aged 1-9 years who were screened for TF were simultaneously asked to provide an ocular swab to be subsequently tested for the presence of C. trachomatis. DNA was extracted from the ocular swabs taken from one eye of the participants and tested for C. trachomatis via real-time PCR using the C. trachomatis/Neisseria gonorrhoeae (Ct/Ng) dual assay. Only C. trachomatis results were evaluated for this study. The samples of this study are still undergoing analysis and results are not ready at the time of this submission. This study will assess the impact of two rounds of MDA and whether trachoma continues to be a public health problem in Nauru. It is also anticipated that results will further support the growing supposition that molecular diagnostics is an important tool in trachoma elimination.

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NEARING ELIMINATION OF TRACHOMA AS A PUBLIC HEALTH PROBLEM IN AUSTRALIA

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Trachoma is an infectious disease of the eye, caused by Chlamydia trachomatis bacteria and is the world's leading infectious cause of preventable blindness. Australia is the only high-income country with endemic trachoma, found in First Nation populations in remote communities in central and northern Australia. The National Trachoma Management Program, initiated in 2006 follows national guidelines for the public health management of trachoma. The guidelines are based on the WHO SAFE strategy with key components being surgery for trichiasis, antibiotic treatment for trachoma, promotion of facial cleanliness and implementation of environmental improvements. First Nation children in remote communities previously identified at risk of trachoma are screened for clinical signs of trachoma, facial cleanliness, and treatment uptake. Data regarding trichiasis screening and surgery and implementation of health promotion activities are also collected at the community and regional levels by public health teams. These data are collated annually through programmatic reporting analysed to guide progress towards established targets. From 2007 to 2022, the number of remote communities identified as at risk of trachoma decreased from 229 to 84. The overall prevalence of trachoma in children aged 5-9 decreased from 14.3% to 2.2%. In 2007 65/123 communities screened reported trachoma prevalence above 5% compared to 30/84 in 2022. At the jurisdictional level, in 2007 prevalence's ranged from 13.5% to 15%, while in 2022 they were between 0% and 3.1%. With all jurisdictions now recording trachoma prevalence in at-risk communities below the WHO target of 5%, Australia needs to maintain these levels for 2 more years to be formally designated as having achieved elimination. Further, we need a plan to ensure trachoma prevalence continues to decrease, particularly in communities with ongoing endemicity, and elimination levels are sustained post-elimination

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OLDER AGE IN SUBARACHNOID NEUROCYSTICERCOSIS REFLECTS A LONG PRE-PATENT PERIOD

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Patients with subarachnoid neurocysticercosis (NCC) are usually older than those with parenchymal disease in all published series. Although it has been theorized that subarachnoid disease may have a prolonged incubation period, it is still unclear whether this age difference seen in clinical settings reflects an extended pre-symptomatic period or a delay in diagnosis owing to its insidious symptoms or poor healthcare access in endemic countries. Using available data from a large consecutive series of patients seen in a referral center in Lima, Peru, we compared the age at symptom onset between parenchymal and subarachnoid disease after adjusting for factors that could distort this relationship. Patients with mixed (parenchymal and subarachnoid) NCC or those with parenchymal cysts in different stages (viable and/or degenerating and/or calcified) were not included. From 408 eligible patients, we retrospectively compared the age at symptom onset in 140 patients diagnosed with parenchymal (pure viable or pure calcified) and subarachnoid NCC who had a confirmatory image available not more than two years after the beginning of symptoms. After controlling by sex and residence in rural endemic regions, the mean age at symptom onset in patients with subarachnoid disease was 13.69 years older than those with viable parenchymal disease (n = 140). Furthermore, our results showed consistency across all cut-off points of years between symptom onset and neuroimage evaluated in the total sample (n = 408). The design of this study allows an individual assessment of the contribution of the pre-patent period itself, adding evidence that this age difference seen on clinical grounds is not the product of delays in diagnosis, imaging, or access to care. Therefore, a long incubation period is a major contributing factor to older age at presentation in subarachnoid NCC.

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SEROPREVALENCE AND RISK FACTORS FOR NEUROCYSTICERCOSIS IN MEXICAN-AMERICANS IN STARR COUNTY, TEXAS

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Neurocysticercosis (NCC) is an invasive cestode infection caused Taenia solium. It is a leading cause of epilepsy and chronic headaches in endemic areas including Latin America, Africa, and Asia. The epidemiology of NCC has not been well-studied in the United States to date, but small epidemiological studies have demonstrated NCC in populations in the US who have immigrated from endemic regions. There is a population living in Starr County, Texas along the Texas-Mexico border in whom the presence of other neglected tropical diseases has been demonstrated due to the intersection of poverty, climate, and high rate of immigration. Our study was a serologic survey and risk factor analysis of NCC in a pre-existing cohort of Mexican-Americans in Starr County, Texas. Using a triplex enzyme-linked immunoassay (ELISA) against NCC-specific antigens, we identified an

overall seropositivity to T. solium in 7.4% (45/605) in the cohort which likely represents a combination of parasite exposure, T. solium disease outside of the central nervous system, old calcified NCC, and viable or degenerating NCC. We used self-reported survey data and neighborhood-level variables to conduct a risk-factor analysis. Female gender, specific occupation and indoor versus outdoor occupation were found to be significantly associated with NCC seropositivity. Twenty-six of the 45 positive cases were employed in healthcare, caregiving, or social service (p 0.009), and 42 of the 45 were employed in an indoor occupation (p <0.001). These occupations could pose a risk for T. solium acquisition. A geospatial analysis of cases at the census tract level showed increased percentage of seropositivity centered around urban cities Rio Grande City and Roma, as well as smaller city La Grulla and census-designated place Alto Bonito. There is a critical need to investigate these seropositive cases of NCC and confirm the diagnosis with imaging, as well as conduct an epidemiological investigation to determine if disease transmission is occurring in Starr County.

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THE POTENTIAL MECHANISTIC PATHWAYS LEADING FROM PARASITE INFECTION TO CHILDHOOD STUNTING

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In 2020, an estimated 149.2 million children under the age of 5 were physically stunted, defined as falling at least -2 standard deviations below the height-for-age World Health Organization (WHO) Child Growth Standards median. Stunting is a visible indicator of a deficient environment, the consequences of which include child morbidity and mortality, reduced and delayed neurocognitive development, and an increased risk of long-term chronic diseases. The underlying aetiology and pathophysiological mechanisms leading to stunting remain elusive, although parasites are thought to play a key role. Here, based on available studies, we present potential mechanistic pathways by which parasitic infection of mother and/or infant may lead to childhood stunting. The most well-recognised pathway to stunting is a 'vicious cycle' between deteriorating nutritional status and infection, which is evolving to encompass dysbiosis of the gut, local and systemic inflammation, alongside energetic, hormonal, and metabolic consequences. Anaemia, which is often presented as coexisting alongside stunting, may in fact be contributing. The bi-directional relationship between intestinal parasites and the microbiota in early life, and their combined effects, may also play a key role in stunting. Finally, epigenetic regulation of gene expression may link parasitic infections and poor gut health in early life to stunting. Guided by these plausible mechanisms, future multidisciplinary longitudinal studies and clinical trials should aim to elucidate the most influential factors, and synergies therein, that can lead to stunting, and ultimately towards finding solutions to successfully mitigate against it.

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PROTEOMIC AND IMMUNOINFORMATIC APPROACH TO IDENTIFY IMMUNE REACTIVE PROTEINS OF TAENIA SOLIUM CYSTICERCI FOR A POTENTIAL MULTIEPITOPE VACCINE CANDIDATE

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Metacestode larvae of Taenia solium is the causative agent for neurocysticercosis, which causes epilepsy. The unavailability of a vaccine against NCC for humans is a major cause for its widespread prevalence across the globe. Therefore, the development of a reliable vaccine against NCC is the need of the hour. We used proteomics along with immunoinformatics to develop a vaccine candidate. The immune reactive cyst fluid antigens (CF) of T. solium were identified by immune-blotting of two-dimensional gels with NCC patient's sera followed by Matrix-Assisted Laser Desorption-Ionization (MALDI) analysis. We performed a detailed proteomic study of these immune reactive proteins by using immune-informatics tools, identified the non-toxic, non-allergic, B-cell epitopes, and collected epitopes with the least sequence homology with human and other Taenia species. These epitopes were joined through linkers to construct a multiepitope vaccine. Different physiochemical parameters such as molecular weight (23.82kDa), instability (39.91), and aliphatic index (49.61) were calculated to ensure the stability of the linked peptides vaccine. The vaccine demonstrated stable interactions with different immune receptors like TLR4 and IgG confirming that it will effectively stimulate the host immune response. We anticipate that our designed B-cell linear epitope-based vaccine will show promising results in in vitro and in vivo assays. This study provides a platform that would be useful to develop other suitable vaccine candidates to prevent helminthic neglected tropical diseases in near future.

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NEUROCYSTICERCOSIS, NEUROLOGICAL DISEASE AND HIV IN THE EASTERN CAPE PROVINCE OF SOUTH AFRICA

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Neurocysticercosis (NCC), caused by the infection with larval stages of the tapeworm Taenia solium, is a leading cause of epilepsy in the Eastern Cape Province of South Africa. Human Immunodeficiency Virus (HIV) is also endemic in the Eastern Cape. Limited literature is available about the epidemiology of co-infections with these two pathogens. This study investigated the difference in prevalence of NCC between patients with different HIV and neurological statuses in the Eastern Cape in 2009-2012. A total of 146 patients were recruited from two local hospitals and categorised into four groups according to HIV and neurological status (epilepsy or headache). Patients were asked to provide blood samples for detection of active infection with T. solium larvae using the B158/B60 antigen ELISA. Patients in groups with HIV or neurological symptoms were offered a CT-scan to detect NCC lesions. Of the 127 patients providing a blood sample, 8 (25%) tested positive for active cysticercosis in Group 1 (HIV+ and neurological disease status +), a percentage significantly higher than all other groups in which 2 (7%), 0 and 2 (7%) tested positive in Group 2 (HIV- and neurological disease status +), Group 3 (HIV+ and neurological disease -) and Group 4 (HIV- and neurological disease -), respectively. Of the 70 patients who underwent CT-scans, 10 (44%) in Group 1 (9 calcified and 1 active, transitory and/or calcified), 12 (41%) in Group 2 (11 calcified and 1 active), and 9 (52%) Group 3 (7 calcified and 2 active) had NCC lesions. There were no significant differences in imaging in the three groups. CD4 counts below 200 cells per cubic millimeter were also not associated with a higher prevalence with the AgELISA or CT imaging. Despite substantial limitations caused by the socio-political climate in South Africa at the time of this study, we demonstrate the relatively high prevalence of NCC in this population with mainly calcified cysts and an increased risk of active T. solium infection among patients with HIV and neurological symptoms. This study highlights the need for improved cost-effective tests, and for further research on this neglected disease in vulnerable populations.

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CONSISTENT MEASUREMENT OF PARASITE-SPECIFIC ANTIGEN LEVELS IN SERA OF PATIENTS WITH NEUROCYSTICERCOSIS USING TWO DIFFERENT MONOCLONAL ANTIBODY (MAB)-BASED ENZYME-LINKED IMMUNOSORBENT ASSAYS

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Diagnosis of human neurocysticercosis (NCC) is complex due to the lack of specific clinical manifestations, because of that the development of new techniques based in serology constitutes a major issue for public health since NCC is one of the principal causes of neurological pathology in most developing countries. Monoclonal antibody (mAb)-based enzyme-linked immunosorbent assay (ELISA) is a complementary diagnosis technique for NCC, which detects circulating parasite antigen (Ag) indicating the presence of viable infection and Ag levels also correlate well with parasite burden. We assessed agreement between two Ag-ELISA techniques for detection of NCC, our in-house TsW8/TsW5 Ag-ELISA based on T solium mAbs and the reference Ag-ELISA for NCC B158/B60 Ag-ELISA for measuring antigen levels in sera from 113 patients with subarachnoid, parenchymal and calcified NCC. Concordance was demonstrated evaluating limits of agreement (LoA) stratified by type of NCC. Both ELISA's detected 47/48 (97.8%) subarachnoid NCC cases. In parenchymal and calcified NCC, the B158/B60 Ag-ELISA detected 19/24 (79.2%) and 18/41 (43.9%) cases, while the TsW8/TsW5 Ag-ELISA detected 21/24 (87.5%) and 13/41 (31.7%), respectively. Parenchymal and calcified NCC obtained a perfect agreement (100%), indicating that all sample results were within the predicted LoA, while for subarachnoid NCC agreement was 89.6%. High concordance between assays was confirmed by Lin's concordance coefficient (LCC=0.97). Patients with viable parenchymal NCC (LCC = 0.95) obtained the highest concordance between assays, followed by subarachnoid NCC (LCC = 0.93) and calcified NCC (LCC=0.92). Antigen detection was highly concordant between assays, suggesting that the TsW8/TsW5 Ag-ELISA can be used as a new alternative tool for this purpose. The reliability of antigen detection assays could contribute to clarify the diagnosis of NCC when neuroimaging is not conclusive or available.

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MULTIPLEX BEAD ASSAY (MBA) FOR THE ASSESSMENT OF ANTIBODY RESPONSES DURING CYSTICERCOSIS IN EXPERIMENTAL INFECTED PIGS

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Taenia solium is the cause of cysticercosis and results in a neurologic disease (Neurocysticercosis, NCC) when the central nervous system is infected. Pigs are the natural hosts and the preferred animal model for NCC. Antibody responses are usually assessed by the serological gold standard, the Lentil-lectin enzyme-linked immunoelectrotransfer blot (LLGP-EITB) assay, but this format is technically challenging, not quantitative and needs complex antigen purification process to obtain the seven diagnostic glycoproteins. Our group has characterized 6 recombinant antigens that represent the main protein families in LLGP-EITB diagnosis. LLGP-EITB antibody patterns in NCC types and stages have been identified, but the response of simultaneous recombinant proteins has not yet been quantified. We developed an immunoassay based on magnetic microspheres (MBA) coupled with all 6 diagnostic recombinant antigens that allows a simultaneous quantification of antibody levels. We evaluated 162 serum samples from 18 pigs who were experimentally oral infected at 1 (n=6), 3 (n=6) and 5 (n=6) months-old, and were bled at 9 time points post infection (PI) until day 90PI. Necropsy data from the original study demonstrated more efficacious infections and more viable cysts in younger pigs, and more degenerated cysts in older pigs. In our 6 antigens-MBA, the high-performance antigens (rGP50, rT24H and sTs14) showed differences in their ability to differentiate pigs with different cyst viability conditions. rT24H and rGP50 detected antibodies in pigs with viable or no viable cysts and during all the course of infection, while sTs14 has a stronger response in viable infections. In addition, there was a progressive increase in the antibody response of rGP50 from day 21PI and from day 28PI for all the other antibodies. Pigs infected at 3 and 5 months-old showed a marked decrease from day 57PI until necropsy. Therefore, our new 6 antigens-MBA was a valuable tool to quantify and compare the simultaneous presence of antibodies against T solium recombinant antigens during the progress of the cysticercosis infection.

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LATERAL FLOW TEST FOR NEUROCYSTICERCOSIS - PRELIMINARY EVALUATION

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Neurocysticercosis (NCC) is an infection of the central nervous system with the cystic form of the pork tapeworm, Taenia solium. NCC accounts for approximately one third of all cases of seizures worldwide and is the most important neurologic disease of parasitic origin according to the World Health Organization. NCC affects over 25 million individuals in endemic, and increasingly non-endemic, regions. In the U.S., it has been found in 2% of seizure patients presenting to hospital emergency departments. Thus, NCC, an officially designated "neglected disease", is an underrecognized but significant global cause of morbidity and mortality. Serological testing has been useful in diagnosing NCC, either to supplement imaging or where imaging is not available. However, the gold standard EITB (enzyme immunotransfer blot) test developed by CDC is of limited availability, and no point-of-care tests for NCC are commercially available. We have developed a prototype lateral flow test for NCC based on recombinant versions of selected glycoprotein antigens used in the CDC EITB. The NCC lateral flow test was evaluated on a panel of 59 sera from NCC patients comprising both parenchymal and extraparenchymal cases, confirmed by imaging and clinical history, 200 sera from healthy blood donors and 38 sera from patients with other disease conditions. The overall sensitivity of the NCC lateral flow test on confirmed NCC sera was 98.3% (58/59) when read with a reader device, or 96.6% when read visually; the single undetected sample was from a patient with a single cyst that was marginally detectable by ELISA. Overall specificity was 99.6% (237/238), with a single false positive blood donor serum detected. The lateral flow assay appears to be a promising candidate for point-of-care use in diagnosis of NCC, subject to further clinical testing, which is underway.

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LATE POST-TREATMENT INFLAMMATORY RESPONSE AND RESIDUAL CALCIFICATION IN NEUROCYSTICERCOSIS

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Neurocysticercosis (NCC) is the leading cause of acquired epilepsy in developing countries. Cysts in the brain go from a viable resting state to complete resolution or calcification. Although it was previously believed that calcified lesions did not cause consequences, residual calcifications are associated with worse evolution of seizure disorders in NCC. We evaluated

the process of degeneration and calcification in the brain of pigs naturally infected with Taenia solium (n=15) and treated with 15 mg/kg albendazole and 25 mg/kg praziquantel orally. antiparasitic. The animals were divided into three groups of 5 animals each and the necropsy was performed at 4, 8 and 12 months post treatment. Inflammation and calcium deposits were evaluated by H&E, Masson's trichrome, Alizarin red, and Von Kossa stains, and immunomarkers such as GFAP, IBA, and neurofilament. The fifteen pigs showed 137 lesions, composed of 62 calcified cysts and 75 fibrotic lesions. The 4M group presented 13 calcified cysts, the 8M group had 35 calcified cysts, and the 12M group presented 14 calcified cysts. The 8M animals presented larger calcified lesions and greater intensity of calcium deposits compared to the other groups, as well as a greater amount of inflammatory cells that were distributed throughout the entire lesion. The 12M group has a greater number of fibrotic cells and has a greater area of fibrosis surrounding the lesion. This longitudinal study provides novel insight into the dynamics of inflammation and calcification and may contribute to the development of interventions aimed to reduce the likelihood of residual calcification.

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INFLUENCE OF EUKARYOTIC ENTERIC PATHOGENS ON THE GUT FUNGAL COMMUNITY IN MALIAN CHILDREN

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Eukaryotic enteric pathogens (EEP) pose a worrying public health issue in tropical countries. Yet, the interactions between EEP and the gut fungal community remain poorly understood. To evaluate the impact of EEP on fungal community, we carried a case control study in Malian children living in Bandiagara, Mali. Cases were defined as children with at least one EEP and control as children without EEP. Sample stools were collected from 296 Malian children to explore gut fungal by qPCR and metagenomics targeting, rRNA ITS1 and ITS2 regions metabarcoding. The 100 (33.8%) children in whom no EEP was detected were considered as controls, and they were compared to: a) 196 (66.2%) children who had at least one EEP; b) 91 (30.7%) children who had only Blastocystis; c) 35 (11.8%) children who had only Giardia intestinalis; and d) 12 (4.0%) children who had another (<1% each) EPP. The gut fungal community structure was homogenous in each of the children's group. Linear size effect discriminant analysis highlighted five species, including Fusarium longipes and Penicillium caseilulvum, which were relatively more abundant in children with at least one EEP whereas 28, including Aspergillus sydowii and Microdochium colombiense were more abundant in controls. Regarding Blastocystis infected children, the abundance of Fusarium, Pyxidiophora, and Stereum genera was higher in infected children whereas Ogataea, and Allocryptovalsa were more abundant in controls. Regarding Giardia intestinalis, Sordariales and Mortierellales abundance was higher in infected children, whereas Agaricales and Capnodiales abundance was higher in controls. Overall, EEP do not significantly impact the global gut fungal community structure, but further studies are warranted to confirm our finding that taxa of the gut mycobiota are associated with susceptibility or resistance to specific EEP.

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HELMINTH INFECTION DRIVES REDUCED SERUM COMPLEMENT AND COMPLEMENT REGULATORY PROTEIN ACTIVATION IN INDIVIDUALS WITH COINCIDENT TYPE 2 DIABETES

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Several clinical, epidemiological, and laboratory studies suggest that helminths could help mitigate the progression of Type 2 Diabetes Mellitus (T2DM) by modulating a host of pro-inflammatory pathways. Because complement hyperactivation has been observed in patients with T2DM and because the complement system can have unwanted consequences if not controlled appropriately (to prevent excessive activation), we sought to examine the effect of the helminth Strongyloides stercoralis (Ss) on the complement activation pathways in T2DM. We examined the circulating levels of the complement proteins C1q, C2, C3, C4, C4b, C5, C5a, and MBL and some of their regulatory components (Factor B, Factor D, Factor H, and factor I) in individuals with T2DM with (n=60; Ss+T2DM+) or without (n=58; Ss-T2DM+) concomitant Ss infection (n=58). Furthermore, we estimated the effect of anthelmintic therapy on complement pathway components 6 months after treatment. Complement levels of C1q (GM of 47.50 ng/ml in Ss+DM+ Vs 63.88 ng/ml in Ss-DM+; p=0.0065), C3 (GM of 125.5 ng/ml in Ss+DM+ Vs 150.1 ng/ml in Ss-DM+; p=0.0003), C4b (GM of 394.9 ng/ml in Ss+DM+ Vs 525.6 ng/ml in Ss-DM+; p=0.0024), C5a (GM of 1876 ng/ml in Ss+DM+ Vs 2319 ng/ml in Ss-DM+; p=0.0191), MBL (GM of 46.41 ng/ml in Ss+DM+ Vs 62.35 ng/ml in Ss-DM+; p=0.0016), Factor B (GM of 41.71 ng/ml in Ss+DM+ Vs 57.93 ng/ml in Ss-DM+; p=0.0010), and Factor D (GM of 38.40 ng/ml in Ss+DM+ Vs 56.11 ng/ml in Ss-DM+; p=0.0002) were significantly lower in Ss+DM+ compared to Ss-DM+ individuals. Following anthelmintic treatment the levels of C1q (an increase of 15%; p=0.0012), C4b (an increase of 11%; p<0.0001), and MBL (an increase of 11%; p=0.0201) were increased in T2DM+Ss+ individuals. Our data imply that Ss infection restricts complement activation and related pathological inflammatory process in T2DM individuals.

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DESCRIPTIVE AND PREDICTIVE ANALYSIS OF SOIL-TRANSMITTED HELMINTHIASIS IN SCHOOLCHILDREN OF TIERRALTA, CORDOBA, COLOMBIA

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Soil-transmitted helminths (STH) infect more than two billion people worldwide, especially in developing countries located in tropical and subtropical regions. The department of Cordoba, Colombia is located in a region with a high prevalence of this parasitic infection. Given the great burden that STH represent in our community, their impact on the normal development of childhood, and the scarce studies with an integrative approach in our country, a descriptive and predictive study was carried out for the evaluation of STH. We sampled 70 children aged 4 to 17 years old from Santa Fe de Ralito School in the municipality of Tierralta, Cordoba. Epidemiological information was collected through surveys and the parasitological diagnosis was performed by Kato-Katz in stool samples. Blood samples were collected to measure hemoglobin and blood cells. A set of inflammatory, anti-inflammatory, and regulatory cytokines were measured by flow cytometry. The prevalence of STH infection was 55.7%. Trichuris trichiura was the most frequent parasite, being present in 92% of infected participants, either as mono-infection or co-infecting with Ascaris lumbricoides or hookworms. The hematological and immunological parameters showed suppression of the anti-inflammatory response with

a predominance of the regulatory cytokine Transforming growth factor-beta. The Monocyte chemoattractant protein-1 had higher levels in the infected participants. Interferon-ɣ-inducible protein-10 was higher in the ones co-infected with two or more parasites. These findings suggest an attenuated immune response against STH, with effectors mechanisms to protect the host's tissues but failing in expelling the parasites. Finally, using the epidemiological data, a statistical predictive model of STH infection was designed with good performance (accuracy: 0.714) as a pilot tool for the prevention of these pathologies at the community and rural levels.

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TRICHURIS TRICHIURA INFECTION ASSOCIATED WITH AN INCREASED RISK OF PLASMODIUM FALCIPARUM INFECTION AMONG POPULATION LIVING IN BATA DISTRICT, EQUATORIAL GUINEA

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Sub-Saharan Africa is known to be endemic for Plasmodium and Soil-Transmitted helminth (STH) infections, where both diseases very often occur in the same host. In the case of co-infection, studies report either a worse or a beneficial effect of STH species on plasmodium infection. The objective of the present analysis was to evaluate the effect of STH infection on malaria in the continental region of Equatorial Guinea, a central African country where such data are lacking. We performed a cross-sectional study between October 2020 and January 2021 in Bata district. Venous blood was collected for Plasmodium infection testing, using mRDTs while stool samples were collected for the diagnostic of Ascaris lumbricoides, Trichuris trichiura, and hookworm infections using Kato-Katz technique. A general linear model was used to assess the association between Plasmodium and STH infections. A total of 340 participants were included in the study with a mean (SD) age of 24.5 (23.7) and 1.22 female-to-male sex-ratio. The prevalence of Plasmodium infection was 52% (95%CI: 46 - 58) while the prevalence of any STH was 60% (95%CI: 55 - 65). The prevalence of Plasmodium and STH parasites co-infection was 37% (95%CI: 31 - 42). Assessing the association with Plasmodium infection, a statistically significant association was found at bivariable analysis for A. lumbricoides (cOR=1.71; 95%CI: 1.11 - 2.66, p-value=0.01) and T. trichiura (cOR=2.64; 95%CI: 1.69 - 4.16; p-value<0.001). After multivariable analysis adjusting for age, sex, and STH species, the association with Plasmodium infection remained statistically significative only for T. trichiura infection (aOR=2.03; 95%CI: 1.23 - 4.16; p-value=0.006). Our results reveal a high prevalence of Plasmodium and STH parasites co-infection in the district of Bata, Equatorial Guinea, where both diseases are highly prevalent and where T. trichiura infection increases the risk of Plasmodium infection. This result calls for more investigation of STH and malaria comorbidity, and more attention on the overlapping of both infections for tailored control programs of those two infections in the country.

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INTESTINAL PARASITIC INFECTIONS AND ASSOCIATED RISK FACTORS, KNOWLEDGE, ATTITUDE AND PRACTICES IN CALABAR, CROSS-RIVERS STATE, NIGERIA

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The prevalence of intestinal parasitic infections, associated risk factors, knowledge, attitude and practices among residents of two LGAs in Calabar, Cross-Rivers State, Nigena was determined. A total of 600 persons who gave their consent to be part of the study made up of 356 females 59.33% and 244 males 40.67% within different age-groups had their faecal samples examined using the formol-ether concentration technique. Structured questionnaires which sought information on socio-demographic data of respondents, risk factors and KAPs regarding IPIs were administered. The results revealed that 321 persons 53.5% were infected with one or more parasites. Ascaris lumbricoides. Entamoeba coli, Entamoeba histolytica, Taenia spp, Hookworm and Trichuris trichiura were the parasites observed. Mixed infections occured 5.83%. More females.53.6% than males 53.2% were infected. Infection was highest in the age group 50-59-years 58.11%, the unemployed 78.8%, persons with no formal education 64.8%, the widows 67.0%, those who did not wash their hands after toileting 94.19%. The highest infection rate occured among the Nsidung community. In terms of risk factors and KAPs, those who used stream 76.6% and rivers 74.3% recorded high prevalences of infection. Those who used the bush and streams as toilets recorded high infection rates of 76.6% and 73.4% respectively. Many knew about IPIs 81.17%. Mode of transmission was attributed to ingesting improperly cooked food 48.33%, infected water 10.33%, Skin penetration 8.33%. Many went to the hospital/ clinic for treatment 49.0%, while some resorted to self-medication 24.5% and use of herbs 10.34%. The Government should show political will by acting now and invest in NTDs. Health education becomes paramount. There is need to progress toward reduction of infection through the implementation of Water, Sanitation and Hygiene (WASH) intervention policy. All should act together to bring an end to these IPIs ravaging our communities in various nations.

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MOLECULAR CHARACTERIZATION OF A NOVEL GHANA STRAIN OF NECATOR AMERICANUS HOOKWORMS

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Laboratory passage of an African strain of Necator americanus hookworms has been sustained through 9 passages in outbred hamsters using larvae (L3) cultivated from human study subjects in Beposo, Ghana. Initial cutaneous infections of 2-day old hamsters were conducted in parallel with subcutaneous (SQ) infections of 21-day old weanlings, with animals provided ad libitum water containing dexamethasone. Subsequent passages were sustained in weanling hamsters by SQ infection. Fecal egg excretion was detected as early as 45 days post infection (PI) and continued beyond 150 days PI. Amplification of β tubulin genomic DNA sequences spanning resistance associated SNPs revealed wild type loci with intronic heterogeneity in 20 adult worms recovered from the initial (F0) hamster passage. Egg hatch assays revealed that the field strain showed comparable benzimidazole sensitivity to an established laboratory strain of Ancylostoma ceylanicum. In silico analysis of an N. americanus reference genome was used to develop methods for amplification of di, tri and tetranucleotide microsatellite repeats of 100, 200, 300 and 400 base pair fragment sizes. Of the 40 loci evaluated using 20 (F0) adult worms, 21 loci showed reliable amplification of the expected size, while 15/21 loci deviated from Hardy-Weinberg equilibrium (p< 0.05). PCR-amplification of COX1

mitochondrial DNA sequences from 20 (F0) adult worms revealed that the Ghana strain is distinct from previously characterized isolates from China and Brazil. A full mitochondrial genome was reconstructed from a single adult worm using long-read sequencing on the Oxford Nanopore MinION. A maximum-likelihood phylogenetic analysis using full mitochondrial genomes further demonstrated the Ghana strain is distinct from N. americanus samples from China and Togo. These data provide the first in vivo, in vitro and genomic analysis of a Ghana strain of N. americanus successfully adapted from humans to an animal model. Use of these methods and the resulting reagents will accelerate the development of geographically targeted therapeutics, vaccines and advanced diagnostics for use in West Africa.

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ASSOCIATED SOCIOECONOMIC AND DEMOGRAPHIC FACTORS WITH SOIL-TRANSMITTED HELMINTHIASIS IN FIVE PROVINCES IN GABON

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Soil-transmitted helminthiases are Neglected Tropical Diseases endemic in Central Africa including Gabon. Populations living in remote areas had a lack of water supply and live in poor hygienic conditions. These populations are not access to anthelminthic drug due to isolation caused by the absence of passable roads. In the aim to help the Parasitic Diseases National Control Programme in Gabon to reach the objective to control Soil-transmitted Helminthiasis until 2030, an epidemiological study was performed in five provinces according to the urbanization level to identifying risk factors. A cross-sectional study was conducted in five provinces in Gabon according to the urbanization between December 18th, 2018 to July 10th, 2019. Socioeconomic and demographic data were recorded in a standardized case report form. After explanations of the fecal collection to participants, samples were analyzed using Merthiolate-Iodine-Formaldehyde coloration and concentration techniques. Data were analyzed by descriptive statistics and Chi squared test. In total, 201 volunteers were included in the study with a sex ratio of 0.71 and a median age of 24.0 [6.0 - 51.5] years. Nearly 60.0% of them lived in rural areas (59.7%; n = 108/181). The proportion of helminth carriage was 11.9% (24/201) with Ascaris lumbricoides, Trichuris trichiura and Necator americanus detected respectively in 7.5 (15/201), 6.5 (13/201) and 1.0% (2/201) of samples. The only association Ascaris lumbricoides + Trichuris trichiura was found in 6/201 participants (3.0%). The factors presenting an association with the infestation by soil-transmitted helminths were the residence in a rural environment (p=0.0012), the level of primary education (p=0.001), the consumption of drinking water (p=0.02), use of toilets outside the main residence (p = 0.05) and use of modern toilets (p=0.04). In conclusion, soil-Transmitted Helminthiases are found in more than one tenth of the study population. Sensitization of the populations and Water, sanitation and Hygiene must to be implemented in rural area where the prevalence was higher.

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THERAPEUTIC EFFICACY OF MEBENDAZOLE AGAINST HOOKWORM INFECTION AMONG SCHOOL CHILDREN IN BAHIR DAR ZURIA DISTRICT, NORTHWEST ETHIOPIA

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Soil-transmitted Helminths (STHs) are widely distributed in tropics and subtropics. Although MDA programs remain the cornerstone for controlling STHs, constant monitoring of benzimidazole resistance in areas where albendazole or mebendazole are periodically given is warranted to detect early rising of resistance in human STHs, prompting interventions to control this emergence in an early stage before genotypic and phenotypic resistance is widespread. This study was conducted to evaluate the efficacy of single-dose mebendazole against hookworm infection in school children. An open-label, single-arm trial was conducted in 4 primary schools from Bahir Dar Zuria district, Northwest Ethiopia from February, 2021 to March, 2022. Stool samples were collected and screened using double slide Kato Katz smear microscopy from 499 participants. A total of 132 hookworm-positive participants were treated with single-dose mebendazole (500 mg). Follow-up was done 21 days after treatment on 115 participants. Statistical analysis was performed by SPSS version 23 and R software version 4.2.1. P-values < 0.05 were considered statistically significant. Out of 132 participants, 50.8% participants were females. The mean age of the participants was 9.98 ±1.8. The mean egg counts per gram stool at baseline and after treatment (95% CI) were 180 (120, 251) and 68 (49, 91) respectively. The cure rate and egg reduction rate (95% CI) were 36.5% (28.3, 45.6) and 62.1% (59.2, 63.7) respectively. None of the variables considered for predicting cure were found statistically significant. The therapeutic efficacy of single-dose mebendazole against hookworm infection is below the WHO recommendation. Therefore; single-dose mebendazole should not be given as preventive chemotherapy against hookworm infection and another treatment regimen should be considered.

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DEVELOPMENT AND EFFICACY OF VARIOUS PAN-HOOKWORM VACCINE TARGETS

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Over 500 million people worldwide suffer from hookworm infections and disease. Despite years of concerted effort at deworming campaigns, hookworm infections remain prevalent due to imperfect anthelmintic efficacies and ease of reinfection. Development of a pan-hookworm vaccine would significantly impact hookworm disease by limiting primary infection and mitigating reinfections. Here we describe the identification and testing of potential targets suitable for vaccine development using two distinct approaches. First, we are using proteomics, transcriptomics (tissue-specific), immunomodulation, comparative bioinformatics, and immunoinformatics to identify >30 hookworm vaccine targets. To date, in addition to our previously published CP1, we have identified at least one other vaccine antigen that shows provides some level of reproducible protection against hookworm infection. Studies are on-going with additional antigens. Second, we are using hookworm extracts of various sorts and stages and have identified two specific conditions that provide a very high level of infection. Current efforts are focused on identification of protective antigens in these mixtures. Here we will present an update on all of these efforts that are making excellent progress towards a protective hookworm vaccine.

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NEW CURE FOR SOIL-TRANSMITTED HELMINTH INFECTIONS

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Gastrointestinal nematodes (GINs; alternatively soil-transmitted helminths or STHs), most notably, hookworms, whipworms, and Ascaris, are nematodes that infect more than 1.5 billion of the poorest people and are amongst the leading causes of morbidity worldwide. For decades, infections by STHs have been treated with small-molecule anthelmintic drugs, the heavy use of which has often selected for drug-resistance or recalcitrance. Bacillus thuringiensis crystal (Cry) proteins are the most widely used biological insecticides in the world and are nontoxic to vertebrates. We have shown that Cry proteins, in particular Cry5B, are highly effective against a broad range of free-living and parasitic nematodes that infect plants and animals. Here, we discuss several new Cry proteins, CryH18, CryH1, and CryH13. CryH18 is highly active against C. elegans and is able to kill C.elegans resistant to Cry5B. We cloned CryH18 into our IBaCC (Inactivated Bacterium with Cytosolic Crystal) expression system. IBaCC takes advantage of dead bacteria to safely deliver recombinant Cry proteins. Here, we report Cry18H IBaCC is toxic in vivo against A. suum, Ancylostoma ceylanicum hookworms, and Heligmosomoides polygyrus bakeri infections. We are also expanding studies on CryH1 and CryH13, both of which have been shown to be highly active against A. ceylanicum infections in vivo. We hypothesize that we might be able to control GINs using Cry18H at a single dose or in combination with different cry proteins to combat GIN resistance and increase clinical efficacy.

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EFFECT OF SOIL-TRANSMITTED HELMINTH INFECTIONS ON THE CYTOKINE BALANCE IN CHILDREN FROM AN ENDEMIC AREA IN MONTERÍA - CÓRDOBA - COLOMBIA

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Helminth infections can result in a strong immunoregulatory activity that affect the capacity of the host, mainly children population to develop co-infections, as well as being a risk factor in events such as asthma and atopy. The effect of these infections on the balance of pro- and anti-inflammatory cytokines in children from an endemic area in Córdoba - Colombia was measured. An analytical observational study was carried out, where seventy (70) school children were selected and studied and grouped into two groups (infected and control) and an epidemiological survey was carried out. Stool samples were processed by the Kato Katz method for identification and quantification of soil-transmitted helminths and blood plasma was used for flow cytometric quantification of cytokines and chemokines. The prevalence of STH was 56% (44.3-67.6); 77% (63.7-90.2) of the infections were mono infections and the remaining percentage were poly infections with at least two STH species. The intensity in most cases was moderate. When comparing cytokines and chemokines between the groups, TNF-α (P=0.0431) and IFN-γ (P=0.0484) had significant differences in both groups, for the chemokine MCP-1, the median values of the control group were significantly higher than that of the infected group (P=0.001). The anti-inflammatory profile cytokine TGF-β1 in the infected group had higher plasma concentrations than in the control group (P=0.0005). For IL4 and IL10, plasma concentrations were slightly higher in the control group than in the infected group, but there were no statistically significant differences between them; as was the case for TGF-β1, where the infected group had higher plasma concentrations than the control group. These data suggest that the STH infections presented by children in this endemic area have a behavior of chronic asymptomatic infections, established with a pattern of overdispersion and with a predominance of immune response with an anti-inflammatory and regulatory profile, apparently generated by TGF-β1.

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INTESTINAL PARASITE INFECTION AND RISK OF CONCOMITANT CERVICO-VAGINAL INFECTIONS IN THE PERUVIAN AMAZON

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Intestinal parasite infections, including helminths and protozoa, remain an important public health concern in tropical low- and middle-income countries, such as Peru, where cervico-vaginal (CV) infection rates are also high. As they establish chronic infection in the human gut, intestinal parasites must regulate the host's immune system to ensure their long-term survival, potentially impacting the host's defense against other pathogens. This cross-sectional study explored the relationship between intestinal parasite and CV co-infections, specifically bacterial vaginosis (BV) and Trichomonas vaginalis (TV) in 30–50-year-old Peruvian women. We enrolled 120 women undergoing routine cervical cancer screening in Iquitos, Peru, between August 2022 and February 2023. Participants provided demographic, clinical, and risk factor information, underwent testing for HPV, HIV, syphilis, chlamydia, BV (via Nugent score), and TV (via wet mount), and submitted specimens for stool ova and parasite microscopy. We used logistic regression to evaluate whether parasite infection was associated with BV or TV co-infection. Of 108 participants, 54.6% had intestinal parasite infection (9.1% (9/108) helminth [88.9% (8/9) Ascaris and 11.1% (1/9) hookworm] and 50.9% (55/108) protozoa [98.2% (54/55) Giardia and 1.8% (1/55) Entamoeba histolytica]). CV infections were: HPV 18.6% (19/102), HIV 0.9% (1/108), syphilis 0.9% (1/113), chlamydia 0% (0/50), BV 36.1% (39/108), and TV 6.5% (7/108). Whereas intestinal parasite infection overall was not associated with TV (p=0.89), participants with Ascaris lumbricoides were 12.84 times more likely to have TV (95% CI: 2.37, 69.52, p=0.0068). Intestinal parasite infection was positively associated with BV (adjusted OR 3.67, 95% CI: 1.02, 13.21, p=0.0466). Sexual and sanitation variables did not differ among women with and without parasite infection. These preliminary findings suggest that certain intestinal parasite infections may increase risk of CV co-infections like TV and BV. Thus, public health measures to reduce community intestinal parasite burden could reduce morbidity from CV infections.

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SUCCESSFUL TREATMENT OF CUTANEOUS LEISHMANIASIS WITH INTRAMUSCULAR INJECTION OF SODIUM STIBOGLUCONATE IN AN 18 MONTH OLD CHILD

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Cutaneous leishmaniasis is endemic in Ethiopia. It is one of the neglected tropical disease for which few treatments with variable success rate are available. Treatment varies depending on the site, size and number of the lesion, the leishmania species type, age of the patient etc. There are few reports available regarding the use of intramuscular sodium stibogluconate use for treatment of cutaneous leishmaniasis in children less than two years of age. In addition most guidelines do not clearly put the use of intravenous or intramuscular use of sodium stibogluconate in children less than two years. Here we present an 18month old male child treated with intramuscular injection of sodium stibogluconate for cutaneous

lesishmaniasis. The child presented with lesion over the face since four month which is asymptomatic. On physical examination there is 3cm x1.5cm erythematous indurated plaque just below the right lower eye lid and close to bridge of the nose with overlying hyperpigmented crust. On skin slit smear examination there is leishmania parasites (leishman Donovan bodies) seen. He was admitted and treated with daily intramuscular injection of 200mg of sodium stibogluconate. He was followed with weekly laboratory investigations which includes complete blood count, liver function test, renal function test, lipase, amylase and electrocardiograph. On the fourth week, 23rd day, he developed hepatotoxicty with more than five times elevation of liver enzymes and the drug was discontinued. At this moment the healing was adequate in which flattening of the lesion and reepithelization reached 80%. After a week the liver function test was normalizing and topical 15% parmomycin (approximately 3gm) was given and he applied it only for 6 days. After 2 months the child has complete flattening and reepithelization of the lesion. In conclusion, sodium stibogluconate can be used in children at least 18 month and older.

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A NOVEL TREATMENT FOR SCABIES

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Scabies is a highly contagious skin disease caused by Sarcoptes scabiei var hominis. It is associated with serious life-threatening secondary bacterial infections caused by Group A Streptococcus and Staphylococcus aureus. There is no vaccine and the most commonly used therapeutics, oral ivermectin and topical permethrin mainly target the parasite nervous system, killing only the motile stages. Therefore, they have sub-optimal efficacies and require repeat treatments. Prolonged use of current drugs and patient incompliance to repeat treatments have led to emerging parasitic resistance. This highlights the importance of a single dose treatment that targets all the stages of the S. scabiei life cycle. We tested two novel scabicides (ADF and FDF) in in vitro bio-assays and pre-clinical, using the porcine scabies model. In vitro results shows excellent miticidal and ovicidal effects of compounds ADF and FDF. When used in combination, the efficacy was significantly raised. The lethal time (LT100) to kill all mites and young eggs was 2h, and for late-stage eggs 8h. Four groups of 8 scabetic pigs were used in pre-clinical evaluation. Single topical application of the combined formulation on scabetic pigs for 4h or 8h resulted in complete cure of the infection by day 5 post-treatment and remained mite-free. The results were significantly better than two doses of ivermectin group and the un-treated control group remained infected. Pharmacokinetics of the compounds are being assessed by mass-spectrometry. In addition, combination treatment showed excellent anti-bacterial effects against scabies associated pathogens with significantly lower minimum bactericidal concentration (MBC) than the scabicidal concentration in vitro. We propose that our novel treatment is a promising next generation scabicide which only require a single application and likely prevents scabies associated secondary bacterial infections.

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KINETICS OF CARDIOVASCULAR AND INFLAMMATORY BIOMARKERS IN CHILDREN WITH DENGUE SHOCK SYNDROME

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Vascular leak is the hallmark of dengue infections which in some patients can lead to the potentially fatal dengue shock syndrome (DSS). Early identification and quantification of leak remains challenging, yet crucial to optimise fluid therapy. Endothelial glycocalyx layer (EGL) disruption and inflammation are implicated in the pathogenesis of vascular leak, however little is known about their association with intravascular volume and clinical outcomes. We investigated the association of EGL and inflammatory biomarkers and their kinetics during fluid resuscitation in DSS patients admitted to ICU. Paediatric patients were enrolled on admission to ICU at shock onset. Three daily blood samples were taken during ICU stay and one at 1-month follow-up visit (FU), for measurements of plasma levels of syndecan-1 (SDC1), hyaluronic acid (HA), suppression of tumorigenicity 2 (ST2), ferritin, and N-terminal pro-B-type natriuretic peptides (NT-proBNP), and atrial natriuretic peptides (ANP). The primary outcome was intravascular volume defined by a percentage haematocrit (HCT) change (values taken at shock onset and baseline at FU). Secondary outcomes were the development of recurrent shock and respiratory distress. 90 patients were enrolled; the median age was 12 years. Recurrent shock occurred in 16 patients and 10 had respiratory distress. Ferritin and ST2 were highest at enrolment (ICU admission), whilst HA and SDC1 peaked 24-hours after admission. These biomarkers decreased over ICU stay and returned to normal at FU. The natriuretic peptides had different trajectories, with increasing trends from ICU stay to FU. HA had a positive correlation with %HCT change ($rho = 0.37$, $p = .02$). None of the biomarkers at admission associated with recurrent shock or respiratory distress. Ferritin had a positive correlation with HA ($rho = .59$, $p < .001$) and SDC1 ($rho = .60$, $p < .001$) at all timepoints. In summary, we have shown the host inflammatory response is associated with EGL breakdown and HA could be a useful surrogate marker of leak severity in patients with DSS.

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THE IMPACTS OF COVID-19 ON THE RESURGENCE OF LASSA FEVER IN NIGERIA

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The Coronavirus (COVID-19) pandemic is one of the worst pandemics in history. Lassa fever is a viral hemorrhagic fever endemic in Nigeria and some other West African countries. This study aims to identify the relationship between the incidence/reporting of COVID-19 and Lassa fever, factors affecting the trends of both illnesses in Nigeria, and how public health agencies can be better prepared for the effects of future pandemics on the incidence/reporting of other diseases. Data was extracted from the Nigeria Centre for Disease Control disease situation reports. Lassa fever reports for [24th to 31st Dec. 2018], [23rd to 29th Dec. 2019], [27th Dec. 2020 to 2nd Jan. 2021] and [26th Dec. 2022 to 1st Jan. 2023], as well as COVID-19 reports for [21st to 27th Dec. 2020], [20th to 26th Dec. 2021], and [5th to 18th Dec. 2022] were obtained. A systematic search was done on PubMed to include the keywords [COVID-19], [Lassa fever], [Nigeria] for the years [2020 to 2022]. The total number of confirmed cases of Lassa fever in Nigeria was 633 in 2018, 833 in 2019, 1,181 in 2020 and 511 in 2021; a 56.7% decrease in 2021. However, the total number of confirmed cases increased by 109% to 1,067 in 2022. As of 27th December 2020, a total of 88,414 COVID-19 cases had been recorded. On 26th December 2021, the figure rose by 168.7% to 237,561 and on 18th December 2022, the number of confirmed cases rose by only 12% to 266,415. While COVID-19 was prevalent, Lassa fever reportage declined. A few reasons that may account for this disparity in the incidence of both diseases, as obtained from the review of literature, include: similarities in clinical manifestations, insufficient modulator laboratories (only 8) for Lassa fever testing in Nigeria, and the similarities in the laboratory and management facilities of both diseases. The 'seasonal' timing and symptoms of Lassa fever and COVID-19 surge are similar. Hence, public health agencies in countries that have such occurrences must be better prepared to adequately test, manage or co-manage multiple disease conditions in the same facility. Such agencies must also increase public awareness of such related diseases occurring concurrently.

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SCRUB TYPHUS AND Q FEVER AMONG HOSPITALIZED PATIENTS WITH ACUTE FEBRILE ILLNESS IN BANGLADESH

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Infection by Orientia tsutsugamushi (scrub typhus) or Coxiella burnetii (Q fever) have previously been reported in Southeast Asia, including Bangladesh, but remains underdiagnosed due to lack of diagnostic capacity and clinician awareness. From September 2021 to February 2023, we randomly enrolled 1,544 hospitalized AFI patients from five tertiary care hospitals across different geographical regions of Bangladesh; 778 were adults and 766 were infants and children (2 months-12 years). AFI was defined as a measured or history of fever (≥ 100.4°F) within the past 14 days. We detected 24 (1.5%) cases of scrub typhus and 7 (0.5%) cases of Q fever from blood samples by real-time PCR assay. Among the detected scrub typhus cases, 50% were male, and 19 (79%) were adult (25-75 years). Ceftriaxone (71%) was predominantly prescribed and doxycycline, the recommended drug, was only used in one patient. The average duration of hospital stay was five days. Of 24 patients, 10 (42%) were discharged with improved status, 13 (54%) left voluntarily before improving, and one died on the 11th day following admission. On follow-up in the 4th week, 54% of the cases reported improvement, 12% reported full recovery, 33% were lost to follow-up, and one additional death occurred.All seven Q fever positive cases were male and adult (20-55 years) and six were from Rangpur Division. Two of the cases reported contact with domestic cows and goats. All cases were treated with ceftriaxone. Only two patients reported improvement at discharge, and after 4 weeks, six reported full recovery.Scrub typhus and Q fever are not commonly detected in clinical settings in Bangladesh. Detection of hospitalized cases of scrub typhus and Q fever suggest that clinicians should consider these diseases as a differential diagnosis of severe AFI in Bangladesh. To support differential diagnosis and better management of these diseases, low-cost appropriate diagnostic tools along with education and knowledge of these diseases should be made accessible to clinicians at the point and time of care.

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TIMELY RETURN OF TEST RESULTS FOR MEASLES AND YELLOW FEVER: A SURVEY OF CARE PROVIDERS IN GHANA

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Laboratory tests are ordered to diagnose and manage patients, but also are critical to outbreak detection. Timely return of results for clinical decisions and surveillance depends largely on the prompt reporting of laboratory results. This study surveyed health care providers for their assessment of the timely return of test results for two epidemic-prone diseases (Yellow fever and Measles) in Ghana.A survey of healthcare providers was carried out in 53 randomly selected health facilities from the three ecological zones in Ghana, stratified by remoteness and population density. Data were collected from providers in hospitals and subdistrict facilities from February 2021 to July 2022. Descriptive analysis characterized providers' assessment of the duration of time between patient onset of symptoms and presentation to health facilities as well as the return of test results for patient management.Providers estimated 9.1 days (95%CI 7.47-10.72) for patients with symptoms of non-severe YF to present for care, compared to 6.4 days (95%CI 4.7-8.02) for severe cases of YF. Patients with non-severe measles were estimated to present in 5.2 days (95%CI 4.08-6.34) and with severe measles in 6.8 days (95%CI 5.98-7.54). All testing was reported to occur by send-out. Both yellow fever and measles testing was estimated to return in a median of 30 days (IQR 14-90 days). The median percentage of yellow fever results estimated to occur in a timely manner for patient management was 0% (IQR 0-40%) and for measles was also 0% (IQR 0-30%). Return of test results for Measles and Yellow fever was delayed, hence the need to strengthen the laboratory network since the potential for the transmission of epidemic-prone disease depended on both the time between infection onset until presentation to health facilities, as well as the time to receive testing results.

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CEREBROSPINAL FLUID CHLORIDE IN THE DIAGNOSIS OF TUBERCULAR MENINGITIS- A PROSPECTIVE STUDY FROM JODHPUR, INDIA

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Tubercular meningitis presents a diagnostic challenge as uniform criteria are lacking, and no single test can definitively rule it out. We explored cerebrospinal fluid chloride and cerebrospinal fluid-serum chloride ratio as diagnostic tools for tubercular meningitis. Adults with clinical suspicion of meningitis were enrolled prospectively from March 2021-September 2022 after informed consent and ethical approval. Tubercular meningitis was diagnosed using a combination of clinical findings, CNS imaging, cerebrospinal fluid analysis and nucleic acid amplification tests. Sensitivity, specificity, and area under the curve for receiver-operating curve were calculated for cerebrospinal fluid chloride and cerebrospinal fluid-serum chloride ratio to diagnose tubercular meningitis. Of 209 included, 56 were diagnosed with tubercular and 61 with viral meningitis, rest were pyogenic and others. The mean cerebrospinal fluid chloride was low in tubercular meningitis (115.4±10.6 mmol/L), as compared to viral meningoencephalitis (127.0±7.5mmol/L, p <0.0001). The mean ratio of cerebrospinal fluid-serum chloride (1.18±0.09) was also significantly lower in patients with tubercular meningitis in comparison to patients with viral meningoencephalitis (1.24±0.06, p =0.04). Area under the curve of cerebrospinal fluid chloride levels for the diagnosis of tubercular meningitis was 0.76 (p <0.0001, 95% CI 0.68-0.84) and cerebrospinal fluid-serum chloride ratio was 0.67 (p <0.0001, 95% CI 0.58-0.75). Cerebrospinal fluid chloride <121 mmol/L had a sensitivity and specificity of 70.5% and the cerebrospinal fluid-serum chloride ratio had a sensitivity and specificity of 65% for diagnosis of tubercular meningitis. Our study showed that absolute cerebrospinal fluid chloride and cerebrospinal fluid-serum chloride ratio are sensitive diagnostic markers for diagnosis of tubercular meningitis and specially to differentiate it from viral meningoencephalitis in the initial course of illness.

6295

A CASE OF MONKEYPOX VIRUS REINFECTION

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We present the case of a healthy man in his early 30's who presented with monkeypox virus infection six months after having completely recovered from a previous one. He identifies as a man having sex with men and is taking pre-exposure prophylaxis for HIV. The first episode was mild with a few umbilicated lesions on the penis. Cutaneous and pharyngeal swabs

were positive by real-time orthopoxvirus PCR. Within two weeks skin lesions resolved without complications. Six months later the patient was seen by his general practitioner for persistent anal pain. The pain had started after his return from Brazil where he had engaged in unprotected sexual intercourses including anal receptive intercourses with multiple partners. The last intercourse was reported two weeks before symptoms onset. He did not develop any skin lesions nor systemic symptoms. The anal swab came back positive for monkeypox virus by real-time orthopoxvirus PCR with a cycle threshold of 27, a repeated swab two week later was negative. Sexually transmitted disease (STD) screening was positive for Chlamydia trachomatis (non LGV) and negative for HIV and syphilis. A colonoscopy revealed an anal fissure but no typical mpox lesions. He was never vaccinated against mpox. Symptoms might have been due to mpox or to the concomitant presence of an anal fissure or Chlamydia trachomatis infection. It is therefore impossible to distinguish between a symptomatic or asymptomatic mpox reinfection. This case, although still anecdotal, suggests that certain individuals might not develop sufficient neutralizing immunity after natural infection and become reinfected when re-exposed to monkeypox virus. From a public health perspective, if reinfection become more prominent, it raises the questions of repeated testing of highly exposed symptomatic individuals regardless of prior infection or vaccination and of extending vaccination to individuals after an infection.

6296

IMPACT OF DIFFERENTIAL AND SYSTEMATIC DIAGNOSIS OF DENGUE, CHIKUNGUNYA AND MALARIA ON PATIENT MANAGEMENT AND ANTIBIOTIC USE IN BURKINA FASO AND IVORY COAST

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Over the last several decades, dengue and chikungunya have become more geographically dispersed with common clinical outbreaks. They are responsible for high morbidity and mortality in endemic areas, such as West Africa where there is limited data. The health systems in these countries therefore face major challenges. This study aims to assess the impact of differential diagnosis of these two arboviruses on febrile patients clinical management, prevention of complications, antibiotic and antimalarial misuses. Differential diagnosis of dengue and chikungunya will be performed using the VIDAS® Diagnostic Tests for the detection of Dengue Virus NS1 Antigen, Anti-Dengue Virus IgM and IgG and VIDAS® anti-CHIKV IgM and IgG (technology developed at the US NIAID, Vaccine Research Center), whereas malaria will be diagnosed by RDTs. 800 subjects with acute undifferentiated febrile illness will be enrolled in a prospective cohort study carried out in two West African countries with respectively one interventional and one control sites per country. In interventional sites, all subjects will be tested for dengue and chikungunya (VIDAS®) in addition to malaria (RTDs). Clinicians' final diagnosis will consider the patients' clinical symptoms and diagnostic tests results. In control sites, on-site routine diagnosis will be used. In parallel, all the biological samples will be tested for dengue and chikungunya (VIDAS®) to obtain the real rate of positive subjects. Clinical outcomes are i) the comparison using a Chi-2 test of antibiotic use in control and interventional sites, ii) the healthcare resource utilization and productivity losses, iii) the subject quality of life using EQ-5D questionnaire. The enrollment is expected to start in April 2023 for a 5 months duration. Intermediate analysis will be performed on 400 subjects and presented in the poster. These findings should highlight the relevance of differential diagnosis in febrile subjects' clinical management, generate seroprevalence data and demonstrate the potential for avoiding antibiotic misuse which amplify the emergence of antibiotic resistance and lead to greater mortality.

6297

INTESTINAL IMMUNOHISTOCHEMISTRY AND HISTOLOGY RELATIONSHIPS WITH FECAL ENTERIC PATHOGENS IN A PEDIATRIC POSTMORTEM STUDY

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Postmortem (PM) intestinal minimally invasive tissue sampling (MITS) has previously been demonstrated feasible and histologically informative despite autolysis concerns. We aimed to determine the informative value of immunohistochemistry (IHC) and pathogen analysis on PM intestinal samples. PM duodenal and rectal biopsies from children with acute illness and/or undernutrition who died as inpatients (MITS in Malawi, n=23), and duodenal biopsies from live children with environmental enteric dysfunction (EED) (Zambia, n=59) or no pathologic abnormality (NPA) (U.S., n=25) were endoscopically biopsied and stained for both hematoxylin and eosin (H&E) and a 14-marker IHC panel. Pathologists semi-quantitatively scored H&E images using a validated EED histology index. IHC images were digitally quantified and normalized to account for tissue size. Enteric pathogens were sought by qPCR on MITS stool, duodenal, and rectal samples. We used multivariable linear regression to (1) compare duodenal IHC readouts from MITS to EED and NPA samples and (2) test associations between fecal pathogens with IHC readouts and histology scores in MITS samples. MITS IHC stain quantification were similar to those of EED and NPA cohorts, but B lymphocyte, intraepithelial lymphocyte (IEL), brush border, and leukocyte proliferation marker readouts were significantly lower in MITS samples while granzyme B signal was higher. At least one pathogen was found per MITS participant, although detection was much more frequent in stool samples and fecal pathogens did not clearly correspond in intestinal samples. Fecal enteropathogenic E. coli was inversely associated with rectal histology summative index score (-0.18; 95% CI: -0.32, -0.05). Stool pathogen-IHC associations included enteroaggregative E coli with duodenal intraepithelial CD3 (-0.06; 95% CI: -0.09, -0.03) and rectal MUC2 (-1.98; 95% CI: -2.59, -1.37), and norovirus with rectal defensin 5 (0.33; 95% CI: 0.21, 0.45) and MUC2 (1.27; 95% CI: 0.01, 2.52). These novel data support the use of IHC along with H&E for histopathologic assessment in PM intestinal samples to improve knowledge of host pathobiology.

6298

TRAVEL HEALTH NEEDS OF CHILDREN IN US MILITARY FAMILIES STATIONED ABROAD

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The Military Health System (MHS) provides care to 9.6 million beneficiaries including uniformed service members, military retirees, and their family members with the mission to provide a medically ready force both at home and abroad. The US Department of Defense requires certain preventative health measures for service members serving abroad; however, many of these service members are living with spouses and children who have their own preventative health needs. We characterize the MHS pediatric population living outside of the United States and the recommended travel health specific preventive services. We assessed the registered country of residence of Active Duty Service Members (ADSM) and their families based on the Defense Enrollment Eligibility Reporting System to quantify the children of ADSM, under the age of 18, living abroad. Data were sorted by age group and region, excluding those living in the continental United States, Alaska, and Hawaii, as well as Canada. Data from Reservists and Retirees were excluded; although also MHS beneficiaries, their location is less likely to be service-related. There are 63,443 children of ADSM living abroad and rotating on a 2-3 year cycle. Of those children, 26,269

are aged five or younger with 37,174 children 6 to 17 years old. The largest populations are in Asia (26,172) and Europe (31,243), reflecting long standing bases in Japan and Korea as well as Germany, the United Kingdom, and Italy, with a sizable population also in Oceania (3,676) due to the US military presence in Guam. Thousands of military children live in countries without permanent military bases and MHS medical assets in these regions and those in Mexico/Central America/the Caribbean (1,658), Africa (397), and South America (297). We map recommended travel specific interventions across this population distribution. The children of military families serving abroad are a unique population in need of a range of preventative health services that differ from their counterparts in the United States. Utilization of preventive services and health outcomes associated with living abroad have not been studied in this population.

6299

VALIDATION OF AN NS1 AND IGM RAPID TEST IN THE EARLY DIAGNOSIS OF DENGUE IN A PRIMARY HEALTH CARE CENTRE IN BUCARAMANGA, COLOMBIA DURING THE YEARS 2018-2020

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Dengue has a broad spectrum of manifestations that difficult the clinical confirmation in regions where the acute syndrome febrile is multi-aetiology. The laboratory diagnostic requires specific and sensitive tests with the good advantage of cost, time, and easier manipulation. The rapid tests to detect NS1, play an important role in the early diagnosis of dengue however the implementation in primary health care is not the rule and the routinary IgM detection may not be useful during the acute phase. This study aimed to validate the use of the NS1 and IgM rapid test in primary healthcare facilities in the early detection of dengue cases during an outbreak in Colombia. From 2018 to 2020, a system was established in the healthcare of public networks in Bucaramanga, Colombia. After the blood counts and using the remaining sample, a commercial rapid test was run for antigen NS1 and IgM. One RT-PCR was performed for the detection of Zika, chikungunya, and dengue viruses. The quick test and the RT-PCR were performed independently and in a specific order: first, the rapid test and second the RT-PCR were done blinding. We estimated sensitivity, specificity, and positive and negative predictive values (SE, SP, PPV and NPV, respectively) for NS1 and IgM against PCR stratifying by disease's duration, considering a range of prevalence between 10-50%. We evaluated 566 patients with complete clinical and diagnostic data (32% were PCR positive). Overall, SE and SP were 81% and 72% for NS1 and 38% and 62% for IgM, respectively. SE increased with the disease's duration from 33.3-54.0% for IgM but remained stable around 80.0% for NS1, whereas SP was similar for both tests and showed a decreasing trend at larger disease duration. PPV and NPV ranged from 52.9-74.2% and 73.6-100.0% for IgM, and from 58.7-95.9% and 98.7-100.0% for NS1 at the disease's onset, respectively. According to our results, testing for NS1 is not only feasible in the context of primary care but also a highly accurate approach to diagnose tools for dengue in endemic areas where the acute syndrome febrile is multi-aetiology, allowing an early and suitable diagnosis to reduce complications due to the disease.

6300

THE EFFECTS OF L-CARNITINE SUPPLEMENTATION ON RATE OF WEIGHT GAIN AND BIOMARKERS OF ENVIRONMENTAL ENTERIC DYSFUNCTION IN SEVERELY MALNOURISHED CHILDREN: A DOUBLE-BLINDED RANDOMIZED CLINICAL TRIAL

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Severe Acute Malnutrition (SAM) and an asymptomatic small intestinal illness, Environmental Enteric Dysfunction (EED), are highly prevalent among children in resource-limited countries like Bangladesh. To best of our knowledge, limited trials have been conducted on malnourished children to evaluate the effects of carnitine, a vital micronutrient for ß-oxidation. Therefore, we sought to explore the role of L-carnitine on the rate of weight gain and EED biomarkers in SAM children. A prospective, double-blinded, placebo-controlled, randomized clinical trial (ClinicalTrials.gov# NCT05083637) was conducted at Dhaka Hospital of icddr,b. Participants were 9-24 months-old severely malnourished children who were randomly assigned to receive commercial L-carnitine syrup (100mg/kg/day) or a placebo for 15 days in addition to the protocolized treatment of SAM at the Nutritional Rehabilitation Unit (NRU). A total of 98 children with a weight-for-length z-score (WLZ) <-3 SD were enrolled between October 2021 and September 2022. All analyses were based on an intention-to-treat basis. The primary outcome variable, mean weight gain (g/kg/day), was comparable between the intervention and placebo groups [2.18 vs. 2.11; ß: 0.06, 95% CI: (-0.95, 1.07), p: 0.902], respectively. After the intervention, the mean difference between baseline and end line values of EED biomarkers were also comparable; for instances- Myeloperoxidase-ng/ml [-1129.99 vs. -152.93; ß: -977.06, 95% CI: (-8837.77, 6883.65), p: 0.806], Neopterin-nmol/L [166.67 vs. 342.44; ß: -175.78, 95% CI: (-719.78, 368.22), p: 0.523], Alpha-1 Antitrypsin-mg/ml [0.39 vs. 0.30; ß: 0.09, 95% CI: (-0.09, 0.27), p: 0.321], respectively, in L-carnitine and placebo groups. Our clinical trial results provided the best available information and laid the groundwork to show the effects of L-carnitine supplementation on the rate of weight gain and EED biomarkers in participants with severe acute malnutrition. A scaling-up of this intervention with high doses in contexts with limited resources should be considered.

6301

BRAINSTEM ENCEPHALITIS AND EXTRAPYRAMIDAL SYNDROME AFTER ZIKA VIRUS INFECTION IN SALVADOR, BRAZIL

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Zika virus (ZIKV) is an emerging flavivirus that caused a widespread outbreak in Brazil in years 2015-2016. In addition, shortly after its introduction in 2015, a cluster of cases with Guillain-Barré syndrome and other neurologic syndromes were described in Brazil. Herein, we present a case of a brainstem encephalitis with extrapyramidal syndrome in a patient in Salvador, Brazil. A 21-year-old Brazilian woman presented with fever, maculopapular rash, pruritus, arthralgia, headache, and edema of hands and feet. She was admitted to the hospital seven days after the onset of viral symptoms when neurological symptoms began: confusion, somnolence, inability to walk, and impairment of speech. After a generalized seizure she was admitted to the intensive care unit (ICU). She was lethargic, had dysphonia and dysarthria, right facial nerve palsy, impaired palate elevation, and severe dysphagia. She had normal muscle strength and brisk deep tendon reflexes. Cerebrospinal Fluid (CSF) was collected seven

days after the onset of viral symptoms, and a serum sample 12 days after the onset of those symptoms. CSF revealed two cells/mm3 (lymphocytes), 43mg/dL (protein), and 64mg/dL (glucose). RT-PCR for ZIKV, CHIKV, and DENV were negative in serum samples. ELISA Anti-ZIKV IgM and IgG antibodies were detected, as well as the ZIKV PRNT. She recovered over the following 34 days. This case report highlights a rapid and severe evolution of symptoms, requiring hospitalization in the ICU, with long-term treatment. Brainstem encephalitis is a rare disease. Herein,it was clinically diagnosed through the presence of cerebellar disorders, altered level of consciousness, and hyperreflexia. ZIKV should be considered a potential etiological agent of encephalitis in endemic regions. Healthcare workers must be aware of the potential severe neurological syndromes associated with ZIKV infection and be prepared to provide prompt diagnosis and supportive care.

6302

EFFECT OF PRIOR DENGUE INFECTION AND SINGLE-DOSE DENGUE VACCINATION ON THE RISK OF SUBSEQUENT VIROLOGICALLY CONFIRMED DENGUE: A FIVE-YEAR PROSPECTIVE COHORT STUDY IN CEBU, PHILIPPINES

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Dengue is a mosquito-borne viral illness causing significant morbidity and mortality. In 2015, a three-dose dengue vaccine (CYD-TDV,Dengvaxia) was licensed for those 9 years and older in dengue-endemic areas. In 2016, the World Health Organization (WHO) recommended that countries consider introduction of CYD-TDV in settings with at least 70% seroprevalence. The Philippines Department of Health (DOH) implemented a three-dose dengue vaccination program in high dengue burden regions targeting children aged 9 to 14 years old. In June 2017, the program was expanded to Cebu province. After a follow-up analysis of the CYD-TDV Phase 3 trials showed that vaccination conferred protection among dengue-seropositive but increased risk for severe dengue among dengue-seronegative participants, the dengue vaccination program was halted with children in Cebu offered only one dose. We conducted a prospective community-based cohort study in Cebu to evaluate the effect of baseline dengue serostatus and a single dose of CYD-TDV on the subsequent risk of virologically-confirmed dengue (VCD). We enrolled 2,996 healthy children 9 to 14 years of age in May 2017. Baseline sera were collected and batch tested by indirect IgG ELISA and focus reduction neutralization test (FRNT). From June to August 2017, 1,790/2,996 (59.7%) children received a single dose of CYD-TDV. Active surveillance for an acute febrile illness (AFI) in the cohort was conducted from November 2017 to October 2023 (5 years). Those who developed AFI were identified, epidemiological and clinical data were collected, and blood drawn for confirmation of dengue by RT-PCR. Incidence was 11 VCD cases/1,000 population/year. Crude (unadjusted) analyses showed that seronegative children at baseline who received one dose of CYD-TDV were more likely to develop VCD (RR 2.12, 95% CI 1.45-3.09), while those who were seropositive at baseline and received one dose of CYD-TDV were less likely to develop VCD (RR 0.47, 95% CI 0.32-0.69). Our findings support the 2018 revised WHO recommendation of pre-vaccination screening prior to administration of CYD-TDV.

6303

MOLECULAR SURVEILLANCE AND EPIDEMIOLOGY OF LEPTOSPIROSIS AND SCRUB TYPHUS FROM PATIENTS WITH FEVER OF UNKNOWN ORIGIN IN URBAN BANGALORE, INDIA

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Acute Febrile illnesses, usually accompanied by fever, malaise, and rashes could be associated with many infectious diseases transmitted by viruses, parasites, bacteria, or fungi in tropical countries. Leptospirosis and scrub typhus are neglected and re-emerging tropical infectious diseases, transmitted by gram-negative bacterium belonging to the Leptospiraceae family. and via the bites of infected chigger mites, spread through a bacterium Orientia tsutsugamushi belonging to the family Rickettsiaceae respectively. Sporadic outbreaks of both these infections have been concerning and over a million cases per annum, reported from South-Asian countries. Early detection and diagnosis of Leptospirosis and scrub typhus are challenging and rely usually on non-confirmatory detection tests such as ELISA respectively in both diseases, leading to underestimation of the actual disease burden. We conducted a molecular surveillance study screening 977 clinical samples across a metro city, Bangalore in South India, in collaboration with local municipal corporation-Bruhat Bengaluru Mahanagar Palike (BBMP). We aimed to understand the seroprevalence of Leptospirosis, Scrub typhus, and coinfections by ELISA and an inhouse designed multiplex TaqMan Probe-based RTPCR from the patient samples. We observed, 69/977 (7.06%) samples, tested positive for Leptospirosis, 134/ 977 (13.72%) for Scrub typhus and 21/977 (2.15%) had coinfection of both. Prevalence of both Leptospirosis and scrub typhus exhibited a significant decreasing trend from July to December ($\chi 2$= 123.44, df =3; P<0.001). The disease prevalence was compared across ELISA and q RT-PCR for both infections ($\chi 2$= 6.262, df =1). The study showcases a unique collaboration with local municipal corporation, contributing to public health surveillance. The study findings shall aid in understanding the actual disease incidence and prevalence using two different detection methods Further, this shall help in creating guidelines and detection protocols for, neglected infectious diseases from patient samples having febrile illnesses in low-resource settings.

6304

A CASE OF TYPE 1 LEPROSY REACTION WITH NASAL SEPTUM PERFORATION

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Leprosy reactions are caused by immune responses against M. leprae antigens. They are divided into Type 1 or reversal reaction (T1R), and Type 2 or ENL (T2R). Type 1 reaction can occur in up to 30% of patients usually after the start of treatment. The majority of the reactional episodes occur in borderline forms. It starts as a sudden worsening of skin lesions and nerve function impairment. Besides pre-reactional lesions presenting with more infiltration and desquamation, previous and newly developing lesions may be bright red, hot, and sensitive to the touch, sometimes ulcerated. We present the case of a 28-year-old male patient who presented to ALERT hospital Dermatology clinic with lesions on the face buttock and leg of 4 months duration. Nose lesion is associated with bleeding and stuffiness. On Physical examination, he had well-demarcated edematous erythematous plaque on the face involving the upper lip and nose with areas of hypopigmentation. The nasal septum is deviated and perforated (.5cm by 1cm). There is a hypo-pigmented erythematous anesthetic plaque of 10cm by 12 cm over the left buttock with ulcerations at the border and ulceration on the right malleolus. He had a hypopigmented patch with fine scales on the right dorsum of the hand. Sensory testing shows that there is loss of sensation on the hand and buttock lesions and the right foot over half of the plantar area. On Investigations slit skin smear is negative. Histopathology showed multiple well-formed granulomatous and giant cells along with mixed inflammatory cells composed of plasma cells and eosinophils. With

the diagnosis of Borderline tuberculoid leprosy with Type 1 reaction he started MDT ((Multi Drug Therapy) and prednisolone 1mg/kg. This case report highlights that new leprosy cases can present with reactions and reactions can occur before starting MDT treatment. Even though nasal involvement is common in the lepromatous leprosy type, it can occur as post-reaction tissue damage in T1R.

6305

PREDICTORS OF VIRAL UNSUPPRESSION AMONG ADOLESCENTS AGED 10 TO 19 ON ANTIRETROVIRAL THERAPY IN THE CITE VERTE HEALTH DISTRICT

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Globally, 37.7 million people were living with HIV in 2020. Adolescents living with HIV is on a steady rise from 1.65 million in 2018 to 1.8 million in 2021 yet very little evidence exists to comprehensively estimate adolescent viral suppression after initiation on antiretroviral therapy (ART). The National AIDS Control Committee 2020 report reveal a 29% viral suppression (<1000copies/ml) against a 93% target set for 2019. This greatly affects most HIV intervention programs as adolescents continue to lag behind in the HIV response with viral unsuppression thereby leading to increased drug resistance, transmission of HIV as well as increased morbididty and motality. This study therefore aims to identify Sociodemographic, Clinical and Behavioral predictors associated to viral unsuppression among adolescents aged 10 to 19. From a quantitative analytical study and using random probabilistic sampling, we collected data from 488 adolescents after informed consent and assent were obtained. Quantitative analysis revealed that59.2% were females, the mean age of adolescents was 15.19 years and median were 15.00 years. 16.4% of adolescent who participated still had an unsuppressed most recent viral load result. Age [(AOR = 1.10, 95% CI 0.51-0.88, P-value=0.017)], level of education [(AOR=1.46 95% CI: 0.84-2.55, P-value=0.007)] , religion [(AOR=0.25, 95% CI: 0.09-0.66)], caregiver type [(AOR=1.40, 95% CI: 0.78-0.99, P-value=0.025)], recieving care from a non-pediatric health facility {(AOR=0.51, 95% CI: 0.28-0.91, P-value=0.025)], treatment line [(AOR=3.81, 95% CI:1.88-7.74, P-vaalue<0.0001)], duration on treatment [(AOR=0.59, 95% CI, 0.34-0.81, P-value=0.044)] and poor adherence [(AOR=19.85, 95%CI, 9.53-41.36, P-value<0.0001)] were found to be predictors associated to viral unsuppression among adolescent. Hence, there is a great need to strengthen the health systems, intensify peer lead Differencial Service Deliver model, Enhanced Adherence Counselling, support groups, and therapeutic education amongs adolescents while promoting psychosocial suppor to both adolelescents and care gives.

6306

INTEGRATION OF FEMALE GENITAL SCHISTOSOMIASIS INTO HIV/SEXUAL AND REPRODUCTIVE HEALTH AND RIGHTS AND NEGLECTED TROPICAL DISEASES PROGRAMS AND SERVICES: A SCOPING REVIEW WITH A SYSTEMATIC SEARCH

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Female genital schistosomiasis (FGS) affects approximately 56 million women and girls across sub-Saharan Africa, and is associated with up to a threefold increased prevalence of HIV. Integrating FGS with HIV programmes as part of comprehensive sexual and reproductive health (SRH) services may be one of the most significant missed opportunities for preventing HIV incidence among girls and women. A search of studies published until October 2021 via Scopus and ProQuest was conducted using PRISMA guidelines to assess how FGS can be integrated into HIV/SRH and neglected tropical diseases (NTDs) programs and services. Data extraction included studies that integrated interventions and described the opportunities and challenges. A total of 334 studies were identified, with 22 eligible for analysis and summarised conducting a descriptive numerical analysis and qualitative review. We adapted a framework for integrated implementation of FGS, HIV and HPV/cervical cancer to thematically organize the results, classifying them into five themes: awareness and community engagement, diagnosis, treatment, burden assessment, and socio-economic evaluation. Most activities pertained to awareness and community engagement (n=9), diagnosis (n=9) and were primarily connected to HIV/AIDS (n=8) and school-based services and programming (n=8). The studies mainly described the opportunities and challenges for integration, rather than presenting results from implemented integration interventions, highlighting an evidence gap on FGS integration into HIV/SRHR and NTD programmes. Investments and will are needed to realise the potential of FGS integration to address the burden of this neglected disease and improve HIV and SRH outcomes for millions of women and girls at risk.

6307

DIAGNOSING A WOMAN PRESENTING WITH FOCAL WEAKNESS AND FACIAL PALSY IN MONROVIA, LIBERIA WITH PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY: A CASE REPORT

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A 45-year-old Liberian female with recently diagnosed HIV-1, stroke, and diabetes mellitus presented to the hospital in Monrovia, Liberia with reported generalized weakness for 2 weeks. On exam, she was hemodynamically stable. She had left lower lung crackles. She had facial asymmetry with cranial nerve VII palsy and left-sided facial paralysis. Right lower extremity strength was 1/5 and left lower extremity strength was 3/5. Right upper extremity strength was 3/5 and left upper extremity strength was 4/5. Admission complete blood count and complete metabolic panel were unremarkable. A CD4 count lateral flow assay showed CD4 <200 cells/μL. HIV viral load was pending. CT head demonstrated non-enhancing white matter hypodensity in bilateral parietal lobes with extension into right anterior limb of internal capsule and right external capsule. Per radiology, there was non-enhancing white matter hypodensity with signals of mild gliosis in aforementioned areas most likely due to progressive multifocal leukoencephalopathy (PML). Brain MRI was recommended. Given cerebrospinal JC virus PCR testing was unavailable, lumbar puncture was not performed. She was re-initiated on an antiretroviral (ARV) regimen of tenofovir disoproxil fumarate/lamivudine/dolutegravir for HIV/AIDS to reconstitute the immune system, which is the mainstay of treatment for PML, and trimethoprim/sulfamethoxazole prophylaxis. She received a course of azithromycin for pneumonia. She clinically improved over her several weeks of hospitalization with increased strength, particularly in the right side of her body. Her caretaker noted her improved functional strength. In summary, clinical and radiologic findings are important tools to diagnose PML. Particularly in limited resource healthcare settings, when diagnostics such as JC virus cerebrospinal fluid testing are not readily available, a clinical syndrome must be recognized. Supportive diagnostics include immunocompromised host factors, clinical symptoms and exam findings of focal neurologic deficits, and congruent radiologic brain imaging findings which can include white matter lesions.

6308

BONE MARROW CRYPTOCOCCOSIS: A RARE PRESENTATION OF A COMMON INFECTION IN AN IMMUNOSUPPRESSED PATIENT

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A 43-year-old man with AIDS (CD4 <40 cells/microliter and viral load 309,000 copies/mL) presented with right sided weakness with associated

6 months of general malaise with recent weight loss of 8kg. On exam, he was afebrile, but tachycardic up to 120. He was cachectic with marked hepatosplenomegaly but no adenopathy. His speech was dysarthric, had right facial paralysis, right hemiparesis with clonus. Labs revealed pancytopenia (Hb of 3.8 g/dL, platelets 31 and WBCs 1.66). CT scan of the chest, A/P and head were unrevealing, but MRI brain revealed a small acute infarct in the left globus pallidus and posterior limb of the internal capsule. CSF studies showed a Cryptococcus titer of 1:1997. Patient was subsequently started on amphotericin and flucytosine for induction therapy. Despite adequate coverage for Crypto, his pancytopenia persisted. This led to a bone marrow biopsy being obtained, which demonstrated Cryptococcus on mucicarmine, PAS fungus, and GMS stains. Due to concerns for bone marrow toxicity, flucytosine was held and ampho was continued. After a hiatus from flucytosine, his blood counts started to recover and normalize. After completing ampho induction, he was stabilized and discharged on fluconazole for maintenance therapy. Although Cryptococcus infection commonly presents with CNS, pulmonary, or skin involvement in patients with CD4 counts <100, bone marrow involvement has been previously described which can present with nonspecific symptoms such as fever, anorexia, weight loss, and fatigue. Bone marrow involvement will have certain implications on treatment as in this case. A known side effect of flucytosine is its bone marrow toxicity. It is important to recognize potential bone marrow involvement, as this makes flucytosine a relative contraindication. Continuing flucytosine in these cases will only worsen the pancytopenia which could cause other adverse outcomes (bleeding, worsening infection, etc.), but the goal should be to continue Ampho for induction therapy which also reaches good bone marrow concentrations and then transition to Fluconazole for consolidation and maintenance therapies respectively.

6309

TUBERCULOSIS CASE NOTIFICATIONS, TB/HIV CO-MORBIDITIES AND TREATMENT OUTCOMES IN AMHARA REGION, ETHIOPIA: A RETROSPECTIVE LONGITUDINAL PROGRAM BASED STUDY

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Globally, TB still remains as one of the major public health problems. Poor treatment outcomes, low TB case detections and its high co-morbidities are the main challenges for the success of TB program in Ethiopia. Therefore, we assessed the effectiveness of national TB control strategies on TB case notifications, treatment outcomes, and its co-morbidities between 2009 and 2018 in Amhara Region, Ethiopia. We conducted retrospective longitudinal program based study to determine the trends of TB/HIV case notifications, treatment outcomes and to identify associated factors from the reports of DOTS (Directly Observed Treatment Short-course) implementing health facilities. We extracted data from the regional TB/HIV program databases using a modified WHO (World Health Organization) reporting formats. Data were entered, cleaned and analysed using R-programming R x64 3.6.1 packages. The Case Detection Rate (CDR) of all forms of TB had increased from 55% in 2009 (95% Confidence Interval (CI) = 54.5% - 55.4%) to 73% in 2018 (95% CI = 72.2% - 73.2%). Over the same period, TB/HIV co-morbidity rate had been reduced from 32.6% (95% CI =30.7% - 34.5%) to 8.4% (95% CI = 8.04% - 8.8%). The odds of being co-morbid with HIV was higher for those TB cases who were diagnosed as extra-pulmonary TB cases [Crude Odds Ratio (COR) [95% CI] =1.26(1.07, 1.47)] compared to other forms of TB. Apart from this, being co-morbid with HIV [COR (95% CI) = 5.91 (5.52, 6.33)] and being diagnosed as extra-pulmonary TB cases [COR (95% CI) = 1.40 (1.35, 1.45)] were important predictors to be significantly associated with unsuccessful treatment outcomes. In conclusion, a huge proportion of all forms of TB cases (36%) remained undetected. Therefore, access to quality of diagnostic services such as fluorescence microscopy and GeneXpert needs to be improved through designing targeted TB case finding strategies for risky groups to TB infection. Additionally, designing of early linkage and treatment follow-up strategies need to be tailored for those groups of TB cases who are at risk to unsuccessful treatment outcomes.

6310

CLINICAL SIGNS AND IMMUNE RESPONSE CHANGES DURING PLASMODIUM FRAGILE CO-INFECTION OF ART-TREATED SIV+ RHESUS MACAQUES

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Plasmodium co-infection in untreated people with HIV (PWH) results in increased viral load (VL), decreased CD4+ T cell counts, and greater incidence of clinical malaria and malaria-related mortality. However, the impact of Plasmodium co-infection in antiretroviral therapy (ART) treated PWH has not been well described. We hypothesized that P. fragile co-infection of ART-treated, SIV+ rhesus macaques (RMs) would result in elevated VL, decreased CD4+ T-cell counts, and neutrophil disruptions. Male RMs (n=4) were intravenously (i.v.) inoculated with SIVmac239 (TCID50=50); initiated daily antiretrovirals (ART) at Week (W) 8 post-SIV infection; i.v. inoculated with P. fragile (20x10^6 infected erythrocytes [iRBCs]) at W12 post-SIV; and received anti-malarial treatment at W14 post-SIV. Peripheral parasitemia, anemia, plasma VL, and CD4 and neutrophil dynamics were monitored via quantification of iRBCs in Giemsa-stained thin blood smears, plasma hematocrit levels, SIV qPCR, and flow cytometry, respectively. Peak VL (median=9.92x10^06 RNA copies/ul) occurred at W3 post-SIV and decreased after ART, with 2/4 RMs becoming undetectable. P. fragile parasitemia occurred at W14 post-SIV (median %parasitemia=25.5% iRBCs) and all animals became anemic (median=19.8% hematocrit). At W13 post-SIV, RMs exhibited detectable VLs, sustained until W17 post-SIV (median=9.34x10^02 RNA copies/ul). Compared to baseline (median=306.905 cells/ul), CD4+ T-cell counts declined by W8 post-SIV (median=140.5 cells/ul), increased after ART (median=193.5 cells/ul), followed by a sustained decline (median=173.59 cells/ul) after P. fragile. Compared to baseline (median=53.58%), neutrophil frequencies increased at W14 post-SIV (median=73.25%), then stabilized to baseline levels after anti-malarial treatment. Our data indicates that P. fragile co-infection lowered ART efficacy and resulted in increased peripheral neutrophil frequencies coinciding with peak parasitemia. Additional studies are underway to characterize the mechanisms by which this cell subset may contribute to disease pathogenesis during SIV/P. fragile co-infection.

6311

EPIDEMIOLOGY OF CO-INFECTIONS IN PREGNANT WOMEN LIVING WITH HUMAN IMMUNODEFICIENCY VIRUS 1 IN RURAL GABON: A CROSS SECTIONAL STUDY

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There is a lack of recent epidemiological data on HIV infection during pregnancy in Gabon. Moreover, it is unclear if HIV-positive pregnant women are more prone to suffer from other common co-infections. Thus, an HIV-prevalence-study was conducted among pregnant women, followed

by a cross-sectional case-control study in which the prevalence of various co-infections was compared between HIV-positive and HIV-negative pregnant women. Data for the HIV prevalence survey were collected retrospectively using routinely collected diagnostic data from 21 antenatal care centres (ANCs). For the cross-sectional co-infection study, all HIV-positive pregnant women and a comparator sub-sample of HIV-negative pregnant women were recruited at the ANC in Lambaréné. Co-infection status of vector-borne (VBI) and sexually transmitted infections (STI) was assessed. HIV positivity was 3.93% (646/16,417) among pregnant women, and 185 pregnant women were recruited.Overall, 63% of HIV-positive and 75% of HIV-negative pregnant women were diagnosed with at least one co-infection. HIV-negative women were more often co-infected with STIs than HIV-positive women (Mean [SD] STIs: 2.59 [1.04] vs 2.16 [1.35], respectively; p=0.056). The crude odds for a concomitant STI was lower in HIV-positive than in HIV-negative women. The change of magnitude from the crude to adjusted OR indicates a differential sexual risk factor profile among HIV-positive and HIV-negative women in this population. This might potentially be explained by the availability of sexual health care counselling for HIV-positive women within the framework of the national HIV control programme, while no such similar overall service exists for HIV-negative women. In conclusion, e found a high prevalence of STIs among pregnant women, an important finding for national policymakers and STI control programmes.

6312

A DECADE IN CHANGING TRENDS IN HIV PREVALENCE AND INCIDENCE IN PREGNANT WOMEN IN SOUTHERN MOZAMBIQUE

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Monitoring HIV rates at the antenatal care (ANC) clinic is needed for evaluating and targeting HIV preventive interventions in this vulnerable group. This study describes the prevalence and incidence trends of HIV over 10 years in pregnant women attending the ANC clinic in southern Mozambique. We analysed data from three studies carried out in HIV-infected pregnant women attending the ANC clinic between 2010 and 2021. HIV incidence was estimated between prevalence points using two validated methods. Method one was based on mortality rates and method two was based on survival information after HIV infection. The trend over time was obtained by fitting a log-regression model. Changes in the prevalence of anemia and rates of HIV vertical transmission during same period were also analyzed. Overall, 10392 pregnant women attending their first ANC visit were included in the analysis. There was a decrease of the HIV prevalence to 21.4% (95% CI: 19.6-23.2%) in 2021, after a peak of 35.3% (95% CI: 30.1-40.8%) in 2016. The peak of HIV tended to increase with age group from 2010 to 2021. The prevalence was the highest in women aged 20-25 in 2010 and then became the highest in those aged 35-40 in 2021. The overall incidence significantly increased from 3.7 per 100 person-years during 2010-2016 to 10.1 per 100 person-years in 2018-2019 but then subsequently decreased to 6.2 per 100 person-years in 2020-2021. In the last decade, HIV burden in pregnant women has declined in this area of southern Mozambique. However, HIV prevalence remains unacceptably high in this particularly vulnerable group, calling for a need to strengthen HIV preventive strategies to ending HIV/AIDs in the country.

6313

DRUG RESISTANCE MUTATIONS DETECTED IN HIV-1 PROTEASE GENES ISOLATED FROM HIV-1 INFECTED PERSONS FROM EASTERN REGION OF GHANA

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Human immunodeficiency virus (HIV) is an important public health concern with about 70% of the global burden in Africa. Since the introduction of antiretroviral therapy, a major problem is the emergence of drug resistance. HIV-1 protease (PR) is a retroviral aspartyl protease, an enzyme involved with peptide bond hydrolysis in retroviruses. Without effective HIV protease, HIV virions remain non-infectious. Protease inhibitors are mostly used as part of the 2nd line regimen following treatment failure. We therefore sought to determine the prevalence of drug resistance mutations in the HIV PR gene in the most endemic region in Ghana (Eastern Region) (2.8%) prevalence. We used purposive sampling to collect blood from 30 consented patients, confirmed as HIV-1 infections by serology. Twenty-one (21) of them were on triple combinations of five first line regimen (Zidovudine, Lamivudine, Nevirapine, Tenofovir, Efavirenz) and 9 were treatment naive. Ribonucleic acid was extracted using High Pure Viral RNA Kit from plasma, amplified via a nested RT-PCR assay and sequenced using gene-specific primers. The protease genes were analyzed for subtype and drug resistance mutations using the Stanford HIV Database. Five out of 30 samples were successfully amplified. The overall mean CD4 for the 30 samples collected was 473.4 and mean viral load was 31,226.17cps/ml. No trend was found between viral load and its implication on sequencing. Three (3) samples out of 5 were successfully sequenced. Two of these were recombinant subtype CRF02_AG and one was subtype G. HIV-1 unusual drug resistance mutations (N88K, K43T, I54N) were identified per patient. The mutations found had no PI drug resistance in the protease gene of the 3 sequenced samples. They did not carry resistant forms of HIV-1. Further investigations are needed on the unusual mutations at the known drug resistant positions. Continuous monitoring of drug resistance among HIV-1 infected patients is essential to improve their clinical management.

6314

CLOSING THE KNOWLEDGE GAP IN HUMAN IMMUNODEFICIENCY VIRUS PREVENTION AMONG ADOLESCENTS IN RURAL SETTINGS, BURKINA FASO

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In sub-Saharan Africa (SSA), HIV continues to pose a significant public health problem despite a 32% reduction in new infections in 2021. Adolescents in SSA account for nearly four out of five HIV infections. There is a lack of knowledge about HIV prevention methods and testing rates remain low among adolescents in Burkina Faso. This study assessed adolescents' knowledge of HIV prevention and testing as well as sexual risk behaviors in Nouna, Burkina Faso.We conducted a cross-sectional survey using a community-based sampling frame with 1,202 adolescents aged 10-19 years via a standardized questionnaire in the Nouna Health and Demographic Surveillance System in Burkina Faso from March to April 2022. We present descriptive results regarding adolescents' knowledge of and behavior related to HIV.The average age of the participants enrolled in the study was 14.1 (95% CI: 13.9-14.3) years old, 43.5% were female, and 59.4 % were students. About 41.9% had never heard of HIV. The

main sources of HIV information were schools (53.6%) and friends (26.7%). Among participants who have heard about HIV, only 4.3% have been tested. Additionally, 15.8% of participants had sexual intercourse in the past and 47.1% of them used condoms. The mean age at sexual intercourse was 16.0 years (95% CI: 15.8-16.2).In rural areas of Burkina Faso, adolescents are poorly informed about HIV and do not use HIV prevention measures. Adolescents need better access to HIV prevention information through innovative interventions. Adolescent reproductive health and HIV prevention awareness will contribute to reaching the 2030 target of ending the HIV/AIDS epidemic. Key words: Adolescents, HIV prevention

6315

KNOWLEDGE AND PERCEPTIONS OF PRIMARY HEALTHCARE PROVIDERS TOWARDS INTEGRATION OF ANTIRETROVIRAL THERAPY SERVICES AT DEPARTMENTAL LEVELS AT SELECTED HEALTH FACILITIES LIRA DISTRICT, UGANDA

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Investigations conducted among healthcare providers to assess their knowledge and perceptions towards the integration of anti-retroviral therapy related services in Sub-Saharan Africa are limited. This study explored the knowledge and perceptions of primary healthcare providers towards the integration of ART management services at departmental levels in health facilities in Lira district. We conducted a descriptive cross-sectional survey that employed qualitative methods of data collection in four selected health facilities in Lira district between January and February 2022. The study involved in-depth interviews with key informants and focus group discussions. The study population consisted exclusively of primary healthcare providers; however, those who were not full-time employees of the participating health facilities were excluded. We used thematic content analysis. A significant proportion of staff especially those who are not directly involved in ART still lack full knowledge of ART services integration. There was generally a positive perception, with some suggesting ART integration can minimize stigma and discrimination. The potential barriers to integration included limited knowledge and skills for providing comprehensive ART services, insufficient staffing and space, funding gaps, and inadequate drug supplies, coupled with increased workload due to enlarged clientele. Whereas healthcare workers are generally knowledgeable about ART integration, but their knowledge was limited to partial integration. The participants had a basic understanding of ART services being provided by different health facilities. Furthermore, participants viewed integration as critical, but it should be implemented in conjunction with ART management training. Given that respondents reported a lack of infrastructure, increased workload, and understaffing, additional investments in staff recruitment, motivation through training and incentives, and other means are needed if ART integration is to be implemented.

6316

PREGNANCY OUTCOMES IN WOMEN WITH INFECTIOUS AND CHRONIC COMORBIDITY IN WESTERN KENYA

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Antiretroviral therapy (ART) protects maternal health and prevents HIV transmission during pregnancy. However, there is evidence that ART started pre-pregnancy compared to during pregnancy increases the risk of other poor pregnancy outcomes. No studies have reported on the risk of poor pregnancy outcomes by timing of ART initiation, while accounting for comorbid infectious and chronic diseases. Here we present results from a large cohort of pregnant women in Western Kenya living without and with HIV (WLHA). Samples and data were collected to identify infectious and non-communicable diseases. Multivariable logistic regression was conducted to assess the effect of HIV on adverse maternal or infant outcomes. Sensitivity analysis further examined timing of ART initiation on poor outcomes. One in four of 1753 women experienced poor pregnancy outcomes. Anemia (57.7% vs 39.1%), malaria (15.2% vs. 11.7%) and COVID-19 (11.8% vs. 9.3%) in pregnancy were more common in WLHA, while obesity and hypertension were higher in women without HIV. By ART timing, malaria (19.0% vs. 12.1%) and hypertension (10.1% vs. 8.0%) were higher in women starting ART during pregnancy than before pregnancy, while obesity (24.1% vs. 30.3%) and diabetes (2.5% vs. 6.1%) were lower in those starting ART during pregnancy than before pregnancy. In multivariable logistic regression neither HIV nor ART timing had significant effect on maternal outcomes. However, women who started ART pre-pregnancy had increased risk of poor infant outcomes compared to women without HIV (aOR1.54 [95%CI 0.94-2.52], p=0.05). Our finding that WLHA on ART are at no significantly increased risk of poor maternal outcomes than HIV-uninfected women demonstrates the remarkable impact of PMTCT programming since the implementation of Option B+'s 'test-and-treat' approach nearly a decade ago. The benefits of ART to maternal health and the infant HIV-free survival are well-documented, and now that PMTCT coverage exceeds 90% in many high-burden settings, more research is needed on quantifying and mitigating other infectious and chronic disease effects on pregnancy outcomes.

6317

SOCIAL MOBILIZATION FOR ENHANCED MICROPLANNING IN DEWORMING PROGRAMS

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The goal was to design, operationalize and evaluate a Social Mobilization (SM) package specifically tailored to improve the quality of community-based treatment/ mass drug administration (MDA) for Soil Transmitted Helminthiasis (STH) and Schistosomiasis (SCH) as a pilot in Vihiga County. Tailoring SM messages and materials for the specific population groups at highest risk or with lower likelihood of participating in MDA and using the right channels of communication drives treatment coverage higher. This study was undertaken to (i) Assess the social contexts for community-based STH and SCH treatment; (ii) Identify potential population segments for tailored messaging; (iii) Development of a tailored social mobilization package in Vihiga county, Kenya; (iv) Produce user-friendly guides/standard operating procedure that other countries or implementing partners could readily adapt to their own contexts; and (v) To track progress and rigorously evaluate learnings. Conducting a formative and summative assessments using mixed methods; and developing and operationalizing a tailored social mobilization package. There was an increase in reach of the messages and materials from (29.9%, n=400) initially to (81%, n=402) during the summative assessment. Data indicated that the community had correct knowledge - transmission/spread of STH i.e., drinking / walking on water contaminated with faeces increased from 19.7% to 47.2% (by 28%) and ingestion of the worm's egg increased by 1% and on SCH, transmission/ spread of SCH i.e., penetration of the worm larvae through the skin and drinking or using contaminated water improved by 35.9% and 8.9%, respectively; the number of people treated in this county was STH (103%, 597,236) and SCH (94.91%28,858 94.91%). However, the community had limited knowledge about SCH. Findings from the pilot in Vihiga County informed scale-up of the SM process to include Bungoma, Kakamega and Trans Nzoia in the western region of the country.

6318

ENGAGING YOUNG PEOPLE AS AGENTS OF CHANGE: A PRIMARY SCHOOL EDUCATIONAL INTERVENTION TO DECREASE ARBOVIRAL AND PROTOZOAL RISK IN GRENADA

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School-based educational programs are effective in mitigating environmental health risks. In this ongoing randomized control study, we use a school-based educational intervention to improve knowledge, attitudes, and practices regarding arboviral and feco-orally transmitted protozoal diseases among 4th-grade students in Grenada. 27 case and 26 control schools were randomly assigned. Students completed pre- and post-intervention questionnaires at baseline and 3 months later. Case schools received a presentation, a video clip on mosquitos and demonstrations. School vector data was collected. Students at 10 case schools used the Our Voice Discovery Tool app to collect geotagged photographic and narrative data on aspects of their environment that make it easy or hard for mosquitoes to transmit diseases. Students have recorded 374 photos (135 good and 194 bad for environment) and 309 narrations. The intervention group reported significant improvements in arboviral and protozoal disease knowledge (53.3% increase), attitudes (15.1% increase), and practices (16.3% increase) at 3-month follow-up ($p<0.01$). In contrast, the control group only reported significant improvements in knowledge (20.9% increase, $p<0.01$), but not in attitudes (0.1% decrease, $p=0.96$) and behaviors (2.5% decrease, $p=0.28$). The intervention schools showed a more significant increase in knowledge (0.83 vs 0.36), attitudes (0.99 vs 0.02), and behaviors (0.55 vs -0.08) compared to the control schools ($p<0.01$). Among case schools, vector data show 26% and 100% reduction in total egg counts and total larvae counts, respectively, at follow-up ($p<0.01$). Among control schools, more indoor egg counts were recorded at follow-up, though they also showed a non-significant 11% reduction in total egg counts. Of 7 Parishes in Grenada, we found Aedes mosquitoes in all 7 regions and Culex in 6 but no Anopheles mosquitoes. 6-month follow-up will be completed by June 2023. Our intervention effectively improves knowledge, attitudes, and practices regarding arboviral and protozoal diseases among 4th-grade students in Grenada at follow-up and reduces vector abundance in schools.

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IMPROVING ACCESS TO MOBILITY MANAGEMENT AND DISABILITY PREVENTION MANAGEMENT OF LYMPHATIC FILARIASIS COMPLICATIONS TOWARDS THE WORLD HEALTH ORGANIZATION 2030 LYMPHATIC FILARIASIS ELIMINATION GOAL: A PILOT STUDY CONDUCTED IN LIBERIA 2022 TO CLOSE THE GAPS IN CASE MANAGEMENT NTDS CARE—LYMPHATIC FILARIASIS

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Lymphatic Filariasis (LF) has high prevalence rate in sub-Saharan Africa with two major complications requiring case management: hydrocele and Lymphedema. In Liberia, LF is prevalent in 13 of the 15 counties survey conducted in 2012. The only strategy for prevention and control of LF has been Mass Drug Administration (MDA) and an evaluation of the intervention (Pre-transmission Assessment Survey and Transmission Assessment Survey (PRE-TAS and TAS). The case management aspect remains a challenge in achieving the elimination target for Lymphatic Filariasis, the WHO Road Map (2030). However, to manage the complications of LF, the Case Management Project of Liberia's Neglected Tropical Diseases Program with Lymphedema care in Liberia, (2016) by providing comprehensive Home-Based Self Care (HBSC) Kits to affected persons with basic training in managing their conditions. Furthermore, in November 2022, the Case Management Project, initiated an integrated campaign to scale up the Mobility Management and Disability Prevention (MMDP) Campaign Project supported by Sightsavers International. The Mobility Management and Disability Prevention (MMDP) Campaign started in late November 2022 in five (5) counties (Bomi, Bong, Lofa, Nimba, and Maryland) with a target to perform 300 hydrocelectomies and distribute additional 260 HBSC Kits to both old and new lymphedema clients. The results against the target are as follows: Bomi (21), Bong (44), Lofa (39), Nimba (54) and Maryland (23). A total of 181 (60.33%) Hydrocelectomies were performed in 11 hospitals with an unmet target of 119 (39.7%) hydrocele cases due to several factors. With resource constraints, the Neglected Tropical Diseases Program remains committed to accelerating the MMDP Project to the remaining 8 counties in Liberia while providing routine care for lymphedema clients. This abstract seeks to explore opportunities to close the service gaps for those affected by LF complications to have adequate access to NTDs services without experiencing any financial consequences.

6320

THE EFFECT OF AN INNOVATIVE COMMUNITY HEALTH EDUCATION ON TRACHOMA PREVENTION AND CONTROL IN NORTHERN NIGERIA

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Trachoma is a leading cause of infectious blindness worldwide and an endemic public health problem in Northern Nigeria. The currently recommended surgery for trichiasis/entropion, antibiotics for active disease, facial cleanliness, and environmental change to reduce transmission (SAFE) strategy targets all key elements believed to be necessary for a short- and long-term intervention program. This study investigated the effect of innovative community health education on trachoma prevention and control in northern Nigeria. This was quasi-experimental study among Internally Displaced Person in Northern Nigeria. Two IDP camps were selected purposively and simple random sampling were used to select final participants for the study. We used a quantitative method approach was using a semi-structured questionnaire developed using SAFE strategy among 294 participants. The SPSS software version 27 was used for all statistical analyses which descriptive and inferential statistics were done at 5% significance level. The mean age of the participants was 33.1±8.8 years, some (45.9%) were male which 17.0% had no formal education. There was increase in the awareness of trachoma from 28.6% to 100.0% after the educational intervention. However, at baseline, few believed that trachoma is caused by curse while no one mentioned that after the educational intervention and they all knew ways trachoma could be transmitted. There was a significant increase in the knowledge level among participants from 20.1% to 73.5% good knowledge ($p<0.001$, CI=5.735 - 4.891, $t=24.795$) as well as positive attitude to trachoma prevention and control from 15.3% to 77.2% after the intervention ($p<0.001$, CI=14.914 - 13.065, $t=29.784$). Also, there was improvement in the prevention and control practices from 56.1% to 94.2% ($p<0.001$, CI=1.114 - 0.648, $t=7.437$). In conclusion, this study revealed that educational intervention can greatly influence knowledge on trachoma as well as the prevention and control attitude and practice.

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GEOSPATIAL RISK PREDICTION OF SCHISTOSOMIASIS AND SOIL-TRANSMITTED HELMINTHS FOLLOWING A SCHOOL PREVENTIVE CHEMOTHERAPY PROGRAM IN HUAMBO, UIGE AND ZAIRE PROVINCES, ANGOLA

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A school preventive chemotherapy (PC) program for soil-transmitted helminths (STHs) and schistosomiasis has operated in Huambo, Uige and Zaire provinces, Angola, since 2013 and 2014, respectively, with an impact assessment conducted in 2021. Conventional methods to assess prevalence at province or district level to inform PC programs do not account for the environmental context of disease prevalence. This analysis provides geospatial risk predictions to provide a more detailed understanding of schistosomiasis and STH distribution to inform control strategies. A two-stage cluster survey design was used to select schools and schoolchildren to detect schistosomiasis and STHs in 2021 via rapid diagnostic tests (RDTs) and microscopy, respectively. School-level georeferenced parasitological data was incorporated with climatic, altitude, vegetation, landcover and distance to water bodies data to develop spatial regression models. Best fit multivariate generalised linear models were then used to develop risk prediction maps for schistosomiasis and STHs and ascertain areas of co-endemicity. Spatial regression models and risk prediction maps are being developed for the baseline survey to better assess the impact of the school PC program on the spatial distribution of these diseases. The impact assessment involved 17,880 schoolchildren from 599 schools for the schistosomiasis survey and 6,461 schoolchildren from 214 schools for the STH survey. Best fit regression models demonstrated considerable areas of moderate to high schistosomiasis risk (≥30% prevalence by RDTs) across all three provinces. For STHs, there remains substantial areas of high risk (≥50% prevalence by microscopy) in Uige province, with more focal areas of high risk in Huambo and Zaire provinces. There are considerable co-endemic areas in Zaire, but not Huambo or Uige. Despite regular school delivery of PC over several years, there remains considerable regions of Huambo, Uige and Zaire provinces that remain moderate to high risk for schistosomiasis and STHs, with focal areas of co-endemicity.

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ENHANCING TIMELINESS OF REPORTING FOR TRACHOMA MASS DRUG ADMINISTRATION THROUGH ELECTRONIC DATA CAPTURE: A PILOT STUDY IN TWO DISTRICTS OF UGANDA

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In 2023, The Uganda Ministry of Health supported by USAID's Act to End NTDs | East piloted an electronic data capture (EDC) mass drug administration (MDA) tally sheet in two trachoma persistent and recrudescent districts (Moroto, Nabilatuk). Previous, after-action review meetings had highlighted substantial delays (e.g. four months) in reporting the MDA data using a paper-based system that involved compiling, cleaning, and summarizing data. In this process one district lost their data when the computer they were using crashed. These delays and losses coupled with data quality issues that included arithmetic errors and wrong entries prompted development of an EDC tool using Open Data Kit (ODK). The EDC tool was rigorously tested and further improved for its accuracy to the original form, validation checks, and user friendliness. Data entry by the field supervisors started 10 days after the MDA field activities in January 2023. The central-level supervisors checked the inputs for accuracy and provided direct feedback to subcounty supervisors through their WhatsApp group and phone calls. The MDA results were produced one month after end of MDA activities. This approach improved MDA reporting turnaround time and 100% of the village level data was captured with no data loss. Furthermore, it was easy for the subcounty supervisors to easily identify errors from the hardcopy forms and fix them while in the field. Of note, this EDC approach did include additional cost including airtime, allowances, and training. These results illustrate the value of timely reporting of MDA data for decision making using EDC tools. This EDC approach also strengthened data ownership by subcounty supervisors who entered their own data, jointly reviewed, and provided feedback to the district-level biostatistician and central-level team. Finally, there was improved quality of data because of the data quality checks and validations embedded in the EDC forms. Expansion of this approach in all trachoma endemic districts would be valuable to the program for timely and accurate MDA data.

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FROM PRIORITY TO PRACTICE: MAKING APPLICATION OF DIGITAL PLATFORMS FOR IMPROVING TRACHOMA MDA PERFORMANCE A REALITY TOWARDS ADDRESSING END GAME CHALLENGES IN LONGIDO TANZANIA

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In the past 2 decades Tanzania has made a significant stride towards trachoma elimination. However, there are nine districts are considered persistent and recrudescent. Longido district is one of the persistent districts whose status is attributable to inadequate MDA coverage, mobile and migrant populations, thus required special strategies to address both challenges during MDA. Our objective is to present a case study on application of digital platforms to address MDA and other end game challenges in Longido, Tanzania, as a template for nationwide. We examine electronic data capture (EDC) and digitalized Supervisor Coverage (SCT) tool development, from inception, team selection, training and pilot testing to tool revision and improvement. The Unstructured Supplementary Service Data (USSD) was developed, and special code was enabled to community drug distributors (CDDs mobile phone for reporting daily MDA coverage summary. This summary was sent to a central server where national supervisors could review data daily on a dashboard. The platform was set to provide an automated text messages back to the village leaders and ward level supervisors with the daily MDA summary. To facilitate the SCT, an ODK collect application was installed in the smart phone for the district and ward level supervisor. GPS codes were captured to ascertain distribution of both CDDs and supervisors across the districts. We found that transitioning from paper-based monitoring tools to electronic motoring was feasible and effective. Daily feedback to village leaders prompted ownership and immediate action to troubleshoot poor coverage. CDDs and supervisors found the tools easy and simplified reporting and tracking. Few challenges, including some errors in the CDD reporting server spotty cellular network were noted for future improvement. Upon MDA assessment, reported coverage increased from 87% in 2019 to 97.5% in 2022.The results suggest that digital platforms to address the trachoma endgame challenges can support improved monitoring and evaluation of MDA and other SAFE relate interventions in line with the WHO target to eliminate trachoma by 2030

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THE IMPACT OF TEN ROUNDS OF TWICE-PER-YEAR TREATMENT WITH IVERMECTIN ON ONCHOCERCIASIS TRANSMISSION IN HYPERENDEMIC AREAS OF JIMMA AND ILLUBABOR ZONES, SOUTHWEST ETHIOPIA

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Onchocerciasis is a disease caused by Onchocerca volvulus and transmitted by the bite of Simulium vectors. Control efforts began in Ethiopia in 2001 with annual mass drug administration (MDA) with ivermectin. MDA must be given for 10+ years to control disease transmission. The program shifted toward elimination of transmission in 2012, commencing semi-annual treatment and targeting MDA to all endemic districts. This decision followed refinement mapping studies done in 2011 that uncovered untreated hyperendemic areas with nodule prevalence >40%. We undertook baseline surveys to document the prevalence of skin microfilaria (mf) in first-line villages in 7 districts in Oromia region. After at least 10 rounds of semi-annual MDA with >80% reported coverage, impact assessments were conducted in these districts in 2016 and 2017. A convenience sample was used for skin snip testing in ≥50 adults per community aged ≥20 years who had lived in the area for ≥10 years. Dried blood spots (DBS) were also taken at this time from 300 children per district aged <10 years. All consented/assented individuals underwent skin snip examination and DBS collection for Ov16 antibody analysis using ELISA following standard methods. In Jimma, 4 districts (Goma, Sokoru, Sigmo, and Setema) showed decreases in mf prevalence. Mf prevalence in Goma declined from 45.2% at baseline (2012) to 5.3% in 2017 (p=0.0), Sokoru dropped from 2.4% to 0% (p=0.08), Sigmo from 6.3% to 1.3% (p=0.02), and Setema from 10.6% to 4.7% (p<0.05). Ov16 antibody prevalence ranged from 0% to 1.6% at the time of follow-up. Three districts were evaluated in Illubabor. Sale Nono had mf prevalence of 54.5% in 2012, with significant reduction to 4.9% at impact assessment in 2016 (p=0.0). Bure and Hallu likewise showed significant decreases in mf prevalence, 28.5% to 1.9% (p=0.0), and 34.9% to 0.5% (p=0.0), respectively in 2016. Ov16 antibody prevalence at the second timepoint ranged from 0.3% to 4%. Twice-per-year treatment with high coverage showed encouraging progress towards the elimination of onchocerciasis transmission in hyperendemic districts.

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ELIMINATING ONCHOCERCIASIS IN LOIASIS ENDEMIC AREAS: ADDED VALUE OF THE SLASH AND CLEAR STRATEGIES

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In areas where onchocerciasis and loiasis are co-endemic, the routine control strategy, community-directed treatment with ivermectin (CDTI) is prohibited as it can lead in potentially deadly serious adverse events (SAEs) in patients heavily infected with Loa loa. It appears compulsory to identify SAEs risk-free alternative or complementary interventions to guarantee complete elimination of onchocerciasis. For this purpose, we carried out our study to assess the efficacy of an environment-friendly vector control approach, so-called the Slash and Clear (S&C). Monthly (3 days per month) capture of blackflies carried out using human landing catching over a period of 12 months along the Kelle River for baseline data collection. The trailing vegetation constituting blackfly breeding sites were destroyed by trained community volunteers (Slash and Clear) every month of the second year (4-5 days/month), and the impact of this breeding site destruction on blackfly densities was assessed by harvesting flies following the same procedure as during the baseline entomological survey. A total of 11,142 flies were collected during the two years, 9,720 before S&C and 1,422 after S&C, for an overall reduction rate of 100% in the head. The average larval reduction rate was 74.5%. These results confirm the significant impact of Slash and Clear on the reduction of blackfly densities, and might help accelerating the elimination of onchocerciasis in areas where loiasis in endemic.

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STRENGTHENING OF THE LOCAL HEALTH CAPACITY FOR THE IMPLEMENTATION OF THE FRAMEWORK FOR ELIMINATION OF MOTHER-TO- CHILD TRANSMISSION OF HIV, SYPHILIS, CHAGAS DISEASE AND HEPATITIS B IN PAMPA DEL INDIO, CHACO, ARGENTINA

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Pampa del Indio is a small locality in the province of Chaco, Argentina, located in the Gran Chaco ecoregion, traditionally a hotspot for Chagas Disease (ChD) due to vector transmission. Continuous vector control and environmental/land changes have reduced this transmission route in the area and vertical transmission of ChD is gaining importance. Given the presence of Mundo Sano in this municipality since 2008, working on vector control in a public-private association with local authorities, activities have evolved to a focus on diagnosis and treatment of ChD and implementation of the Elimination of Mother-To- Child Transmission (EMTCT) Plus initiative recommended by the World Health Organization (WHO) to eliminate mother-to-child transmission (MTCT) of ChD together with HIV, syphilis, and Hepatitis B. The activities are centered on achieving and sustaining the EMTCT of the four infections and to promote comprehensive access for pregnant women to high-quality control of their pregnancy and post-partum, specially focused on ensuring access to health to pregnant women living in rural communities. This is possible due to bi-monthly visits by a local mobile specialized team that perform the controls using rapid tests and a mobile ultrasound (US). Since its implementation in April 2022 and up to December 2022, five visits were performed in the urban area and rural settlements of Pampa del Indio with a 92.0% coverage of pregnant women (450 out of 489 estimated annual pregnancies for the area). All 450 women were screened for the four infections, and they all had access to US controls with an average of 2.3 comprehensive controls per woman. Hepatitis B and HIV infections were not detected while the prevalence of ChD and syphilis was 4.2% (n = 19) and 2.4% (n = 11), respectively. The use of rapid tests assured immediate application of treatment protocols and the planning of epidemiological actions to test other family members.

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MONITORING TRACHOMA MASS ADMINISTRATION USING AN ELECTRONIC SUPERVISOR COVERAGE TOOL

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An electronic Supervisor Coverage Tool (SCT) was developed and deployed in trachoma endemic districts in Uganda during the mass drug administration (MDA) implemented in August 2022 (round one) and January 2023 (round two) with the aim of improving MDA coverage. The surveys were carried out in Moroto and Nabilatuk. The main aim of the SCT was to measure MDA coverage and take immediate corrective action related to low MDA coverage. The SCT uses lot quality assurance sampling to classify communities coverage. The levels of coverage for trachoma are good coverage (80% and above), cannot conclude that coverage is good (55% to less than 80%) and inadequate coverage (less than 55%). Communities (supervisory areas) with previously low MDA coverage were purposively sampled, 20 households randomly selected, and one respondent per household randomly selected to be surveyed. In each district, 21 communities were visited in round one while 89 were visited in round two. Data was collected with android phones using Open Data Kit. Central, district, and subcounty supervisors administered the SCT. Data was analyzed using real-time data monitoring within the data collection form followed by post survey analysis in Stata. The number of communities with good coverage increased from 17 (81%) in 2022 to 80 (90%) in 2023, while 2(9.5%) and 7(8%) had inadequate coverage, and 2 (9.5%) and 2 (2.2%) had bad coverage, respectively. In 2023, 98% of surveyed individuals had been offered medicines while in 2022 it was only 87%. The main reasons for not being offered medicines in both 2022 and 2023 were similar: not present at home, distributor not come to home, busy/occupied, and unaware of MDA. The main immediate action taken was mop-up by distributors targeting missed individuals. SCT results can be used to make changes or enhancements to MDA while in the field, identify low performing communities, proportion reached and those that swallowed the medicines. Additionally, use of electronic data collection allows for central display of real time results for all communities surveyed, timely follow-up with supervisors at different levels and immediate action taken as needed.

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THE ROLE OF MICROBIOTA AND CO-LOCALIZATION IN THE DISSEMINATION OF VECTOR TRANSMITTED PATHOGENS

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Insect vectors are important agents in the transmission of infectious diseases. Through a processcalled dissemination, many pathogens can enter the body of a host through the bite of an insectvector and then exit the skin to cause a systemic infection. The details about how and whendissemination occurs are still unclear and elucidating this is important for understanding diseasepathogenesis and the development of new therapies and vaccines. Leishmaniasis is a vector-bornedisease, and in its visceral form, Leishmania spp. parasites can disseminate from the skin to internalorgans. Various factors from the host, vector and parasite have been implicated in thedissemination process, including the microbiota derived from the from the insect vector gut.However, while vector microbiota is required for dissemination, it is not sufficient. The goal ofthis study is to determine whether the micro-colocalization of parasites, vector- and host-derivedfactors, including the microbiota that occurs following sand fly bite versus bolus injection is arequirement to induce the physiological conditions that facilitate dissemination. The resultsobtained will contribute to a better understanding of the pathophysiology of leishmaniasis. Wehypothesize that bacteria, co-localized with other host and vector factors, influence the physiologyof the skin and facilitate the dissemination of Leishmania spp. To evaluate this, we will first studydissemination in wild type mice and mice deficient in several innate TLR-related signallingpathways employing a novel model of Leishmania spp. infection, the skin prick, that co-localizedthese factors in the skin. We will then determine the requirement of bacteria and co-localization,using skin-prick, bolus, and sand fly models of infection in Germ-Free (GF) mice allied with thetechniques of flow cytometry and Live Cell Imaging.

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INFECTION OF MONOCYTES WITH LEISHMANIA INFANTUM CAUSES DIFFERENCES IN EXTRACELLULAR VESICLE MIRNA PROFILES

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Leishmania infantum is an obligate intracellular protozoan that is spread through the bite of a sand fly and causes visceral leishmaniasis. Both the parasite and infected macrophages release extracellular vesicles (EVs), including exosomes. EVs contain proteins, lipids, mRNAs, and microRNAs that can spread widely and have biological activities throughout a host. Our lab has previously shown that the protein content of EVs from MDMs infected with L. infantum differs from uninfected MDMs. We wanted to question whether the miRNA content of EVs would differ between uninfected and infected MDMs. miRNA are potent regulators of post-translational gene expression. Blood from 3 healthy human donors were obtained from the University of Iowa blood bank. Monocytes were infected with L. infantum, and after 48 hrs EVs enriched in exosomes were purified from extracellular medium and analyzed on the nanosight to investigate concentration and size. Small RNAs were extracted from EVs, and the abundance of known or putative human miRNAs was screened using a NanoString human miRNA panel. There was a trending increase in the overall production of Evs from infected MDMs compared to uninfected control but no difference in mean or mode size. hsa-miR-29a-3p and hsa-miR-575 were significantly upregulated in EVs of infected MDMs and hsa-miR-1305 and hsa-miR-1285 were downregulated compared to EVs of uninfected MDMs. Known functions of these miRNAs include the upregulation of genes contributing to the M2 phenotype and possible suppression of proinflammatory response. Infection with L. infantum shows a trending increase of exosomes released from human MDMs as well as a change in miRNA content. Evs from infected cells show an increase in miRNAs that might influence M2-type polarization and target proinflammatory genes. These data suggest that Ev miRNAs of MDMs infected with L. infantum might alter the surrounding environment to potentially dampen local inflammatory or curative immune responses.

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PEOPLE WITH DIFFERENT CLINICAL PRESENTATIONS OF LEISHMANIA DONOVANI INFECTION HAVE DIFFERENT MICRO-RNA PROFILES IN CIRCULATING PLASMA

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Visceral leishmaniasis (VL) is a tropical neglected disease caused by Leishmania donovani, results in significant mortality in the Indian subcontinent. Several microRNAs have been associated with either susceptibility or resistance to leishmaniasis, including miR-210 (Leishmania major), miR-122 and miR-146a (L. donovani), and miR-21 in (L. infantum). miRNAs are ~22 nt non-coding RNAs that can regulate many biological

and molecular functions at the post transcriptional level. Mainly they function by base pairing in the 3' or 5' UTR of target mRNAs and interfering with targeting the mRNA for degradation or modifying translation. Some miRNAs modify immune responses but the precise target of miRNAs implicated in leishmaniasis are unknown. There is a paucity of prior studies of miRNAs in primary human samples from subjects with VL. Most circulating miRNAs are packaged into micro vesicles called exosomes, which can circulate free of cells in the blood. Hence, we investigated the roles of miRNAs in circulating exosomes of patients from Bihar, India with different manifestations of L. donovani infection. We selected 6 candidate miRNAs to screen in human plasma: miR-21, miR-122, miR-155, miR-206, miR-146-a and miR-let-7c. Plasma from subjects with VL or post-kala azar dermal leishmaniasis (PKDL) were compared to healthy, endemic controls. We isolated plasma exosomes and confirmed isolation by transmission electron microscopy imaging and Nano particle tracking analysis. Small RNAs were extracted and differential expression of candidate miRNAs were evaluated by TaqMan miRNA assays. When compared to endemic control subjects, expression of miR-146a was increased plasma of both VL and PKDL patients compared to controls ($p<0.05$), whereas miR-206 was decreased in VL plasma compared to control samples. This is consistent with data from murine models and human monocyte derived macrophages indicating miR-146a skews infected macrophages from M1 to M2 phenotypes. miR-206 is reported to target FOXP-1 expression and influence macrophage function. We hypothesize these miRNAs may be critical determinants of immune response to L. donovani infection.

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PREVALENCE OF CUTANEOUS LEISHMANIASIS IN ENDEMIC COMMUNITIES OF THE VOLTA REGION, GHANA

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Leishmaniasis continues to affect countries in the tropics and subtropics with previously non-endemic areas experiencing infections. In Ghana, an outbreak of suspected cases occurred in 1999 which led to the discovery of cutaneous leishmaniasis (CL) after Leishmania major was identified. Since then, various studies have been conducted in endemic communities that have revealed multiple Leishmania parasites. This has raised much public health concern, especially regarding effective control and treatment strategies. The study reports the baseline prevalence of CL infection in three communities in the Ho district of the Volta Region of Ghana. A total of 535 subjects were screened using Leishmanin Skin Test (LST) for detecting Leishmania exposure and finger prick blood for anti-leishmania IgG antibody levels. There was no significant difference ($p=0.9313$) in LST positivity (LST+) in all three communities. However, the highest LST positives were recorded by the age group 41-65 (62.8%) whiles the lowest (25%) was from the age group 6-18. It was also observed that the median levels of IgG units between both males and females were significant ($p=0.0002$). LST positivity correlated to higher levels of antibodies, suggesting their potential as a risk marker for CL acquisition in Ghana.Current reports from the Health Services of Volta region suggest ongoing infections in communities, thus control efforts need to be implemented to reduce the disease burden.

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EXPRESSION OF ENDOPLASMIC RETICULUM STRESS RESPONSE MARKERS IN CUTANEOUS LEISHMANIASIS

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Cutaneous leishmaniasis (CL) is an intracellular parasitic infection that can cause loss of endoplasmic reticulum (ER) homeostasis by disrupting the protein folding process. This leads to the accumulation of unfolded proteins in the ER lumen and stimulates ER stress response to restore protein homeostasis in the ER. The present study aimed to immunohistochemically validate the endoplasmic reticulum stress response in CL by determining the expression of the Inositol Requiring Enzyme1 (IRE1), Protein Kinase RNA like ER kinase (PERK) and Activating Transcription Factor6 (ATF6) sensory proteins in lesion tissues. Sections (4 µm) of formalin-fixed paraffin-embedded tissue samples from thirty leishmaniasis-confirmed patients and thirty control participants were mounted on positively charged slides. The tissue sections were deparaffinization in xylene and rehydrated with graded alcohol. Antigen retrieval was conducted by microwave-boiling of the slides in 10mM Sodium citrate buffer (pH 6.0) for IRE1 and ATF6, and EDTA buffer (pH 9.0) for PERK. Endogenous peroxidase was blocked by incubating in 3% hydrogen peroxide for 10 minutes followed by washing in deionized water. The tissue sections were incubated overnight at 4°C with rabbit polyclonal antibodies against IRE1 (ab37073), PERK (ab79483), and ATF6 (ab203119). The antigen-antibody complex was detected with the labeled streptavidin-biotin (LSAB) method. Visualization was done by reacting with 3,3′-Diaminobenzidine (DAB) and counterstained with hematoxylin. Staining was observed by a histopathologist, and data were analyzed using SPSS (version 25.0). Staining was observed in the patient samples in contrast to the control samples which showed minimal staining. A significant difference ($p<0.05$) was observed between gender and expression of IRE1, PERK, and ATF6 markers and the histological grading of CL tissue and ER stress marker expression. In conclusion, this study demonstrates a significant difference in the expression of ER stress markers with regard to gender and histological grading of infected tissue.

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IMPACT OF DECLINING DISEASE TRANSMISSION ON MAINTENANCE OF IMMUNOLOGICAL MEMORY IN SUBJECTS WITH PAST HISTORY OF VISCERAL LEISHMANIASIS

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Visceral leishmaniasis (VL) is a visceralizing form of leishmaniasis caused by L. donovani and its cure is associated with IFNγ dominant Th1 immune response. Infection induced immunological memory and its maintenance is crucial for resistance to re-infection. A loss of recurrent antigenic exposer in areas with no transmission may lead to loss of memory T cells responsible for this resistance and may increase the possibility of disease re-emergence. Although India is marching towards achieving the goal of elimination and current transmission may be very low to absent, the risk of VL re-emergence and future outbreaks cannot be neglected. The present study aims to identify soluble leishmanial antigen (SLA) specific cytokine responses and reactive T central memory (Tcm) and effector memory (Tem) cells profile with effector and proliferative potential in subjects with past history of VL from area of no transmission (NT; areas with no reported cases in last five years), continuous transmission (CT; areas with continuous

reported cases) and outbreak (OB; areas with reappearance of cases after a brief period of absence). Th1, Th2 and Th17 cytokines production was determined in supernatants of SLA stimulated whole blood using cytometric bead array (CBA). Also, peripheral blood mononuclear cell (PBMC) treated with SLA was assessed for the frequency of Tcm and Tem cells expressing activation and proliferation markers using flowcytometry. A significant increase in pro-inflammatory cytokines like IFNγ, IL-6 and IL-2 along with anti-inflammatory IL-10 was observed in the SLA stimulated whole blood of NT and OB groups. In addition to this increased activation of Tcm and Tem cells of both CD4+ and CD8+ types were observed in response to the antigenic stimulation. Only CD4+ Tcm of OB group exhibited proliferative potential. Overall, our current findings are suggestive of a mixed cytokine profile in OB and NT groups which indicates the persistence of possible immune regulatory mechanisms, similar to the active disease and the proliferative response of CD4+ Tcm may be an implication of recent antigenic exposer due to ongoing transmission in OB group.

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MULTIMODAL THERAPEUTIC TREATMENT FOR CHRONIC CHAGAS DISEASE

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Chagas disease is a neglected tropical disease that is caused by the parasite Trypanosoma cruzi, which is spread by a triatomine bug, also known as the “kissing” bug. The acute stage of this infection can result in flu-like symptoms and can be treated by killing the parasite with anti-parasitic treatments. Treatments such as Benznidazole and Nifurtimox are effective in the acute stage, though they may cause severe side effects. However, most infected patients will not present signs and symptoms until they have reached the chronic stage, which often leads to cardiomyopathy and enlargement of other internal organs. Unfortunately, antiparasitics have poor efficacy during chronic disease. Studies have shown that an appropriate immune response to the parasite, with a balanced TH1/TH2/TH17 cytokine response, correlates with better cardiac health.Our overall goal is to develop a multimodal therapeutic treatment strategy to improve treatment efficacy. Here we tested combination treatments using the small-molecule STAT3 inhibitor, TTI-101, as well as a recombinant protein vaccine containing the Tc24-C4 antigen and different doses of benznidazole. We infected female BALB/c mice with 5000 blood form bioluminescent H1 strain trypomastigotes and started treating these mice 70 days post infection (dpi). Vaccinations were given subcutaneously twice, three weeks apart. Benznidazole (100mg/kg and 25mg/kg) and TTI-101 (50 mg/kg) were administered orally once daily for 20 days. Mice were given one, two or three treatments sequentially. Mice were euthanized at 234 dpi, then blood and tissues were collected to evaluate cytokine responses. Our results show that combining our Tc24-C4 vaccine with a low dose of benznidazole and TTI-101 induced an antigen specific TH1/TH2/TH17 cytokine response with increased levels of IFNγ, IL-6, IL-2, IL-4, IL-10, IL-22 and IL-17A. This suggests that multimodal treatment induces a balanced cytokine response that could lead to reduced tissue pathology and improved cardiac health.

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INTESTINAL MICROBIOTA MEDIATE PROTECTION AGAINST GIARDIA INFECTION INDEPENDENT OF HOST ADAPTIVE IMMUNITY

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Giardia lamblia (Giardia) is a nearly universal gut pathogen in undernourished children. In these children, Giardia frequently persists for long durations, however, the specific mechanisms underlying this susceptibility to persistent infections are poorly understood. Experimental murine models indicate that intestinal microbiota may contribute to Giardia clearance. Whether microbiota protect against Giardia colonization by enhancing host immunity and/or by non-immune mediated pathways is unknown. Using gnotobiotic techniques, we challenged germ-free (GF) wild-type (WT) or immunodeficient (Rag2-/-) mice with axenic Giardia cysts either alone or together with a standardized murine cecal intestinal microbiota transfer (cIMT). In all GF mice, small intestinal Giardia colonization persisted at high burdens (≥ 106/4 cm) and for at least 21 days after challenge, regardless of diet. In contrast, all mice conventionalized with IMT were protected against Giardia colonization. Immune responses to Giardia extracts in splenocyte recall assays were similar between cIMT-conventionalized and mono-associated WT mice. In addition, the standardized cIMT was equally protective against Giardia colonization in Rag2-/- mice, despite absence of T/B cells in these immunodeficient hosts. In contrast, a fecal IMT (fIMT) from a different mouse colony permitted high-burden and persistent colonization. 16S rDNA amplicon profiles demonstrated differences in Clostridium spp. among other sequence variants differentiating cIMT-conventionalized Rag2-/- mice that were protected against Giardia colonization and fIMT-conventionalized Rag2-/- mice that were not. Our models indicate a crucial role for intestinal microbiota-mediated protection against Giardia colonization that occur through pathways independent from host-dependent adaptive immunity. These findings warrant further studies to determine how specific intestinal bacteria may alter susceptibility to Giardia infection, and whether similar interactions occur in undernourished children who also demonstrate impaired immunity and disruptions in intestinal microbiota.

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COMPARISON OF DERMAL AND SYSTEMIC IMMUNE RESPONSES IN PROGRESSIVE STAGES OF CANINE LEISHMANIOSIS

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Canine leishmaniosis (CanL), caused by the zoonotic obligate intracellular protozoan parasite Leishmania infantum, is a significant public health concern for humans and domestic dogs, the primary reservoir. In endemic areas, vector transmission by sandflies predominates, while vertical transmission has been found as an alternate important means of transmission. Leishmania spp. has significant dermal tropism. However, in xenodiagnoses studies, the most severe CanL cases had less transmission to naïve sandflies than mild to moderate CanL cases, despite dermal parasite burden increasing as disease progressed. These results indicate that additional host-parasite factors influence transmissibility. The interplay between parasites and systemic host immune cells linked disease progression to immune exhaustion and a shift in the systemic immune response from pro-inflammatory to regulatory. Due to continuous environmental antigen exposure, the cutaneous immune environment is more immunotolerant, potentially influencing its responses during CanL progression and altering transmission. Cutaneous immune cells/parasite interactions, which affect transmissibility to competent vectors, have not been evaluated. RNAscope, a sensitive immunofluorescence technique, was used to assess how the cutaneous immune environment correlates

with parasite presence and burden across clinical stages, determined by the LeishVet staging guidelines. An amastin probe identified amastigotes, and dermal macrophages were marked with a CD14 probe. Parasite and macrophage counts, along with spatial relationships between amastigotes, dermal macrophages, and cutaneous structures were evaluated and correlated with H&E-stained slides. Future work will investigate lymphocyte responses in the dermal immune environment and integrate spatial transcriptomics data to further characterize the cutaneous immune environment across CanL clinical stages. This is essential for understanding the host-parasite interactions that influence transmission of Leishmania from canines to sandflies.

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EVALUATION OF BLT2 RECEPTO IMMUNOREACTIVITY IN CARDIAC TISSUE FROM RATS INFECTED WITH TRYPANOSOMA CRUZI AT DIFFERENT POST-INFECTION STAGES

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Chagas disease is a public health problem caused by Trypanosoma cruzi. In the chronic stage of the disease, the leukotriene receptor type 2 (BLT2) pathway is linked to inflammatory mechanisms. BLT2 increases the mobilization of Ca2+, leading to a greater production of nitric oxide (NO). The released NO could interact with superoxide to form peroxynitrite, followed by nitration and dysfunction of cardiac cells with important pathological consequences, thus an exacerbated proinflammatory environment at the myocardial level could be involved in an increase in fibrosis at the cardiac level. In the present study, the immunoreactivity of the BLT2 receptor and its relationship with fibrosis were evaluated in a Chagas model using Holtzman rats infected with 2x104 trypomastigotes of Y strain, via the intraperitoneal route, thus having 7 groups, each group with 6 rats and the control groups. (uninfected rats). Sacrifices were made at 7, 15, 30, 3, 90, 6, 270, and 365 days post infection (DPI). Evaluation used immunohistochemistry, Masson's trichrome staining, and hematoxylin and eosin. Amastigotes were observed in cardiac tissue at 7 and 15 DPI. However, at 7 DPI it is possible to observe few mononuclear cells and an increase of these at 15 DPI. No nests of amastigotes were observed after 30 DPI; however, inflammatory foci were observed at the tissue level. Likewise, from 90 DPI, a slight increase in significant interstitial fibrosis/scarring is observed without mononuclear cells; on the other hand, it was found that the immunoreactivity of the leukotriene B4 type 2 receptor is higher in the acute phase and decreases after three months. To corroborate this, the analysis of BLT2 immunoreactivity was performed in infected rats and compared with controls, finding that this receptor is more expressed at 7 ($p<0.001$), 15 ($p<0.01$) and 30 DPI ($p<0.01$). Therefore, it is concluded that in the acute phase of the disease there is a correlation between inflammation and expression of the BLT2 receptor ($p<0.05$). This could be because LTB4 is a chemotactic eicosanoid. However, no relationship was found between increased fibrosis and expression of this receptor ($p>0.05$).

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PEPTIDE SELECTION VIA PHAGE DISPLAY TO INHIBIT LEISHMANIA-MACROPHAGE INTERACTIONS

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Leishmaniasis represents a complex of diseases caused by protozoan parasites from the Leishmania genus that causes life-threatening manifestations depending on the species responsible for the infection. Given the high toxicity and cost of the current therapies, leishmaniasis is a public health problem. New interventions to hinder the interaction of the parasite with phagocytic cells are urgently needed to accelerate the development of new treatments or vaccines. Here, we used a phage display library to identify peptides targeting interaction of metacyclic promastigotes of L. amazonensis (causative agent for cutaneous leishmaniasis) and L. infantum (causative agent for cutaneous and visceral leishmaniasis) with phagocytic host cells. We identified one L. amazonensis binding peptide (La1), and two L. infantum binding peptides (Li1 and Li2). Importantly, peptide binding to the parasite surface impairs parasite internalization into THP-1 macrophages. The La1 peptide inhibits L. amazonensis only. However, Li1 and Li2 inhibit both L. amazonensis and L. infantum. Li1 and Li2 show promise for multi-species vaccine development, while La1 is an alternative option for species-specific vaccine development.

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IN VITRO INTERACTION OF MACROPHAGE U937 WITH LEISHMANIA (VIANNIA) ISOLATES INFECTED WITH LEISHMANIA VIRUS IN PANAMA, CENTRAL AMERICA

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The presence of the RNA virus (LRV) in parasites of the genus Leishmania and its association with increased pathology and treatment failure in individuals with skin infections have been described. Categorized as LRV-2 in the Old World and LRV-1 in the New World, this virus was detected in Leishmania isolates in American countries such as Brazil, French Guyana, Colombia, Peru, Ecuador, and Costa Rica. However, in Panama it is unknown whether the presence of LRV in the Leishmania parasite influences the pathology and therapeutic response of cutaneous leishmaniasis (CL). It is hypothesized that LRV-1+ isolates are more infective, and therefore cause more severe pathologies. In this regard, in this study the in vitro behavior of LRV-1 positive and negative Leishmania isolates were studied, evaluating the differences in infectivity in U937 human macrophages at 24, 48 and 72 hours post infection. Ten fields were counted for each slide, obtaining a total of 100 cells per slide. This was done in triplicate for each isolate for the different infection times. To calculate the infection index, the percentage of infected macrophages was multiplied by the ratio of amastigotes/macrophages. Fourteen isolates were used, 7 LRV+ and 7 LRV-, including species of L. (Viannia) guyanensis, L. (V.) panamensis and L. Viannia sp. from the ICGES biobank. Additionally, 3 reference strains of L. (V.) guyanensisLRV+, L. (V.) panamensis LRV- and L. (V.) braziliensis LRV- were evaluated as controls. The presence of LRV was detected by the RT-PCR methodology with the primers LVR ORF-1/2 (850bp) and LVR-1F/1R (240bp) and confirmed by Sanger sequencing as LRV-1. Comparison analysis of infection index showed increased infectivity of Leishmania ViannaLRV+ compared to LRV- isolates. These results showed that Leishmania Viannia LRV+ isolates may be more infective than

LRV- for U937 human macrophages. Future studies are recommended to evaluate the anti and pro-inflammatory cytokine profile induced during in vitro infections with Leishmania LRV+ isolates.

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DETECTION OF LEISHMANIAVIRUS IN ISOLATES OF LEISHMANIA VIANNIA IN PANAMA, CENTRAL AMERICA

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Leishmaniasis is a vector disease caused by protozoa of the genus Leishmania that affect humans producing a wide spectrum of clinical forms. Recently, the association of some Leishmania species with the presence of an endosymbiont double-stranded ribonucleic acid virus from the Totiviridae family called leishmaniavirus (LRV) have been described, showing increased pathology and treatment failures in individuals with cutaneous and mucocutaneous forms of the disease. Two types of LRV have been describes, type 1 circulates in the Americas while type 2 in the Old World. In America, the presence of LRV has been reported in Leishmania isolates from French Guiana, Brazil, Peru, Colombia, Ecuador, and Costa Rica. In a recent pilot study in Panama, 10 L. (V.) panamensis LRV-1+ isolates were detected by RT-PCR. In Panama, it is unknown if there are other species of Leishmania Viannia (L. (V.) guyanensis and L. (V.) braziliensis) associated with the presence of LRV-1. Therefore, the aim of this study was to detect LRV-1 in 100 Leishmania Viannia isolates from different leishmaniasis-endemic areas in Panama cryopreserved at ICGES biobank. Samples were collected between 2015 and 2022. Two molecular methodologies were used based on a RT-PCR that amplify the RNA of the ORF1 and ORF2 regions of the viral capsid. The results show that, it was possible to detect seven L. Viannia LRV+ (7/100: 7%), characterized as LRV-1 by Sanger sequencing analysis. With the LRV ORF-1/2 primers (850bp), one isolate of L. (V.) guyanensis LRV+ was found, and seven with the LVR-1F/1R primers (240bp), including species of L. (V.) guyanensis, L. (V.) panamensis and L. Viannia sp. These results demonstrate the circulation of LRV-1 in leishmaniasis endemic areas of Panama, and in different Leishmania (Viannia) species.

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CELL-BASED CARDIOMYOPATHY MODELS FOR CHAGAS DISEASE BIOMARKER DISCOVERY

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Chagas heart disease (CHD), the malignant cardiomyopathy triggered by Trypanosoma cruzi infection, is among the most prevalent neglected tropical diseases. Lacking relevant in vitro models, biomarker development for CHD prognostication and precision care has lagged.Methods; Murine and human cardiomyocytes were infected with trypanosomes to model CHD in vitro (CHD-CMs). Trypanosomes from variable genetic strains were assessed of cytopathogenicity (RTCA eSight). Motion vectors (SI8000 Imaging System) and calcium handling (FDSS/µCELL) analyses characterized CHD-CM excitation/contraction features. Transcriptomic analysis, in bulk and in single-cell resolution, and secretory phenotyping of CHD-CMs were applied for elucidating the host response signatures and its pseudotime trajectories.Results; 'Tc I/II' genetic strain Trypanosomes evoked evident cytopathogenic effects in vitro ($p < 0.05$). CHD-CMs recapitulated the excitation/contraction abnormalities in CHD and the extent of phenotypic deterioration was associated with tissue tropism per trypanosome genotype. Trypanosome infection led to differential expression of chemokine/cytokine activation-, heart beta-oxidation-, and oxidative stress-related genes. Along with known CCL/CXCL (MCP-1 and IP-10), an emerging signaling peptide GDF-15, was identified to be upregulated upon infection ($p < 0.001$). Co-culture experiments of CHD-CMs with other cardiac cell types (e.g. fibroblasts etc) indicated humoral factor-specific pathogenic roles in intra-cardiac cellular communication.Conclusions; Cardiomyocytes act as the upstream sentinels of pathogen encounter. Signatures of the CHD-CM response against trypanosome invasion constitute candidate CHD biomarkers.

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GENETIC TAXONOMIC ANALYSIS OF CHILOMASTIX GENUS

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There are many species named Chilomastix, such as C. caulleryi, C. cuspidata, C. wenrichi, C. cuniculi, C. bettencourti, C. caprae, C. gallinarum, C. equi, C. sulcatus, C. motellae Alexeieff. These species have been named based on morphology, with varying naming conventions such as author names or local host vocabulary, and generally lack gene-based evidence. To address the molecular taxonomy of Chilomastix species appropriately, the 18S small subunit of ribosomal RNA (18SrRNA) gene locus of Chilomastix spp. detected from 356 stool samples isolated from humans and 380 stool samples isolated from animals which were collected in Wainyapu Village, Sumba Island, Indonesia were analyzed. From 100 18SrRNA partial positive sequences, 52 unique genotypes (1,425-1,986 bp) were confirmed and phylogenetically analyzed with the references of GenBank. Based on estimated posterior probability values, we clustered the DNA haplotypes of Chilomastix spp. into Subgroup1 and Subgroup2. Subgroup 1-A (human-specific, containing C. mesnili reference sequences), Subgroup 1-B (pig/human/buffalo/dog specific), and Subgroup 1-C (chicken specific, which we consider C. gallinarum). Subgroup 2 is mainly Rodent-hosted. But divide into two separate subtypes Subgroup 2-A (rodent-single host) and Subgroup 2-B (Rodent-Duck-buffalo hybrid, which includes a C. caulleryi reference sequence). In conclusion, the Chilomastix species that infect each host have a certain degree of specificity, and although the number of examined samples was limited, we could address a wide variety of genetic diversity of this species. The accuracy of the molecular epidemiology of Chilomastix can be improved by further registering reference sequences.

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MOLECULAR STUDY OF THE NUCLEOLAR METHYLTRANSFERASE FIBRILLARIN OF THE HUMAN PATHOGEN LEISHMANIA MAJOR

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Fibrillarin is the enzymatic component of box C/D small nucleolar ribonucleoparticles (snoRNPs) involved in early processing and modification of ribosomal RNA (rRNA) primary transcript, and ribosome subunits assembly. Despite its importance, little is known about the functions

that Fibrillarin performs in the ancestral protozoan parasites of the genus Leishmania, microorganisms that cause different debilitating to fatal diseases. In this work, we initiated the molecular characterization of the Fibrillarin orthologue of L. major (ID:LmjF.36.3070; LmFib). Our in silico results showed that LmFib possesses the typical and conserved GAR region and methyltransferase domain. In addition, the predicted three-dimensional structure of LmFib is similar to the one reported in Saccharomyces cerevisiae. Furthermore, we generated transgenic L. major parasites that express a PTP-tagged version of LmFib to identify proteins that interact with it. By tandem affinity purifications, mass spectrometry and bioinformatic analyses, we found several activities (RNA helicases, GTPases, methyltransferases, among others) reported in yeast and human to interact with Fibrillarin, as well as approximately 65 structural ribosomal proteins. Notably, we also purified several interesting nucleolar proteins whose function has not been described. We are currently identifying the snoRNAs to which LmFib binds and analyzing if LmFib interacts with rRNA genes. PAPIIT IA200623

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ESTABLISHMENT OF AN IN VITRO CULTURE MODEL OF TOXOPLASMA GONDII BRADYZOITE CYSTS

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Toxoplasma gondii is an apicomplexa with a prevalence of 30% worldwide. The presentwork focuses on the chronic stage of the disease that is produced by the bradyzoite tissue cyst, as it tends to be drug resistant and is of high risk in immunosuppressed patients, so the study of its biology is of great importance. In the present study, we developed an in vitro model of bradyzoite cysts using LLCMK2 cells as host, with the aim of obtaining the highest number of cysts, the cells were cultured in 6-well plates containing cover slips where we infected the monolayers with the RH strain in a 1:1, 1:5 and 1:10. The initial phase of infection was performed in RPMI medium with 2% FBS at pH 7.2, at 37°C in the presence of CO2 for 24 hours for the correct establishment of the parasite. After this time, the medium was changed to RPMI 2% FBS, pH 8.5, at 37°C and in the absence of CO2. Four times were analyzed after the change of culture conditions: 72, 96, 120 and 144 hours post-change (h.p.c.). To identify bradyzoite cysts, cover slips were fixed with methanol:acetone, then stained with Giemsa and another group was fluorescence assayed using biotinylated Dolichus biflorus agglutinin (DBA) as primary marker and Alexa 594 streptavidin as secondary marker, together with DAPI. It was observed under a confocal microscope and then bradyzoite cysts and tachyzoite were counted in 50 fields using epifluorescence microscopy. As a result, at 120 h.p.c there was a better yield of bradyzoites/tachyzoites in relation to the other 3 times, however, being still low (10%) and showing high loss of the monolayer due to the high amount of extracellular tachyzoites. It is expected that with the 1:5 and 1:10 concentration the yield will increase and the monolayer and monolayer will remain intact. The next strain to be tested will be ME49, known to be highly cystogenic. It is expected that the results from this strain will have a better yield and number of cysts. Once standardized, these bradyzoites will be used to generate specific chronic phase antigens and thus implement a chronic phase diagnosis.

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DRUG REPURPOSING AND SCREENING OF LIBRARIES OF CHEMICAL COMPOUNDS TO IDENTIFY NEW ANTI-PARASITIC AGENTS

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The Trypanosoma and Toxoplasma spp, are etiological agents of diseases capable of causing significant morbidity, mortality, and economic burden, predominantly in developing countries. Currently, there are no effective vaccines for the diseases caused by these parasites; therefore, therapy relies heavily on antiprotozoal drugs. Non-biased screening of libraries of chemical compounds including the repurposing of well-characterized compounds is emerging as viable approach in identifying lead candidates for early drug development against parasitic diseases. As a proof-of-principle screen to identify effective anti-parasitic agents, we evaluated libraries of natural product (503), FDA-approved (640) compounds as well as imidazole derivatives (26) for potential to inhibit T. gondii growth. We identified 39 new compounds that potently and selectively restrict the growth of T. gondii. Furthermore, we evaluated some these compounds for activity against Trypanosoma growth both in vitro and in animal models. Findings revealed eight (8) imidazole derivatives active against Trypanosoma growth. Together, the findings are new and promising, and do not only strengthens the prospects of drug repurposing and the screening of wide range of chemical compounds as a viable approach in drug discovery toward effective anti-parasite therapy but also support imidazole-based compounds as alternative source of effective anti-parasitic agents.

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DEEP LEARNING APPROACH SUCCESSFULLY IDENTIFIES FDA APPROVED MOLECULES TO PRESENT ANTI-LEISHMANIA EFFECT AT THE PROMASTIGOTE STAGE

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Drug repositioning, a cost-effective approach in drug discovery, identifies new therapeutic applications for existing 'drugs' against NTDs, including Leishmaniases. An example of a successfully repurposed molecule is the anticancer treatment, Miltefosine, the first oral drug licensed for the treatment of leishmaniases. In this context, we have conducted a computer-aided drug repositioning approach based on the deepDR pipeline, an artificial intelligence (AI) tool. Then, we evaluated their activities in vitro against the promastigotes of three strains belonging to L. infantum (2) and L. major (1) species, using an MTT assay with the standard anti-Leishmania drugs Amphotericin B and Miltefosine as positive controls. We have selected, in silico, 14 FDA approved drugs to be potentially effective against leishmaniases, out of which 6 were previously described as anti-Leishmania agents and 2 tested on human and/or in vivo. We could confirm the anti-Leishmania effects for 2 out of the 8 molecules previously described, Posaconazole and Ketoconazole. Their IC50 values ranged from 5 to 35 µg/mL on our strains, out of the most published range. As these molecules are azoles, known to interfere with the sterol biosynthesis, we investigated the effect of Fetal Bovine Serum (FBS) as an exogen source of cholesterol on their activities. The experimental conditions "in absence of FBS" improved the IC50s values of ketoconazole, and led to the identification of two active compounds belonging to another class of molecules. One of these compounds, never described for its anti-Leishmania effect, presented an IC50 < 5µg/mL on our strains in the absence of FBS suggesting that it may target the sterol pathway or be sensitive to FBS content. To conclude computer-aided repositioning of FDA approved molecules as anti-leishmanial agents identified azoles, already known as antileishmanial molecules that we reconfirmed as effective on additional Leishmania sp promastigotes, and another class of molecules among which one is highly promising and calls for further investigations on intracellular forms of the parasites and its mechanisms of action.

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IN VITRO ANTITRYPANOSOMAL, ANTIOXIDANT AND CYTOTOXICITY ACTIVITIES, LC-MS ANALYSIS AND MOLECULAR DOCKING ANALYSIS OF BIOACTIVE COMPOUNDS FROM ANOPYXIS KLAINEANA AGAINST TRYPANOSOMA BRUCEI'S UDP-GALACTOSE 4`-EPIMERASE (TBGALE)

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African Trypanosomiasis is a major public health concern worldwide, especially in developing countries. Current chemotherapies are highly toxic, resistant and ineffective. Hence, novel effective and potent trypanocides are needed. Medicinal plants have been documented to be a potential source for the development of antitrypanosomal compounds. Anopyxis klaineana is an ethnomedicinal plant used in west Africa to treat many ailments including protozoan diseases. In this study, we investigated the in-vitro effects of crude methanol extracts and fractions of A. klaineana for their antitrypanosomal activities against Trypanosoma brucei using Alamar blue assay. Additionally, the crude extract's antioxidant and cytotoxicity activities were also determined. The phytochemical profiling of the crude extract was determined using LC-ESI-QTOF-MS to identify major bioactive compounds present. A. klaineana crude extracts and fractions (hexane, chloroform and ethyl acetate) exhibited potential anti-trypanosomal activities with IC50values of 21.25,4.35,2.57and 22.92ug/ml respectively. Moreover, the crude extracts showed moderate cytotoxicity against HepG2 and PNT2 cells, with IC50 values of 68.0±2.05 and 78.7±2.63ug/ml respectively. Antioxidant potential was observed in the crude extracts of A. klaineana. LC-MS analysis revealed the presence of 24 bioactive compounds. Furthermore, the bioactive compounds identified were subjected to molecular docking studies to identify novel compounds against Trypanosoma brucei's UDP-Galactose 4`-Epimerase (TbGalE). Three potential leads CID 5078, CID 4615 and CID 10347880 with binding energies -10.8, -9.9 and -9.6 kcal/mol respectively were identified. Molecular Dynamics simulation and Molecular Mechanics-Poisson Boltzmann Surface Area calculation were performed to elucidate the stability and the binding free energy of the potential leads' complexes. These compounds will further be investigated experimentally to determine their potential efficacy and could serve as candidates for the design of novel anti-trypanosomal therapeutics.

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HIGH LEVEL OF 'NEVER TREATMENT' IN MASS DRUG ADMINISTRATION AGAINST NEGLECTED TROPICAL DISEASES IN KENYA, NIGERIA, DEMOCRATIC REPUBLIC OF CONGO AND CAMEROON

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Mass Drug Administration (MDA) to eliminate Neglected Tropical Diseases (NTDs) has been ongoing for many years. Recently, there has been interest to measure the magnitude and impact of 'never treatment (NT)', understand the associated factors and how to address them within programmatic setup. 'Never treatment' refers to people in endemic areas (receiving MDA) who have never taken any MDA treatment. Sightsavers has been conducting coverage evaluation surveys (CES) in evaluation units in supported countries. We focus here on NT measurement nested within CES in the following EUs: four Local Government Areas for onchocerciasis and Lymphatic Filariasis MDA in Nigeria; one Sub-County in Kenya for trachoma following a failed impact survey; 12 Health Districts in Cameroon and four in Democratic Republic of Congo (DRC) for routine MDA programme evaluation for schistosomiasis and soil-transmitted helminthiasis (Shisto/STH). Within the selected EU, a two-stage cluster sampling with the village segment as the primary sampling unit and household the secondary sampling unit was employed to select participants. Sample size and selection were guided by the WHO coverage sample builder. At EU level: in Nigeria, NT varies from 15.4-69.9% among people ≥ 10 years of age; in DRC and Cameroon, from 1.7- 8.3% and from 0-25.5% among school aged children (10-14 years), respectively; and 29.6% in Kenya among ≥5 years. There was marked variation and more pronounced NT level among clusters within each EU - with some reaching 100% NT. Of those NT, a vast majority were not treated in the last round of MDA as a result of them not being offered the drug mostly due drug distributors failing to visit. Study is needed in districts/clusters with high NT levels to clarify drivers of low coverage, the transmission potential of these NT and highlight mitigating actions ensuring they are reached in future campaigns. Programmes should consider NT as a key indicator for programme performance for NTD elimination and as a potential proxy to failed impact survey and vice-visa.

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OPHTHALMOLOGICAL COMPLICATIONS IN VISCERAL LEISHMANIASIS AND POST KALA-AZAR DERMAL LEISHMANIASIS

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Recent reports of ocular complications in post kala-azar dermal leishmaniasis (PKDL) patients have propelled ocular safety as a research priority in Leishmaniasis. A systematic review of all published studies was carried out to collate ophthalmological events reported in patients with Visceral Leishmaniasis (VL) or PKDL. A total of 1821 records were identified of which 1683 were excluded at title/abstract screening and 85 excluded at full-text stage leading to 53 unique records included (1924-2022). From 37 records in VL, 120 ocular events were reported of which 32 occurred at baseline, 61 following a treatment and the time of occurrence was unclear in 27. The following events were reported at baseline: uveitis (n=13), retinal haemorrhage (n=8), papillary alteration (n=2), ocular motor dysfunction (n=1), endophthalmitis (n=1), retinitis (n=1), foveal haemorrhage (n=1), conjunctival involvement (n=2), blindness (n=1), chorioretinitis (n=1), and roth spots (n=1). The following were reported following a treatment: night blindness (n=39), uveitis (n=6), conjunctivitis (n=7), retinal haemorrhage (n=3), eye movement disorder (n=2), blindness (n=2), keratitis (n=1), macular haemorrhage (n=1). The following had unclear occurrence time: retinal/foveal haemorrhage (n=12), cotton wool spots (n=2), retinal involvement/detachment (n=6), uveitis (n=5), conjunctivitis (n=1), and blindness (n=1). From 17 unique records in PKDL, 38 complications were reported of which 1 occurred at baseline (conjunctival involvement), 33 occurred after a treatment, and the time was unclear in 4. The following were reported after treatment: keratitis (n=10), uveitis (n=8), keratopathy (n=4), scleritis (n=4), blindness (n=2), Moreen's ulcer (n=2), corneal involvement (n=1), retinal involvement (n=1), and conjunctival oedema (n=1). The following reports had unclear time: conjunctivitis (n=1), blindness (n=1), uveitis (n=2). This preliminary research suggests that ophthalmological outcomes should be actively solicited in clinical studies and in surveillance programme. Further work is ongoing to collate the events by treatment regimens.

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HOST, PARASITE AND DRUG DETERMINANTS OF TREATMENT OUTCOMES IN VISCERAL LEISHMANIASIS: AN INDIVIDUAL PATIENT DATA META-ANALYSIS USING THE INFECTIOUS DISEASES DATA OBSERVATORY DATA PLATFORM

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There is a geographical variation in the efficacy of the current first line therapies in use against Visceral Leishmaniasis (VL). An individual patient data meta-analysis (IPD-MA) was undertaken to explore the determinants of therapeutic outcomes using the Infectious Diseases Data Observatory (IDDO) VL data platform. Hierarchical logistic regression models were fitted in one-stage IPD-MA to identify risk factors associated with relapse; between study clustering was considered using random intercepts for study sites. Thirty-four studies (31 published; 3 unpublished; 2000-2019) from the IDDO VL data platform were included in the IPD meta-analysis. Of the 9,207 patients enrolled in these studies, 5,778 (62.8%) were from the Indian sub-continent (ISC), 2929 (31.8%) were from Eastern Africa (EA), 377 (4.1%) from Brazil and 123 (1.3%) were from Greece. Of the enrolled, 664 (7.2%) were <5 years old, 3,402 (37.0%) were 5-15 years old, 5,129 (55.7%) were aged 15 or older and age was missing in 12 (0.1%). Miltefosine was administered in 2,109 (22.9%), pentavalent antimony (PA) in 1,912 (20.8%) patients, amphotericin B (non-liposomal) in 1,213 (27.3%), liposomal amphotericin B (L-Amb) in 485 (5.3%), paromomycin in 900 (9.8%), combination of one or more drugs in 1,283 (13.9%), and placental extract in 5 (0.1%) patients. In univariable analysis, the following variables were associated with an increased risk of relapse: male sex and treatment with a monotherapy drug. Multivariable analysis was undertaken by including the following predictors: age, sex, geographical region, drug regimen, calendar year, and baseline haemoglobin measurement of which male sex and geographical region remained significantly associated with the increased risk of relapse. Males were at 1.61 [95% confidence interval (CI): 1.25-2.07] increased odds of relapse compared to females and patients from the ISC region were at 3.17 [95% CI: 1.24-8.07] increased odds of relapse compared to those from EA. Further analysis is ongoing to delineate the relationship between different host, parasite and drug related characteristics on initial cure, definitive cure, and mortality.

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SAROCLADIUM STRICTUM SECONDARY METABOLITES BLOCK PLASMODIUM FALCIPARUM TRANSMISSION TO MOSQUITOES

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Malaria is a deadly disease caused by mosquito-transmitted protozoan Plasmodium parasites. There are more than 200 million malaria cases every year worldwide. Fungal secondary metabolites provide a great resource to discover malaria transmission-blocking drugs because of their structural and active diversity. We screened our Global Fungal Extract Library (GFEL) and found the 10 µg/ml Sarocladium strictum ethyl acetate extract could completely block the transmission from Plasmodium falciparum to Anopheles gambiae by using standard membrane feeding assays (SMFA). The fractionation of the extract was conducted by using column chromatography, thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC), followed by the antimalarial activity-guided method. We found four fractions that significantly reduced the number of oocysts in mosquitoes compared to the control at 1 µg/ml. Two bioactive pure compounds are being isolated and identified from these activity fractions. The active fungal secondary metabolites are potent leads to stopping malaria transmission.

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VACCINE-LINKED CHEMOTHERAPY AS A NOVEL STRATEGY FOR CHAGAS DISEASE

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Chagas disease, caused by infection with the protozoal parasite Trypanosoma cruzi, affects almost 7 million people globally. Parasite persistence causes chronic myocarditis and progressive fibrosis, which can manifest clinically as chronic Chagasic cardiomyopathy (CCC). Current antiparasitic treatments with either Benznidazole (BNZ) or Nifurtimox have limited efficacy beyond early disease and do not address the underlying host pathology. We developed a candidate therapeutic vaccine based on a mutated version of the T. cruzi calcium-binding flagellar protein, Tc24, designated Tc24-C4 that contains recombinant Tc24-C4 protein and a TLR4 agonist adjuvant. In mouse models of acute infection, the vaccine induces a balanced TH1/TH2/TH17 immune response, reduces tissue parasite burdens, and reduces cardiac inflammation and fibrosis. More recently we have demonstrated that vaccine-linked chemotherapy, combining a low dose of BNZ with therapeutic vaccination with the Tc24-C4 vaccine, leads to reduced cardiac inflammation and fibrosis in mouse models of acute T. cruzi infection and improved cardiac remodeling and function in a mouse model of chronic T. cruzi infection. In the current study, we evaluated a new vaccine-linked chemotherapy strategy in our mouse model of chronic infection that combined Tc24-C4 vaccine and BNZ with TTI-101, a small-molecule STAT3 inhibitor shown to reduce tissue fibrosis in non-infectious mouse models of lung and liver fibrosis. Female BALB/c mice were inoculated with bioluminescent T. cruzi H1 strain trypomastigotes. At 70 days, mice were administered the Tc24-C4 vaccine, BNZ, or TTI-101 alone or sequentially in combination. Vaccination was given subcutaneously twice, three weeks apart; BNZ and TTI-101 were administered orally once daily for 20 days. Cardiac structure and function were evaluated by echocardiography and electrocardiograms approximately once monthly, then endpoint cardiac fibrosis was evaluated by microscopy at approximately 8 months of infection. The impact of TTI-101 on further reducing cardiac fibrosis and improving cardiac structure and function over time will be discussed.

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SURVEILLANCE OF ENTERIC VIRUSES AND SARS-COV-2 IN SELECTED LEAFY VEGETABLES AND FARMERS IN THE OFORIKROM DISTRICT, KUMASI, GHANA

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The emergence and spread of enteric viruses and SARS-CoV-2 have increased concerns over food safety and the potential for foodborne

transmission. Green leafy vegetables such as cabbage, lettuce, and green onions are commonly consumed raw and have been implicated in outbreaks of enteric virus infections. Also, the recent pandemic has raised the question of whether the virus can be spread through the fecal-oral route or contaminated food. Farmers who work with these crops may also be at risk of infection. This suggests that there may be a high prevalence of enteric viruses and SARS-CoV-2 in green leafy vegetables and farmers may not be aware of the potential transmission of these viruses through the vegetables they cultivate. Therefore, this study sought to determine the burden of enteric viruses and SARS-CoV-2 in farmers and the green leafy vegetables they grow and identify potential sources of contamination. The study involved the collection of cabbage, lettuce, and green onions, oral swabs, and stool samples from 10 different farm sources followed by laboratory methods of detecting viral RNA by RT-PCR. The current results of the study for SARS-CoV-2 detection in vegetables and farmers are negative implying that they did not have an active infection with the virus at the time the samples were collected or the viruses were inactivated due to exposure time and some environmental factors. However, testing the samples for the other viruses is yet to be done. This study will highlight potential sources of contamination, reduce the risk of foodborne transmission and create awareness of the possible transmission of viruses through food.

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HOUSING STRUCTURES AND VISCERAL LEISHMANIASIS TRANSMISSION IN BARINGO COUNTY, KENYA

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Visceral leishmaniasis (VL) is endemic in Baringo County, Kenya, and contributes significantly to the burden of disease in the region. Housing structures and other environmental risk factors contribute to transmission dynamics, but these have not been widely studied in Baringo. Drought, famine, and insecurity in the region have changed the disease landscape in recent years. This study aims to examine environmental risk factors in relation to VL transmission in Tiaty East and West sub-counties. Data collection began in February 2023 and will continue through May 2023 at Chemolingot Sub-County Hospital and patients' homesteads. Data collection is being performed via questionnaires of primary VL patients being treated and VL follow-up patients that still reside in the same house as when infection occurred. Factors being assessed are housing materials, distance to termite towers, proximity to animals and animal sheds, sleeping behavior, use and access to insecticides, and previous health education. 18 household interviews were performed in March 2023 where heads of households were asked in-depth questions about housing structure choices, behavior, and access to VL prevention materials. 3 key informant interviews were performed in March 2023 with community health volunteers (CHVs) regarding VL awareness and environmental challenges in the communities. A baseline assessment of housing types through direct observation including materials, distance to water sources, distance to vector sites, and overall homestead condition is ongoing. Preliminary data indicates that the majority of VL patients reside in stick and mud houses and within proximity to animals. Most patients do not take any actions to prevent sandfly bites or sandflies from entering their home. Preliminary data from household interviews indicate that some individuals would prefer to build their house out of iron sheet because it is more permanent but lack the finances to do so. Current household building materials do not allow for adequate protection from VL, and other environmental factors likely exacerbate this risk. Strategic environmental interventions are imperative.

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A PREDICTIVE MODEL ACCOUNTING FOR DEFORESTATION ACROSS TEMPORAL AND SPATIAL SCALES IDENTIFYING ANNUAL SHIFTS IN THE ODDS OF EBOLAVIRUS ZOONOTIC SPILLOVER

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Outbreaks of filoviruses, such as ebolaviruses, typically result from zoonotic transmission from infected animals, and most recent outbreaks have resulted from zoonotic spillover. Past analyses of ebolavirus emergence have found relationships between ebolavirus spillover and forest loss (FL), however, FL data has not ever been incorporated into predictive analyses of ebolavirus emergence. We developed a novel predictive model of ebolavirus zoonotic spillover incorporating FL, vegetation, population, and meteorological data from 2001-2021 using model ensembles fit with boosted regression trees. FL was measured across multiple spatial and temporal scales, as it is unknown whether spillover is driven by FL on local or regional scales, and whether a temporal lag exists between FL and ebolavirus emergence. Models were fit for all ebolavirus species (All-species analysis) and Zaire virus only (Zaire-only analysis), as Zaire virus has a unique ecology compared to other ebolavirus species, and annual predictions of the relative odds of spillover were generated. Model fit was slightly better in the Zaire-only analysis (AUC: 0.91) compared to the All-species analysis (AUC: 0.87). Resulting predictions identified specific areas throughout equatorial Africa with elevated relative odds of spillover as high as 30 times the baseline odds, which shifted annually based on recent forest loss. Predictions which accounted for FL were distinct from previous models that ignored FL data, leading to identification of new locations where elevated spillover odds were driven by FL. Relative importance of FL variables in predicting spillover was higher in the Zaire-only model than in the All-species model, suggesting that FL may play a more important role in Zaire virus ecology compared to Sudan and Bundibugyo viruses. Spillover events from 2022-2023 in DRC and Uganda both occurred in locations predicted to have a relative odds ratio >5. FL variables improved the predictive ability of models, suggesting the importance of habitat disruption in ebolavirus ecology, and its value in prioritizing ebolavirus surveillance and prevention efforts.

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INTEGRATING ECOLOGY AND EPIDEMIOLOGY TO EMPOWER ONE HEALTH: A STUDY OF RIFT VALLEY FEVER

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Emerging zoonoses, such as Rift Valley fever (RVF), require a One Health (OH) approach to predict, mitigate and prevent outbreaks. An arbovirus, RVF virus (RVFV) causes periodic, yet widespread outbreaks with high rates of abortion and death in ruminant livestock. People often have mild influenza-like symptoms with rare but serious complications: hemorrhagic fever, hepatitis, retinitis, and meningitis. Outbreaks have been linked to complex climatic events (El Niño/La Niña) that drive favorable environmental conditions for large populations of mosquito vectors. The integration of human, livestock, wildlife, and environmental health data requires multidisciplinary methods, integrating ecological and epidemiological

approaches. We conducted a OH study of RVFV seroprevalence in livestock and people in South Africa. Here we provide an example of an approach for the collection and analysis of OH zoonotic disease data. We used a systematic grid of geographic points to achieve a probability proportional to size sampling framework for each species (human, cattle, goats, and sheep). We demonstrate how joint models can be used to determine risk factors for RVFV seroprevalence in people, cattle, sheep and goats with demographic variables, risk behaviors, husbandry characteristics and environmental variables. This method improves the ability to identify and compare risk factors across species, is explicitly designed to account for correlation amongst species, reduces multiple testing and the need for p-value correction. Examples of multiple testing include using the same predictors for multiple outcomes (e.g. seroprevalence of RVFV and Sindbis virus), siloed analyses evaluating the results in people separate from those in animals and/or environmental data or variable selection resulting in higher false positive rates, requiring p-value correction (Bonferroni) and loss of statistical power. Joint estimation is suited for reducing multiple tests without the resultant loss of power. As OH study design becomes increasingly integrated, it is important to develop adequate analysis methods that can harness the power of a OH study design.

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EVIDENCE AND GAP MAP FOR MULTI-SECTOR AND ONE HEALTH RESEARCH IN ZOONOTIC NEGLECTED TROPICAL DISEASES

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Directly referenced in the WHO's 2030 road map for the Neglected Tropical Diseases is the need for a "One Health" approach in addressing diseases possessing zoonotic components. This report aims to map where the current research evidence lies across the human, animal, and environmental health sectors and multisector (human-animal, human-environment, animal-environment, One Health) regarding the transmission, surveillance, and control of the zoonotic Neglected Tropical Diseases (zNTDs) by presenting the information in simple, accessible Evidence and Gap Maps. These Maps may serve as interactive tools for users while providing a structured framework that serves to highlight current research gaps in the field. A comprehensive search strategy was implemented across MEDLINE, EMBASE, and GLOBAL HEALTH databases. Overall, 6920 records were screened by titles, abstracts, and keywords from articles published between 1990 and 2020. A total of 2269 articles were excluded for not being a journal article, not focusing on a zNTD, and not discussing transmission, surveillance, or control in some capacity, leaving 4732 records which met the inclusion criteria. These articles were subsequently coded using a standardized tool according to their relevant zNTD, health sectors, and areas of evidence (transmission, surveillance, control). Three evidence and gap maps were generated. In general, across all zNTDs, individual health sectors were disproportionately represented in the evidence, with multisector and One Health approaches lacking across the zNTDs. Despite the cross-sectoral aspects of zNTD transmission, surveillance and control, there is a clear segregation of the evidence into single-sector research. Visual presentation of the existing literature in the form of Evidence and Gap Maps should serve as a powerful tool for researchers, policymakers, and academics implementing and advocating for cross-cutting approaches to achieve the zNTD control targets set in the WHO's 2030 road map.

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PREVALENCE, DISTRIBUTION AND DIVERSITY OF BARTONELLA IN SMALL MAMMAL AND BAT COMMUNITIES ACROSS CAMBODIA

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Bartonella species are Gram-negative, facultative intracellular bacteria that represent the only genus in the family Bartonellaceae. Small mammals and bats are natural reservoirs of many Bartonella species. We investigated Bartonella presence, distribution and diversity in small mammals and bats across 249 locations in 23 provinces across different habitat types in Cambodia from 2016 to 2020. A total of 3,515 small mammal and bat blood and lung spleen kidney (LSK) samples were screened with pan-bartonella PCR primers targeting the beta subunit of bacterial RNA polymerase (rpoB) gene. Bartonella DNA was detected in 19.32% (337/1,744) of bats and 8.3% (147/1771) of small mammals collected during this project including 26 small mammal species and 61 bat species. Highest prevalence was detected in Rattus complex from deciduous forest (34%) and Rhinolophus acuminatus from evergreen forest (38.89%). Phylogenetic analyses of 203 rpoB gene sequences showing the Bartonella genotypes circulating in the small mammal (58) and bat (145) populations across Cambodia are presented.

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EPIDEMIOLOGY OF ANIMAL BITES AND POST-EXPOSURE PROPHYLAXIS (PEP) OF RABIES IN RUPANDEHI, NEPAL

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Animal bites remain an important public health problem in Rupandehi District, Nepal. The secondary data from Jan to Dec, 2022 were obtained from Anti-rabies vaccination record of Bhim hospital, Bhairahawa. The data were entered into MS Excel and later analyzed by SPSS for descriptive statistics. The objective of the study was to estimate the burden of animal bite victims and the requirement of anti-rabies vaccines in Rupandehi District, Nepal. Out of total 3,617 cases of animal-bites reported, 65.00% (2,369) were males, 26.10% (944) were children of 0-10 years age group and 50.00% (1,823) victims hailed from urban areas. Dogs (93.22%, 3,372) were responsible for a majority of bites. The maximum number of bites were reported from January to April and in December of 2022. Leg (59.71%) was the commonest site of bite followed by hand, trunk and head. The majority of bites belong to Category II of the WHO classification (98.41%). Among the total bite victims, 94.91% (3,433) were found to complete the full course of vaccination. 13.98% of the victims received their first dose of PEP on the same day of exposure while 67.68% of the victims received it after 1 day of exposure. 90.36% and 89.23% of the bite victims received their 2nd and 3rd doses respectively on time. A well-planned vaccination program should be implemented to ensure the compliance with anti-rabies PEP schedule after animal bites. All age groups from both rural and urban areas should be prioritized for awareness and education programs to improve their treatment and PEP seeking behavior.

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DETECTION AND MOLECULAR CHARACTERIZATION OF MULTI-RESISTANT ENTEROBACTERIACEAE CARRIED BY HOUSEFLIES IN THE CITY OF BOBO-DIOULASSO, BURKINA FASO

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Houseflies (Musca domestica) are synanthropic insects that are vectors of a wide range of pathogens (multidrug resistant) responsible for infectious diseases. This study aimed to detect and characterize multidrug-resistant Enterobacteriaceae carried by houseflies in the city of Bobo dioulasso. A total of 500 houseflies were captured in 25 hospital and non-hospital environments in the city of Bobo-Dioulasso. They were divided into 125 batches of 5 flies for bacteriological analysis. Multidrug-resistant bacteria, isolated on MacConkey agar supplemented with cefotaxime 4µg/ml, were identified on the basis of biochemical characteristics. Antibiotic susceptibility profiles were determined by the agar diffusion method. Detection of blaCTX-M resistance genes, quinolone resistance genes (PMQR) and determination of E. coli phylogroup were done by conventional PCR. Among 115 bacterial strains obtained, 26 were extended-spectrum beta-lactamase (ESBL)-producing enterobacteria: E. coli (15), Klebsiella pneumoniae (6), Enterobacter cloacae (4), Morganella morganii (1). This carriage was statistically more important in hospitals (9/30, p=0.03). No carbapenem-resistant strains were observed. ESBL resistance genes (CTX-M group 1) (25/26) and quinolone resistance genes (QnrS) (6/26) were found. Houseflies in the city of Bobo-Dioulasso are vectors of transmission of multidrug-resistant enterobacteria. Surveillance of the associated risks to public health is necessary.

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HIGH PREVALENCE OF TETRACYCLINE RESISTANT ESCHERICHIA COLI ISOLATES IN AMERICAN CROCODILE CROCODYLUS ACUTUS LIKE BIOINDICATOR IN CAÑAS GUANACASTE COSTA RICA

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In recent years bacteria have acquired resistance genes causing "antibiotic resistance". The agricultural, animal, and aquaculture industries are one of the main causes, of the excessive use of antibiotics that are released into the environment. The American crocodile found in this type of ecosystem becomes a bioindicator. The aim of the research is to characterize antibiotic resistant bacterial isolates of Escherichia coli obtained from the American crocodile sewer in a tilapia production system. The study was in collaboration with the company AquaCorporación in Cañas and the samples were of 53 crocodiles captured in the tilapia ponds. Each of the captured animals made a swab of the cloaca and it is introduced to a nutritious broth and transported to the laboratory at a cool temperature. The swabs were inoculated on selective agars until obtaining pure isolates of E. coli were. Then an antibiotic sensitivity profile was performed with the Vitek 2 equipment on the isolates. Those for veterinary use were evaluated in dishes with antibiotics and the Minimum Inhibitory Concentration (MIC). Resistance isolates were sequenced from the entire genome by MicrobesNG on the Illumina HiSeq platform with a 250 bp end protocol. The results obtained from the resistant isolates were for florfenicol (11.8%), Ampicillin (16.4%), Ampicillin Sulbactam (7.3), Nalidixic Acid (3.6%), Trimethoprim/ Sulfamethoxazole (3.6), and a high prevalence of tetracycline (75%), with a MIC 50 of 32 µg/ml and MIC 90 of 128 µg/ml. Complete genome sequencing can visualize a variety of types of MLST and the transport of known mobile genes that encode resistance against antibiotics and, various plasmid sequences were detected. This work concludes that the information obtained in this research is important because resistance detected in wild animals is also associated with a production system and that in the future may become a risk to public health and the environment. Finally, it is important to assess in the future the role of dispersion of the resistance mechanisms detected and possible changes that may occur in the natural structure of ecosystems

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WHOLE GENOME SEQUENCING TO ELUCIDATE THE ZOONOTIC TRANSMISSION OF STRONGYLOIDES STERCORALIS AND ANCYLOSTOMA CEYLANICUM BETWEEN DOGS AND SCHOOL AGED CHILDREN LIVING IN THE SAME COMMUNITIES

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Strongyloides stercoralis and Ancylostoma ceylanicum are parasitic soil-transmitted helminths that impact on the health of humans and dogs in the tropics. Both parasites are categorised as agent of neglected tropical diseases by the World Health Organization. The ability of these parasites to transmit between humans and dogs living in closed proximity via contaminated environments is of particular concern in areas characterised by poor sanitation . Despite this, there is a lack of understanding about the extent to which these parasitic nematodes are transmitted between different host species, particularly humans and community dogs. To quantify the zoonotic potential and transmission of S. stercoralis and A. ceylanicum, we isolated single eggs of A. ceylanicum from faecal samples of 14 children and 25 dogs and single larvae of S. stercoralis from 20 children and 35 dogs living in the same communities in Cambodia. Whole genome amplification was performed on extracted DNA to increase concentration for whole genome sequencing. By analysing genetic variation within and among parasites, the intra- and interspecies transmission and dispersal between communities of these parasites can be traced, with the ultimate goal of identifying genetic markers associated with specific human/animal host species. This information will help elucidate the risk of transmission from domestic animals to humans and inform the parameterisation of multi-host transmission dynamics models. These findings will be essential to the development of effective elimination strategies for these zoonotic parasites of major public health and socio-economic importance.

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DETECTION OF BRUCELLA IN HUMANS AT TEKNAF, COX'S BAZAR IN BANGLADESH

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Human brucellosis is a serious infectious disease caused by a gram-negative bacteria of the genus Brucella. Brucellosis in humans is considered as a neglected and underreported disease. From February 12, 2022 to July 31, 2022, a routine examination was conducted to detect brucellosis in patients who presented with fever using a triple antigen test along with Salmonella and Rickettsia at Severe Acute Respiratory Infection, Isolation and Treatment Centre (SARI, ITC), icddr,b, Teknaf, Cox's Bazar, Bangladesh. From SARI, ITC, 120 patients were enrolled for the test. Based on the findings, we investigated the positive patients from August 03-05, 2022. Among 7 patients, we could trace 5 during this investigation. After taking verbal consent, we interviewed the patients and collected blood specimens for further investigation and laboratory confirmation by the TaqMan real-time PCR test at icddr,b Biosafety level 2 laboratory. Further, we conducted a small survey at the same hospital from October 4, 2022, to December 14, 2022. We enrolled the patients who were admitted to the hospital with ≥ 7 days of fever, muscle ache, headache and joint pain coming from different villages in the host population and from the refugee camps of Forcibly

Displaced Myanmar Nationals as well. We collected blood samples from 33 patients. We also collected demographic information and the history of exposure to livestock and livestock products of the patients to identify the source of infection. Among the patients tested by triple antigen, 7 were positive for Brucella spp (5.8%). Among them, 5 patients we could trace during the investigation, 1 confirmed positive by PCR. During the survey, out of 33 patients, 1 was found to be positive both by triple antigen test and PCR (3%). The positive patients, their families, and their neighbors had a history of raw milk consumption and exposure to livestock. Among the patients, enrolled for the survey, 21% reported consuming raw milk by them or their families. Consumption of raw milk might be considered as one of the important causes of Brucellosis in this area. Therefore, intervention should be carried out in this area to avoid raw milk consumption.

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MAPPING HOUSEHOLD-SCALE LIVESTOCK HUSBANDRY IN LOW- AND MIDDLE-INCOME COUNTRIES BY ANIMAL TAXON: A BAYESIAN PREDICTION MODEL OF A KEY INFECTIOUS DISEASES RISK FACTOR

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Around 70% of the world's 880 million rural poor depend on traditional animal husbandry systems for their livelihoods which, while having numerous economic and health benefits, can be a significant source of infections through exposure to fecal contamination and respiratory pathogens. It is estimated that over 60% of human pathogens are zoonotic, and we are living in the age of pandemics resulting from the spillover of a zoonotic pathogen, such as Ebola, SARS-CoV2 and Mpox yet there have been few attempts to estimate the interphase of human and domestic animal interaction at a global scale. This represents a barrier to the improved understanding of the dynamics of both endemic and emerging infectious diseases. This analysis aimed to map the distribution of household-scale livestock husbandry in LMICs by animal taxon. Data on animal ownership were compiled from around 300 nationally representative, population-based household surveys, and species were classified into ruminants, monogastrics and poultry. A novel georeferencing methodology was implemented and a suite of time-static environmental and demographic spatial covariates were compiled based on their hypothesized associations with the outcome variables. Variable values were extracted at the georeferenced cluster locations and a Bayesian Multi-level based logistic regression approach was used to model associations and generate predictions for all LMICs at a 6km resolution. A Markov Random Field (MRF) smooth algorithm was employed to improve spatial correlation and continuity of the prediction maps. Model evaluation statistics were mixed, but weighted average recall was 0.89 for monogastric, 0.78 for ruminant and 0.74 for poultry ownership. High prevalence of poultry ownership was predicted across the Tibetan Plateau and in pockets in the Andes, Ethiopia, and Kenya, while ruminant ownership rates were high in parts of Amazonia, Syria and Yemen. The resulting prediction maps can be used by policymakers and program planners to generate disease burden estimates, target outbreak prevention interventions geographically and identify hotspots of risk for zoonotic spillover.

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ISONIAZID URINE COLORIMETRY FOR EVALUATION OF TUBERCULOSIS PHARMACOKINETICS IN ADULTS AND CHILDREN

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Treatment failure and emergence of drug-resistance in tuberculosis (TB) can be caused by suboptimal pharmacokinetics. Dose adjustment can be personalized by measurement of peak serum concentrations; however, the process involves cold-chain serum preservation and sophisticated laboratory procedures unavailable in many high-burden TB settings. Isoniazid is an important drug in many TB treatment regimens. Urine colorimetry provides a low-cost alternative with simple sampling and quantification methods. We enrolled 56 adults and 89 pediatric patients in a prospective, observational study of patients taking first-line anti-TB medications that was conducted in Tanzania (children) and the United States (adults). Serum was collected pre-dose and 1, 2, 4, 6, and 8 hours post dose for measurement of isoniazid concentrations using validated LC-MS/MS methods. Urine was collected between 0-4, 4-8, and 8-24 hour intervals post dose, and pooling was done to determine concentrations at 0-8 and 0-24 hours, with urine concentrations measured using colorimetric methods. The average peak serum concentrations were 4.8 mg/L and 6.4 mg/L for adults and pediatric patients, respectively. The average total serum exposure over 24 hours was 16.4 mg*h/L for adults and 26 mg*h/L for pediatric patients. Correlation between serum parameters and urine values was highest at the 0-4 hour collection interval for adults (r=0.7) with area under receiver operator characteristic curve (AUC of ROC) of 0.9 (CI: 0.7-1) for urine values predicting subtherapeutic serum concentration for dose adjustment. Unexpectedly in children, correlation was lower than that observed in adults and occurred for urine at the 8-24 hour (r=0.5). Isoniazid urine absorbance correlated with serum concentrations at different urine collection intervals in adults and pediatric patients. Colorimetric methods may improve feasibility of personalized dosing in high-burden TB regions but requires further study of dose adjustment based on urine thresholds in adults, and exploration of urine trough measurements in children.

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PERFORMANCE OF SARS COV-2 IGG ANTI-N AS AN INDEPENDENT MARKER OF EXPOSURE TO SARS COV-2 IN AN UNVACCINATED WEST-AFRICAN POPULATION

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The determination of previous SARS-COV-2 infection is hampered by the absence of an accurately sensitive standardised test. The most relevant marker used to assess previous exposure is IgG antibody to the nucleocapsid (IgG anti-N), although it is known to wane quickly from peripheral blood. The sensitivity and specificity of seven antibody tests either singly or in combination namely, virus neutralization test, IgG anti-N, IgG anti-S, IgG anti-RBD, IgG anti-N + anti-RBD, IgG anti-N + anti-S and IgG anti-S + anti-RBD were evaluated on 502 cryopreserved serum samples collected pre-vaccination rollout in 2021 in Kumasi, Ghana. Accuracy of each index test was measured using a composite reference standard based on a combination of type neutralization and IgG anti-N

antibody tests. According to the composite reference, the most sensitive test was virus neutralization test that yielded 95.4% sensitivity (95% CI: 93.6-97.3), followed by 79.8% for IgG anti-N + anti-S (95% CI: 76.3-83.3) and a ROC value of 0.98. The most specific tests were virus neutralization and IgG anti-N, both with specificity 100% (95% CI: 100-100). Arbitrarily, viral neutralization and IgG anti-N + anti-S were the overall most accurate tests with specificity/sensitivity of 100/95.2% and 79.0/92.1% respectively. In conclusion, our findings indicate that IgG anti-N alone is an inadequate marker of prior exposure to SARS COV-2 in an unvaccinated population. Virus neutralization assay appears to be the most accurate assay in discerning prior infection. A combination of IgG anti-N and IgG anti-S is also highly sensitive and specific, and suited to low resource settings in the assessment of SARS COV-2 exposure prior to vaccination.

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FEASIBILITY OF CASH TRANSFERS TO FACILITATE TUBERCULOSIS SCREENING AMONG HOUSEHOLD CONTACTS OF TUBERCULOSIS PATIENTS IN TANZANIA

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Tanzanian tuberculosis (TB) guidelines recommends facility-based TB screening for household contacts (HHCs) of TB patients who are symptomatic or under the age of 5 years. However, many households are unable to complete HHC screening due to cost barriers. Here, we evaluate the feasibility of unconditional cash transfers to facilitate completion of HHC screening and explore factors that impact screening completion in a rural setting with high TB prevalence. In this prospective cohort study, we consecutively enrolled index TB patients within 8 weeks of TB treatment initiation from the TB clinic at Haydom Lutheran Hospital and surrounding dispensaries in Haydom, Tanzania. The study provided a cash transfer of up to 40,000 Tanzanian Shillings ($17.09) to affected households to facilitate HHCs TB screening and covered medical cost incurred from screening activities. In addition, telephone reminders occurred every 2 weeks for 2 months to follow up on screening progress. We collected data on demographics, TB diagnoses, and socioeconomic/household characteristics, as well as feedback on the utility of cash transfers and additional interventions. The study enrolled 120 index TB patients and their households from July 13th through December 21st, 2022 with total 397 HHCs. Median age for index patients 35 years, 63% males. 69 (58%) of participating households completed the recommended screening for all HHCs. Only 48 households (40%) were able to fully cover the cost of HHC screening. In a logistic regression model, households that were able to fully cover the cost of HHCs and households that received sputum collection containers through a separate program were significantly more likely to complete HHC screening for all members (aOR 3.46 and 3.98 respectively, $p<0.01$). The use of cash transfer is feasible and positively impacts the completion of HHC screening in Haydom, Tanzania. Exploring additional support to households impacted by TB including cash transfers to cover TB screening cost, telephone reminders, and sputum collection containers can further improve completion of HHC TB screening.

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THE EFFECT OF THE COVID-19 PANDEMIC ON HEALTHCARE SEEKING IN AN INFORMAL URBAN SETTLEMENT IN NAIROBI AND A RURAL SETTING IN WESTERN KENYA, JANUARY 2016 TO AUGUST 2022

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The COVID-19 pandemic caused widespread disruptions to healthcare seeking. There are limited studies on the effect of the COVID-19 pandemic on healthcare-seeking patterns in low-and middle-income countries (LMICs), especially in rural settings and informal urban settlements with limited access to healthcare. We investigated the effect of the COVID-19 pandemic on reported healthcare seeking at health facilities and pharmacies using household morbidity data among study participants in a well-established longitudinal disease surveillance platform located in two diverse sites in Kenya: Asembo, a rural setting in western Kenya, and Kibera, an urban informal settlement in Nairobi. We described healthcare seeking before (1st January 2016 to 12th March 2020) and during the pandemic (13th March 2020 to 31st August 2022) using frequencies and percentages. We used a generalized estimating equation with an exchangeable working correlation structure to assess the effect of the pandemic on healthcare seeking in the two sites. Overall, there was a 15% (adjusted odds ratio, aOR: 0.85; 95% CI: 0.82 -0.88) reduction in health facility-based healthcare seeking in Asembo during the pandemic, and 23% (aOR: 0.77; 95% CI: 0.74 -0.81) reduction in Kibera. The pandemic resulted in increased care seeking at pharmacies in the two surveillance sites (aOR: 1.25; 95% CI: 1.21-1.28 in the Asembo site, and aOR: 1.42; 95% CI: 1.36 -1.48 in the Kibera site). We observed higher odds of healthcare seeking among ill participants who reported respiratory syndromes (e.g., in Asembo, aOR (95% CI) for Acute Febrile Illness was 2.80 (2.69-2.92), Acute Respiratory Illness was 1.40 (1.30-1.51, and for Severe Acute Respiratory Illness was 3.75 (3.58-3.93)). However, there was a decrease in healthcare seeking at pharmacies among ill participants who reported severe acute respiratory illness. This study highlights interruptions to healthcare facility utilization in resource-limited settings due to the COVID-19 pandemic. Strategies are needed to optimize healthcare provision and utilization at health facilities during pandemics.

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HEPATITIS B AND INFLUENZA VACCINE COVERAGE AMONG HEALTHCARE WORKERS IN SELECTED HEALTH FACILITIES IN BANGLADESH

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Healthcare workers (HCWs) carry a higher risk of both hepatitis B and influenza virus infection due to occupational exposures. Despite the availability of a safe and effective vaccine, routine adult immunization programs against these infectious pathogens among HCWs are overlooked in low-middle-income countries like Bangladesh. This study aims to investigate the extent of hepatitis B and influenza vaccine coverage among HCWs. From July 2021 to March 2023 we recruited a cohort of healthcare workers from 13 primary, 2 secondary, and 5 tertiary care hospitals of four administrative divisions across Bangladesh. Field staff interviewed the HCWs to collect demographic information and records of hepatitis B, and influenza vaccination using a structured questionnaire. We summarized the data using descriptive statistics. We enrolled 3684 HCWs: 22% (810) physicians, 48% (1763) nurses, and 30% (1111) support staff. Of 3684,

70% (2583) were recruited from tertiary, 22% (793) from primary, and 8% (308) from secondary-level healthcare facilities. The median age of the HCWs was 35, (IQR= 29-44) years and 67% were female. In the cohort, 8% (289) of HCWs reported to receive the influenza vaccine for the current influenza season and 53% (1968) reported to complete three doses of the hepatitis B vaccine. Overall, 8% of physicians, 10% of nurses, and 6% of support staff reported to receive the seasonal influenza vaccine. Hepatitis B vaccine uptake was highest among physicians (81%), followed by nurses (56%), and support staff (28%). Seasonal influenza vaccine uptake was highest in tertiary-level facilities (10%) followed by secondary (5%) and primary-level facilities (3%). In contrast, hepatitis B vaccine uptake was highest in primary-level facilities (60%) followed by tertiary (54%) and secondary-level facilities (34%). Both hepatitis B and influenza vaccine coverage were low among HCWs in Bangladesh, especially among support staff. Educational interventions to build awareness and subsidized vaccination policies for HCWs may improve vaccine uptake among this high-risk group.

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ASSOCIATION OF ALTERED BASELINE HEMATOLOGICAL PARAMETERS WITH ADVERSE TUBERCULOSIS TREATMENT OUTCOMES

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Tuberculosis (TB) treatment monitoring is an essential tool for effective TB treatment management. Identifying parameters that predict adverse TB treatment outcomes (failure, recurrence and death) could significantly improve clinical management. The association of hematological parameters with poor TB treatment outcomes is not well defined. To study the relationship of hematological parameters with TB treatment outcomes, we examined data from pulmonary tuberculosis (PTB) patients with successful and unsuccessful treatment outcomes. We enrolled 68 cases (poor treatment outcomes) and 133 controls (good treatment outcomes) through a nested 1:2 case; control study, matching for age, sex, body mass index, diabetes status, alcohol and smoking. Median age of the study population is 45 years and it ranges from 36 to 52 years. Hematological profiling showed significant differences in the absolute counts of white blood cells (WBC), lymphocytes, neutrophils and monocytes between cases and controls. In addition, increased neutrophil to lymphocyte (NL) ratio and monocyte to lymphocyte (ML) ratio were present in cases in comparison to controls. Similarly, decreased hematocrit and red blood cell counts were detected in cases when compared with controls. Univariate and multivariate analysis demonstrated a significant association of absolute counts of WBC, neutrophils, monocytes NL and ML ratios with poor treatment outcomes. Altered baseline hematological parameters are clearly associated with poor TB treatment outcomes, showing potential for clinical prediction to enhance the management of at-risk cases.

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SARS-COV-2 OMICRON VARIANT DETECTION WITH BINAXNOW, PANBIO, AND ID NOW RAPID TESTS

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The SARS-CoV-2 pandemic has seen multiple variants of concern arise and spread around the world. Throughout 2022 the omicron variant has diversified and spread, with dozens of subvariants in multiple waves. With each new variant, it is important to evaluate whether currently available diagnostic assays continue to accurately detect the virus. Here, we sequenced SARS-CoV-2 omicron variant lineages from patient nasal swabs collected over 12 months and tested them with Alinity m SARS-CoV-2, BinaxNOW COVID-19 Antigen Self Test, Panbio COVID-19 Ag Rapid Test Device, and ID NOW COVID-19 diagnostic tests. Patient nasal swabs in VTM from confirmed SARS-CoV-2 infections were collected between December 2021-November 2022 from South Carolina, Wisconsin, and New York. Viral load was measured on a quantitative research use only m2000 assay to determine genome equivalents per milliliter (GE/ml) and genomes were sequenced from xGen-enriched metagenomic libraries on Illumina platforms followed by classification with Pangolin and Nextclade tools. Sufficient genome coverage was achieved for classification of n=635 VTM samples. In parallel with viral load testing, VTM samples were tested on BinaxNOW (LOD; Log 4.5 GE/test) and Panbio (LOD; Log 5 GE/test) assays without specimen inactivation. Selected variants with sufficient volume were tested on ID NOW (LOD; Log 2.5 GE/test) and Alinity m (LOD; Log 10 copies/mL) assays after inactivation at 65oC for 30 minutes. Samples collected between January and November of 2022 spanned the full diversity of omicron, including BA.1, BA.2, BA.3, BA.4, and BA.5 variant waves and more than 70 subvariant lineages. All tested SARS-CoV-2 omicron variants were successfully detected by BinaxNOW, Panbio, Alinity m and ID NOW at levels consistent with expected assay limits of detection for freshly collected specimens. All four assays robustly detect circulating omicron variants, confirming that current rapid diagnostic tests are effective at detecting SARS-CoV-2 omicron infections at expected levels of sensitivity compared to previous variants of concern.

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ANALYTICAL PERFORMANCE OF 17 COMMERCIALLY AVAILABLE POINT-OF-CARE TESTS FOR C-REACTIVE PROTEIN TO SUPPORT PATIENT MANAGEMENT AT LOWER LEVELS OF THE HEALTH SYSTEM

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C-reactive protein (CRP) is an acute phase biomarker. A glycoprotein produced by the liver and released into the blood stream within a few hours of tissue injury; occurring, at the start of an infection, or due to other sources of inflammation. CRP levels are typically below 3 mg/L in healthy patients, ranging from 10 to 100 mg/L during a mild infection, reaching as high as 500 mg/L in patients experiencing severe inflammatory responses. Point-of-care (POC) tests for CRP are increasingly used in primary care to assist general practitioners (GPs) in the case management of various health complaints, including acute cough and abdominal pain, and to differentiate between mild and severe respiratory tract infections. To support health care providers in the clinical management of patients, it is crucial that the CRP tests used are accurate, precise and reliable. In this study, we compared the performance of 17 commercially available POC CRP tests. Eight quantitative and nine semi-quantitative tests were evaluated using stored samples (n=660) which had previously been tested for CRP using the Cobas 8000 Modular analyzer (Roche Diagnostics International AG, Rotkreuz, Switzerland), which represented the reference standard for evaluation. CRP values fell within the clinically relevant range (10-100 mg/L) and were grouped into four categories (<10 mg/L, 10-40 mg/L or 10-30 mg/L, 40-80 mg/L or 30-80 mg/L, and > 80mg/L) for majority of the semi-quantitative tests. Of the eight quantitative POC tests evaluated, the QuikRead go and Spinit exhibited a higher level of agreement with the reference method, (slope =0.963 and 0.921, respectively). The semi-quantitative tests showed a poor percentage agreement for the intermediate categories and higher percentage agreement for the lower and upper limit categories. More generally, analytical performance varied

considerably for the semi-quantitative tests. Our findings suggest that the quantitative tests might represent the best choice for a variety of use cases, as they can be used across a broad range of CRP categories.

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EVALUATION OF TUBERCULOSIS TREATMENT OUTCOME AND THEIR PREDICTORS IN PUBLIC AND PRIVATE HEALTH INSTITUTIONS, SOUTHEAST, NIGERIA; AN IMPLICATION FOR POLICY IMPLEMENTATION, CLIENT CENTERED EDUCATION AND TREATMENT FOLLOW-UP

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Although Tuberculosis (Tb) treatment centres exist in Nigeria, information on treatment outcomes and their predictors especially in private hospitals are poorly documented. Identification of predictors of poor treatment outcomes may enable understanding and development of interventions to improve outcome. This study therefore evaluated tuberculosis treatment outcomes and their predictors in public and private hospitals in Abakaliki, Nigeria. A retrospective study of clients managed in the two hospitals over a five year period (Jan 2018 to Dec 2022). All clients who have completed treatment over the study period were enrolled. Relevant information from the case register was retrieved and entered into proforma and study forms. Treatment outcomes were evaluated according to WHO and National Tuberculosis Control Program guidelines. A total of 522 and 732 clients were enrolled in AE-FUTHA and M-4H with mean ages 45.3±7.2 years and 46.1±3.8 years respectively. Majority (84%) were new cases with treatment success rate of 82.6% in both facilities. Treatment outcome showed that relapse, treatment failure and death were 1.5%, 1.0% and 4.6% respectively in AE-FUTHA, 1.4%, 1.2% and 6.4% respectively in M-4H with default averaging 10% in both facilities. Age (15-29), far distance to health facility (>5km) and Tb category (re-treatment) were predictors of poor treatment outcome in AE-FUTHA while area of residence (rural), far distance to health facility (>5km) and Tb category (re-treatment) were predictors of poor treatment outcome in M-4H. Clients were mostly males with twice (1.6%) DRTb than females. Although treatment success rate was close to the 85% WHO bench mark, there were still large pockets of default with similar predictors of poor treatment outcomes in both facilities. Young people on treatment need close monitoring for improved treatment outcome. Defaulter rate can be reduced by patient-centered education and counseling, follow-up reminder system, effective contact tracing, and referral to support group. Decentralization of treatment centres to rural areas would further reduce defaulter rate.

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ISONIAZID MONORESISTANT TUBERCULOSIS (HR-TB) IN ODISHA, INDIA, DURING 2019

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We conducted this study to determine the prevalence of Hr-TB (rifampicin-susceptible, isoniazid-resistant), and mutations in katG and inhA genes in Odisha, India, during 2019. The retrospective data analysis from January-December, 2019, was performed at the National Reference Laboratory (NRL), at ICMR-Regional Medical Research Centre Bhubaneswar, Odisha. NRL Bhubaneswar offers diagnostics services to 10 districts of Odisha under the National Tuberculosis Elimination Programme. The line probe assay (LPA) was performed using GenoType MTBDR plus assay version 2, (Hain Life Sciences, Germany). A total of 3282 Mycobacterium tuberculosis (MTB) positive samples from 8 districts of Odisha, for which LPA results were available, were analyzed. Of the 3282 samples, 90.2% (2961/3282) samples were smear positive, and LPA was performed directly from samples. For 9.8% (321/3282) samples which were smear negative, automated liquid culture using Mycobacteria Growth Indicator Tube (BACTEC MGIT 960 system, United States) was performed, followed by LPA assay from the positive liquid culture samples. Resistance patterns were observed in 60 isolates, of which 10 (16.7%, 10/60) had resistance to both RIF and INH, and 50 (83.3%, 50/60) had Hr-TB (INH resistance only). The prevalence of Hr-TB during the study period was 1.53% (50/3272) with a range of 0 to 3.4% in the 8 districts. Among the 50 Hr-TB strains, katG mutation and inhA mutations were seen in 74% (37/50) and 26% (13/50) strains respectively. In conclusion, compared to other Indian studies, the lower prevalence of Hr-TB in Odisha could be due to the success of Directly Observed Treatment Short-course (DOTS) leading to effective treatment of drug-susceptible TB cases in the state and decreased transmission from primary DR TB cases.

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INFLUENZA, RSV, AND SARS-COV2 SURVEILLANCE IN MACHA, ZAMBIA IN 2022

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Respiratory infections are a major cause of morbidity and mortality worldwide but are relatively understudied in sub-Saharan Africa. In December 2018, surveillance for influenza-like illness (ILI), influenza virus, respiratory syncytial virus (RSV), and later SARS-CoV2, was established at Macha hospital, which is located in a rural part of southern Zambia, and is ongoing. Here, we report on the burden of ILI, influenza A/B virus, RSV, and SARS-CoV-2 among outpatients in 2022 and compare to prior years before (2019) and during the COVID-19 pandemic (2020-2021). All outpatients were screened for ILI and an age-stratified sample of outpatients with ILI were enrolled. A nasopharyngeal swab was collected for testing for influenza A/B virus, RSV, and SARS-CoV-2 using the GeneXpert platform. Testing of samples from 2022 is ongoing and will be completed by July 2023. The annual and monthly pathogen prevalence among outpatients with ILI will be estimated. From January 1 to December 31, 2022, 21,630 outpatients were screened for ILI and 1693 (7.8%) participants had ILI. The proportion with ILI in 2022 was comparable to 2021 (6.9%) and 2020 (9.7%) and lower than 2019 (16.9%) prior to the COVID-19 pandemic. In 2022, 502 outpatients with ILI were enrolled. In January and February 2022, 7 participants to date tested positive for influenza A virus and 12 for SARS-CoV-2. No participants tested positive for influenza B virus or RSV. Through this surveillance platform, we continue to document the burden of respiratory viruses in this underrepresented region and provide important information in this changing context to inform prevention and control efforts.

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IMPORTANCE OF SEROLOGY DIAGNOSTICS FOR CHRONIC PULMONARY ASPERGILLOSIS IN POSSIBLE TUBERCULOSIS PATIENTS IN COTE D'IVOIRE

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Some patients with apparent pulmonary TB don't have TB but chronic pulmonary aspergillosis or CPA. However, the lack of diagnostic capacity for fungal infections and low index of suspicion for fungal respiratory infections among clinicians has been a challenge to CPA diagnosis and management in resource-limited settings. The most sensitive laboratory test for CPA is

Aspergillus IgG (doi: 10.3201/eid2408.171312) The study aimed to provide serological evidence of persistent Aspergillus infection among PTB patients in Cote d'Ivoire.This was a pilot cross-sectional laboratory-based study conducted in the last trimester of 2022. The study population was 39 adult patients with persistent clinical symptoms of pulmonary TB despite anti-TB treatment. Sputum samples were subjected to microscopy and standard fungal culture. Serological detection of Aspergillus fumigatus IgG was done using an enzyme-linked immunosorbent assay (BIO-RAD®). The procedures and results were done and interpreted according to the manufacturer's protocol. The cut-off value is 10 UA/mL for positive results and borderline when concentrations are between 5 and 10 AU/ml.Preliminary data showed that serological evidence of CPA or fungal sensitization was positive in 8 Xpert TB negative patients (20.5%); 5 (12.8%) positive and 3 (7.7%) borderline positive. The most common clinical features of the patients positive for Aspergillus IgG were productive cough and fever; 2 (25%) presented with hemoptysis. The most fungal isolates from positive sputum were Aspergillus fumigatus 4(50%).Our findings suggest that CPA is common in GeneXpert MTB/RIF® negative patients and could be the cause of persistent clinical symptoms in PTB patients in our setting, as described by others in West Africa. We recommend the validation of these findings in a larger cohort study. This will be important to contribute to efforts in the expansion of the TB program to include CPA as an integral component of care.

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SEX DIFFERENCES IN PLASMA CYTOKINE PROFILES BETWEEN TUBERCULOSIS PATIENTS BEFORE AND DURING TREATMENT

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Tuberculosis (TB) remains a global public health threat, with men bearing a higher disease burden than women. Men's higher burden is associated with more significant socio-economic and cultural risk factors. Host biological factors may also account for this difference, yet there is little information on sex differences in host immunity to Mycobacterium tuberculosis (Mtb). This study, therefore, aimed to explore sex-specific differences in cytokines and inflammatory mediators in plasma supernatants before and during TB treatment to understand the sex bias in TB disease. Supernatants from whole blood of HIV-negative female (n=19) and male (n=21) adults with active pulmonary TB were collected at TB diagnosis, two and six months of treatment. Supernatants were then analyzed using Luminex Multiplex assay to quantify seventeen different cytokines and inflammatory mediators of importance in the pathogenesis of Mtb: MMP-1, MMP-2, MMP-8, MMP-9, Myeloperoxidase/MPO, S100A8, S100A9, TNF-alpha, IFN-gamma, IL-1 beta/IL-1F2, IL-8/CXCL8, IL-12/IL-23 p40, IL-10, IL-13, NCAM-1/CD56, CD40 Ligand/TNFSF5, GM-CSF. A similar proportion of men and women had moderate to far advanced TB disease at diagnosis (54.1% vs. 45.9%, p=0.7850), while more men had worse severity six months after treatment (88.2% vs. 11.4%, p<0.0001). Sixteen of the seventeen cytokines and inflammatory mediators in unstimulated samples were elevated at the time of TB diagnosis and significantly declined at two- and six months following treatment. The decline was observed in both men and women. Higher median levels of MMP1 and MMP8 were detected in men compared to women at baseline (MMP1: 3754 vs. 1507, p=0.0012; MMP8: 31623 vs. 16346, p<0.0001) at two months (MMP1: 1404 vs. 680.9, p=0.0028; MMP8:10405 vs. 6830, p=0.0204) and at six months post-treatment (MMP1: 1084 vs. 517.3, p=0.0230; MMP8: 7498 vs. 4910, p=0.1042). MMP1 and MMP8 levels are higher in men before and after treatment. Further understanding of the observed differences in the context of clinical disease outcomes may advance our understanding of sex biases in TB.

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BURDEN OF TUBERCULOSIS AMONG CHILDREN UNDER FIVE HOSPITALIZED IN THE RESPIRATORY UNIT OF THE LARGEST DIARRHEAL DISEASE HOSPITAL IN BANGLADESH: A PROSPECTIVE CROSS-SECTIONAL STUDY

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Detection of tuberculosis (TB) in children remains challenging even in high-risk populations. We sought to determine the burden of TB among hospitalized under-five children at risk of TB. In this prospective cross-sectional study we stratified three high-risk groups of 0 to 59 months children to screen them for TB disease between December 2020 and Dec 2021. Group I had conventional presumptive criteria of TB, group II had severe malnutrition with pneumonia, and group III was severely malnourished children unresponsive to nutritional rehabilitation. Here severe malnutrition included severe wasting z score weight for length less than -3 of the WHO median or nutritional edema or severe underweight z score weight for age less than -4 of the WHO median. Children unresponsive to nutritional rehabilitation were defined as failure to gain weight at least 5 gm/kg/day for 3 successive days during rehabilitation or the presence of edema by day 10 after admission. In addition to symptom-based history and clinical examination, we performed a tuberculin skin test, chest radiography, and Xpert Ultra of induced sputum and stool for diagnosing TB. During the study period, the burden of TB among 272 enrolled children was 22% (59/272). Our study confirmed tuberculosis by microbiological detection in 14.33% (39/272) of children, of whom 25 by Xpert Ultra in sputum, and 24 by Xpert Ultra in stool, and among them, ten children were confirmed in both sputum and stool samples. Twenty (7.35%, 20/272) children had been clinically diagnosed with tuberculosis. Our study affirms that the burden of childhood TB is as high as 14.3% among high-risk populations which underscores the importance of the introduction of routine screening of TB in such children in resource-limited settings.

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HYPOXAEMIA PREVALENCE, MANAGEMENT AND OUTCOME AMONG CHILDREN PRESENTING TO LOW-LEVEL HEALTH FACILITIES IN TANZANIA AND RWANDA

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Hypoxemia is a known predictor of death in acute respiratory infections. In primary care settings in low- and middle-income countries, oxygen is often not accessible. The Integrated Management of Childhood Illness (IMCI) chartbook recommends using pulse oximetry (POX) when available, to identify severely hypoxemic children (oxygen saturation <90%) for classification as severe pneumonia and referral to the hospital. Evidence on the impact of this approach is scarce. ePOCT+ is a digital clinical decision support algorithm that guides primary care clinicians in managing

acutely sick children aged 1 day to 14 years in Rwanda and Tanzania. The algorithm recommends POX for all young infants and older children with IMCI pneumonia. We conducted a post-hoc analysis of ePOCT+ data to assess the prevalence of severe hypoxemia among paediatric outpatients attending participating health facilities. We further analysed the overlap with IMCI danger signs, the referral status, and the 7-day outcome of severely hypoxemic children. Our analysis included 28'294 consultations from 36 health facilities conducted between December 2021 and October 2022. 4% of children were <2 months, 77% 2-59 months, and 19% 5-14 years. 4'003/28'294 (14%) children met the criteria for POX measurement, which was performed in 86% of these cases. 68/4'003 (1.7%) children had severe hypoxemia, including 8 aberrant results. The prevalence was lower in dispensaries than in health centres (1.3% and 2.0%, respectively). 14/68 (21%) children had at least one other IMCI danger sign warranting referral. Of the 54 children requiring referral based on the POX results alone, health workers referred only 14 children, and 6 were actually hospitalized. None of the severely hypoxemic children died. Our results show that prevalence of severe hypoxemia was low, and POX changed the actual management in only 0.05% of all children. Further studies are needed to assess the impact of POX on morbidity and mortality in low-level health facilities in resource-constrained settings. Training of health workers is essential to improve the quality of POX measurement and compliance with referral guidelines.

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FACTORS CONTRIBUTING TO DISPARITIES IN RESPIRATORY CARE AT ADAMA HOSPITAL MEDICAL COLLEGE, ETHIOPIA

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Prior research suggests disparities exist in respiratory care in low- and middle-income countries. We assessed 1) the structure and processes in place for respiratory care, including mechanical ventilation (MV) management, at Adama Hospital Medical College (AHMC) in Ethiopia and 2) reported barriers faced by staff when caring for respiratory patients. We conducted a single-center cross-sectional study of healthcare workers (HCWs) and hospital leadership involved in respiratory care at AHMC between January and February 2023. We administered paper surveys, which included qualitative and quantitative items to assess the current care practices, educational background, the self-reported confidence level in the provision of respiratory care (including MV use), barriers encountered, and perceived impact on patient outcomes. Participants (n=90) mainly included 39 nurses, 35 nurse practitioners, and four physicians. Five are in hospital leadership. Most worked in the intensive care unit (ICU) (n=44) or emergency department (n=17). Among the HCWs who manage patients with MV, 62% provided daily care. However, most (82%) lacked specific training in managing MV, with 23.2% feeling uncomfortable and 24.4% feeling somewhat comfortable in managing MV. The most significant barriers to effective care were lack of training in MV management, difficulty troubleshooting malfunctioning ventilators, and lack of necessary diagnostic tests. The five leaders reported similar barriers to quality respiratory care, including a lack of trained staff in MV management, poor staff-to-patient ratios, limited equipment, diagnostic tests, and ICU beds. Nearly half (40%) of participants felt preventable MV-related complications increased ventilator days, while 60% believed these complications prolonged hospital stays, increasing healthcare costs and mortality. Lack of training and resources for healthcare workers managing respiratory illnesses and MV creates health disparities for patients at AHMC. This study highlights the need for targeted interventions, such as training programs to ensure equitable respiratory care for all patients at AHMC.

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THE EFFECT OF SOAP USE CONDITIONS ON SCHISTOSOME CERCARIAE IN WATER

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To move towards eliminating schistosomiasis as a public health problem, a comprehensive control strategy which incorporates water, sanitation and hygiene (WASH) interventions is needed. Since the successful penetration of schistosome cercariae during water contact (e.g., washing clothes, bathing) is the key component in disease transmission, the use of soap, as part of good hygiene, might play a critical role in schistosomiasis prevention by reducing human exposure to cercariae. According to our recent systematic review, soap has the potential to reduce Schistosoma infection risk and there are two potential protective aspects of soap: (1) soap has direct adverse effects on cercariae (i.e. in terms of mortality, motility, morphology, infectivity, viability); (2) soap on the skin prevents cercariae from penetrating into skin, developing into adult worms and producing eggs in the human body. For the first protective aspect, laboratory experiments have been carried out to quantify the effect of different soaps on cercarial mortality, using two powder and two bar soaps which are commonly used in Tanzania. S. mansoni cercariae were exposed to different concentrations of soap from a few minutes up to one hour. All four soaps were able to kill cercariae, with their effectiveness related to the soap concentration and exposure time. We will also report on other protective mechanisms of soap (e.g. rendering cercariae incapable of finding a host's skin or penetrating skin) which will form the basis of comprehensive guidance for soap use in endemic regions to prevent schistosomiasis.

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COST-EFFICIENT SURVEY DESIGNS FOR MONITORING AND EVALUATION OF SOIL-TRANSMITTED HELMINTHS CONTROL PROGRAMS

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To monitor and evaluate soil-transmitted helminth (STH) control programs, the World Health Organization (WHO) recommends screening stools from 250 children across 5 schools, deploying Kato-Katz thick smear (KK). However, it remains unclear whether these recommendations are sufficient to make adequate decisions about stopping preventive chemotherapy (PC) (prevalence of infection <2%) or declaring elimination of STH as a public health problem (prevalence of moderate-to-heavy intensity (MHI) infections <2%). We developed a simulation framework to determine the effectiveness and cost of survey designs for decision-making in STH control programs, capturing the operational resources to perform surveys, the variation in egg counts across STH species, across schools, between and within individuals, and between repeated smears. Using this framework and a lot quality assurance sampling approach, we determined the most cost-efficient survey designs (number of schools, subjects, stool samples per subject, and smears per stool sample) for decision-making. For all species, employing duplicate KK (sampling 4 to 6 schools and 64 to 70 subjects per school) was the most cost-efficient survey design to assess whether prevalence of any infection intensity was above or under 2%. For prevalence of MHI infections, single KK was the most cost-efficient (sampling 11 to 25 schools and 52 to 84 children per school). KK is valuable for monitoring and evaluation of STH control programs, though we recommend to deploy a duplicate KK on a single stool sample to stop PC, and a single KK to declare the elimination of STH as a public health problem.

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ASSOCIATION OF FEMALE UROGENITAL SCHISTOSOMIASIS WITH HIGH-RISK HUMAN PAPILLOMAVIRUS AMONG WOMEN IN ZAMBIA: BASELINE RESULTS OF A LONGITUDINAL COHORT STUDY (THE ZIPIME WEKA SCHISTA STUDY)

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Female genital schistosomiasis (FGS), caused by Schistosoma haematobium (Sh) egg-deposition in the female genital tract, is highly prevalent in sub-Saharan Africa (SSA). Women in SSA also face the highest cervical cancer incidence and mortality rates globally, caused by high-risk (HR-) human papillomavirus (HPV) infection. FGS and HR-HPV infection share socio-demographical and behavioural risk factors related to disease exposure. Cross-sectional studies previously found an increased risk of HR-HPV infection in women co-infected with Sh compared to those without. Yet, the interplay of these infections is unknown. We explored the association between Sh and HR-HPV co-infection in two communities in Zambia from an ongoing longitudinal community-based study, the Zipime Weka Schista! Study. Women were recruited by community health workers at home. A urine sample, two cervicovaginal self-swabs, HIV and Trichomonas self-tests were obtained and a questionnaire completed. Clinic follow up was done by a midwife who performed point-of-care colposcopy and obtained genital samples. Urine microscopy was used for Sh-egg detection and cervicovaginal self-swabs were tested by GeneXpert and PCR for HR-HPV and Sh DNA detection respectively. A total of 2,511 women aged 15-50 years old have been recruited to date (median age 28 years, [IQR] 22-36). Preliminary results from 2,488 urine samples and 1,547 cervicovaginal self-swabs revealed a prevalence of egg-patent Sh and HR-HPV infection of 5.3% (131/2,488) and 27.4% (424/1,1547), respectively. Multivariable logistic regression adjusted for age and Trichomoniasis status, revealed women with egg-patent Sh were significantly more likely to be HR-HPV positive compared to those without (OR=1.9, p=0.03). Women aged 15-25 had 1.6 higher odds of having HR-HPV compared to women aged 26+ (OR=1.6, p<0.01). Further analysis exploring the association of HR-HPV infection and cervical precancer with FGS status by PCR and colposcopy is ongoing. These findings will inform possible points for integration of FGS and cervical cancer screening strategies.

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INVESTIGATING THE GENETIC DIVERSITY OF THE SCHISTOSOMA MANSONI TRANSIENT RECEPTOR POTENTIAL MELASTATIN (SMTRPMPZQ) CHANNEL IN RESPONSE TO PRAZIQUANTEL TREATMENT IN NATURAL UGANDAN S. MANSONI POPULATIONS

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Schistosomiasis is a neglected tropical disease (NTD) caused by parasitic trematodes (Schistosoma genus), with the highest burden in sub-Saharan Africa. The disease is treated with praziquantel (PZQ) which is typically delivered annually through large scale mass drug administration programs in endemic countries. These programs have been successful in reducing the prevalence and intensity of infection but their impact on the evolution of drug resistance is unknown. As control efforts to eliminate schistosomiasis intensify to reach the WHO NTD roadmap targets, there is a need to detect and track PZQ resistant Schistosoma isolates. The transient receptor potential melastatin praziquantel channel (SmTRPMPZQ) is now recognised to be involved in the mode of action of PZQ with mutations in this target resulting in drug resistance. However, this was conducted in a single Brazilian S. mansoni laboratory-selected resistant strain; it is unclear if this mechanism will be conserved in African S. mansoni populations, in which little is known about the extent of genetic variation of SmTRPMPZQ in natural Schistosoma populations. This project aims to analyse natural Ugandan S. mansoni populations (pre- and post-PZQ treatment) to identify polymorphisms associated with drug resistance. We sequenced the whole genomes of single S. mansoni miracidia from a clinical trial in Lake Albert, Uganda. We developed a high throughput amplicon deep sequencing method to screen genomic regions encoding the PZQ binding site to identify PZQ resistance polymorphisms. Overall, our preliminary baseline (pre-treatment) data suggests that there is limited genetic diversity within the PZQ binding site in SmTRPMPZQ. Our data will provide valuable insights into the genetic variation SmTRPMPZQ in field collected schistosome populations and suggest how this may affect treatment efficacy. Monitoring for changes in the frequency of PZQ resistance mutations will reveal how natural S. mansoni populations are evolving in response to PZQ treatment.

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LIVESTOCK CATTLE AS PREDICTOR OF TRANSMISSION OF SCHISTOSOMIASIS IN NIGERIA

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Schistosomiasis, a neglected tropical disease, remains a parasitic disease of public health concern, especially in sub-Saharan African countries where reported cases are predominant. The focus of this study is to examine the relationship between prevalence of schistosomiasis and livestock cattle index in Nigeria. The study's data came from three sources: the demographic and health survey, the malaria indicators survey, and the expanded special project for the eradication of neglected tropical diseases. Analysis of variance, correlation, and logistic regression were used to investigate the mean difference in schistosomiasis prevalence across geopolitical zones, the association between schistosomiasis prevalence and livestock cattle, and the risk of schistosomiasis in each geopolitical zone when the cattle index was known, respectively. According to disaggregated and combined data for 2018 and 2021, the prevalence of schistosomiasis and livestock cattle index are highest in the country's North Central, North East, and North West geopolitical zones (P <0.05). The association between the prevalence of schistosomiasis and livestock cattle was found to be positive and statistically significant (r =0.029, P<0.05). The likelihood of schistosomiasis decreases in the North-Central, North-East, and South-South as livestock increases, while the chance increases in the North West, South East, and South West as livestock increases. The estimated risk difference of the disease from one geopolitical zone to the next is marginal; however, it is highest in the South East and North West zones and least in the South West. The possibility that livestock cattle are a predictor of transmission of schistosomiasis cannot be disparaged; hence, policies that will curtail this mode of transmission should be developed and implemented in the risk regions identified in this study.

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HUMAN SCHISTOSOMIASIS RISK AND SNAIL ABUNDANCE HAVE A UNIMODAL RELATIONSHIP IN THE NATURAL ENVIRONMENT

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Non-linear relationships in host-parasite interactions can complicate the prediction and control of human infectious diseases, including

schistosomiasis. Schistosomiasis affects 200 million people in 52 countries and is caused by parasites released by freshwater snails. A dynamic energy budget (DEB) model predicts that parasite production by snails should be low both when snail densities are low and also, paradoxically, when they are high (as there is less energy per capita for parasite production). To test whether such a unimodal relationship between parasite and snail densities occurs in nature, we estimated snail densities, environmental food availability for snails, and per capita parasite production every other week for a year at four water bodies in West Africa. Consistent with DEB theory, we show that unimodal patterns exist between snail host densities and per-capita parasite production for both Schistosoma haematobium and S. mansoni. The interaction between snail densities and food resources was significant and non-linear for total parasite production (human risk), likely because at high snail densities there is greater competition for food resources. These patterns may explain why field snail densities are often not associated positively with human schistosomiasis prevalence and suggest that the greatest risk to humans may not coincide with peak snail densities at sites. Further, epidemiologic models for schistosomiasis based on non-linear relationships between snails and parasites may improve predictions of risk to humans.

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RISK FACTORS AND PREVALENCE OF SCHISTOSOMIASIS AND INTESTINAL PARASITES INFECTIONS IN VILLAGES IMPACTED BY AGRICULTURAL ACTIVITIES IN THE NORTH AND SOUTH OF GABON

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The installation of the Olam group in the North and South of Gabon has encouraged a migratory flow of populations from urban areas to rural areas and the creation of favorable conditions for the transmission of intestinal parasites and schistosomiasis. The aim of this study was to assess the prevalence and risk factors of schistosomiasis and intestinal parasitosis infections (IPIs) in Olam villages and surrounding villages. A cross-sectional study was conducted in the North (in Bitam and Minvoul) and in the South (in Mouila) of Gabon among school-age children and adults > 60 years old between August 2019 and January 2020. Each participant presenting eligibility criteria for inclusion and having given his consent by his guardian was included. A total of 419 participants were approached and 326 gave their consent to participate in the study. The median age of the participants was 11 [10-12] years old. Five cases of schistosomiasis were found mainly in Olam villages of Mouila. The IPIs were found in 65.7% (175/266) of cases. Among them, protozoa and nematodes were diagnosed in 36.4% (99/226) and 42.1% (122/226) participants respectively. The proportion of IPIs was similar between the villages of Olam (69.2%; 63/91) and the surrounding villages (66.2%; 116/175) (p = 0.9). On the other hand, it was significantly higher in Bitam (82.0%; 114/139) compared to Minvoul (52.8%; 28/53) and Mouila (44.5%; 33/74) (p=0 ,03). Living in Mouila (p=0.01), being between 11-16 years old (p=0.04), living in a Earthen house (p=0.02), the use of latrines (p=0.01) and medicinal plants (p=0.01) was risk factors associated with IPIs. Median parasite density of participants infected with T. trichiura was more higher in Olam villages compared in surrounding villages (p<0.001). This work revealed a predominance of schistosomiasis in Olam village of Mouila. IPIs were more frequent in Bitam and the intensity of the transmission of ascariasis and higher trichocephalosis in Mouila and Minvoul would make it possible to orient the interventions of the program.

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COMBINING GENOMICS DATA WITH SOCIAL AND ENVIRONMENTAL CONNECTIVITY MEASURES TO IDENTIFY PATHWAYS OF SCHISTOSOMA JAPONICUM IMPORT IN RURAL CHINA

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Persistent transmission hotspots remain for several high burden parasitic diseases despite control efforts. One hypothesis is that infectious parasites are moving along social and environmental gradients, by human or animal movement, or along hydrological channels. In this study, we investigate how import has contributed to infections in a region where schistosomiasis transmission has persisted in spite of aggressive control programs. We also evaluate whether import is linked to social and hydrological connectivity pathways. This study leverages data collected in 2007 from 53 rural farming villages located in Sichuan, China with recent schistosomiasis reemergence. Within each of our sampled villages, all household members over the age of five and all bovines were invited to participate in schistosomiasis infection surveys. Participant demographics, household GPS coordinates, and household- and village-level mobility were assessed via head of household and village leader surveys. Survey data was paired with open-source environmental data to generate metrics that describe each village's potential to attract migrant parasites along social and hydrological gradients, taking into account road networks, drainage patterns and attractive resources within villages (e.g., schools, commerce). Individual Schistosoma japonicum samples, collected from infected human and bovine hosts, were whole genome sequenced to estimate the genetic relatedness and historical migration patterns among villages. Multivariable regression models will be used to model the association between the inferred connectivity between villages using genetic data and our social and hydrological connectivity metrics. As a result of this analysis, we expect to obtain insight into the geographic scale, pathways of import, and overall importance of parasite migration events to residual infection hotspots. Additionally, our study allows us to evaluate the utility of pairing social, environmental and genomics data to identify likely sinks and sources of persistent infections for use in targeted end-stage parasite elimination programs.

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PROTEOMICS OF ADULT PARAGONIMUS KELLICOTTI EXTRACELLULAR VESICLES RELEASED IN VITRO OR PRESENT IN LUNG CYSTS

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Paragonimiasis is an important zoonotic, food-borne trematode infection that affects some 21 million people (mostly in Asia). Trematode parasites release extracellular vesicles (EV) in vivo that contain parasite proteins and RNA cargo that may interact with other parasites and with the host. Here we detail the composition of Paragonimus kellicotti EVs purified from both adult worm excretion/secretion products in vitro (EV ESP) and from lung cyst fluid of infected gerbils (EV CFP). Electron microscopy showed that most of the EVs were 30-50 nm in diameter, but small (10-20 nm) and large (90-120 nm) subpopulations of vesicles were also present. We identified 548 P. kellicotti-derived proteins in EV ESP by mass spectrometry. The three most highly represented GO terms in the molecular function category were ATP hydrolysis activity, ATP-dependent activity and ribonucleoside triphosphate phosphatase activity. We detected 8 proteins in the EV CFP of which 7 were also present in EV ESP. A cysteine protease (MK050848,

CP-6, previously reported as useful for serology) was the most abundant protein found in EV CFP in all technical and biological replicates. Immunolocalization of CP-6 showed no staining in lung tissue of uninfected gerbils. However, strong labeling for CP-6 was observed in the tegument of adult P. kellicotti and in the diseased lung cyst tissue that contained worm eggs. These results suggest that CP-6 is released within EVs by adult worms in vivo. This study has provided new insights regarding interactions between Paragonimus worms and their mammalian hosts.

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EFFECT OF INTENSIVE TREATMENT FOR SCHISTOSOMIASIS ON VACCINE SPECIFIC RESPONSES AMONG UGANDAN ISLAND ADOLESCENTS: THE POPVAC A TRIAL

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Helminths have long been proposed as modulators of vaccine-specific responses. We hypothesised that Schistosoma mansoni (Sm) infection suppresses responses to unrelated vaccines, and that this effect can be reversed, at least in part, by intensive praziquantel treatment intervention. We conducted a randomised-controlled trial of intensive versus standard intervention against Sm among school children in Koome islands, Uganda. Participants in the intensive arm received three doses of praziquantel (40mg/kg) each two weeks apart (the last of these 2-4 weeks before the first immunisation, BCG, at week 0), followed by quarterly during follow up. Participants in the standard arm were not treated until the week 8 primary endpoint. Participants received five vaccines: BCG [week 0], Yellow Fever, oral typhoid, HPV prime [week 4], HPV booster, tetanus/diphtheria [week 28]. Data were collected at baseline and at each follow up visit; primary outcome was vaccine responses at week 8, and for tetanus/diphtheria, at week 52. Sm infection status was determined retrospectively through plasma measurement of circulating anodic antigen (CAA). We enrolled 478 participants, 239 in each arm. Among the Sm positive at baseline, preliminary data (intention to treat) indicates that intensive Sm treatment significantly reduced infection intensity by week 0 (median [IQR] CAA concentration, pg/ml, 29[7;226] vs 1527[317;9105] in the standard arm), and significantly improved the week 8 BCG-specific IFN-γ response as assessed by ELISpot: geometric mean ratio SFU/106 PBMC 1.30 (95%CI 1.03-1.64). There was no effect on the yellow fever-, oral typhoid- and tetanus/diphtheria-specific antibody response. Data analysis on HPV-specific IgG responses is underway. Our preliminary data support the hypothesis that current helminth infection reduces the BCG-specific response, and may have different impact on cellular versus humoral vaccine-specific responses. Our data contribute to the debate on whether effective control of Sm infection improves vaccine responses (and by extension efficacy) in endemic settings.

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TRANSFORMING GROWTH BETA LEVELS IN INDIVIDUALS WITH SCHISTOSOMIASIS IN FEDERAL CAPITAL TERRITORY, NIGERIA

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Schistosomiasis is a public health concern, globally and specifically in Nigeria that has one of the highest burden. Morbidities occur with genito-urinary and gastrointestinal presentations such as haematuria, chronic anaemia, stunted growth, abdominal distention affecting multiple organs, female genital schistosomiasis etc and could lead to several complications. Transforming growth factor-β (TGF-β) signaling has been found to play vital role in pathogenesis of Schistosomiasis-associated complications. This study evaluated the profile of TGF-β in persons with Schistosomiasis. A descriptive, cross-sectional study design was conducted on eighty (80) individuals of different age groups with symptoms suggestive of schistosomaisis. Stool, urine and venous blood samples were collected from the individuals, screened for Schistosomiasis and TGF-β in plasma samples were quantified using Enzyme linked immune sorbent assay (ELISA).The prevalence of schistosomiasis in the study area was 58.8%, 46 (57.5%) females and 34 (42.5%) males participated in the study, their age ranged from 5-15 years and with mean age of 16.5±10.2 years. The geometric mean of TGF-β was 2194.1 (range of 49.0 - 48,780.3). The geometric mean TGF-β of female participants, 2220.6 was higher than that of male participants, 2007.1, though not significant (P=0.677). There was no association between TGF-β and age of the participants (P=0.080) although the geometric mean TGF-β decreased as age of participants increased from <10 years, 2875.7 to 16-20 years, 925.7 but increased to 2298.6 in those above 20 years. This study has demonstrated increased serum levels of TGF-β in patients with Schistosomiasis compared with uninfected patients. There was a negative correlation (γ = -0.097) between TGF-β level and density of eggs from the samples collected but not significant (P-value = 0.448). The level of TGF-β in individuals infected with schistosomes did not differ with the infecting schistosome specie. Increased serum levels of TGF-β in patients with Schistosomiasis suggests that this growth factor may contribute to pathophysiologic remodeling in the disease.

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MEASURING WATER QUANTITY USED FOR PERSONAL AND DOMESTIC HYGIENE IN A LOW-INCOME URBAN COMMUNITY IN BANGLADESH

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There is a paucity of recent research on direct water quantity measurement for personal and domestic hygiene. We aimed to measure the water quantity used for personal and domestic hygiene and to explore the reasons and determinants for variation of water usage. We conducted this study from September 2014 to June 2016 in a low-income urban community in Dhaka. In 12 households, the team conducted a day-long bimonthly ethnographic observation for one year to measure the volume of water used per activity per person. They conducted 28 in-depth interviews to explore the reasons for changes of water usage. Participants used a median of 75 L (61–100) of water per capita per day (LCPD) and of this 75 LCPD they used a median of 39 LCPD (26–58) for personal hygiene. Women used less water than men. Individual and social norms, beliefs, and weather determinants determined personal hygiene. Water availability determined domestic hygiene (e.g., washing dishes, toilets and bathrooms). This study helps to elucidate a range of determinants of water usage of the participants from the participants' perspective. The quantity of water used for domestic and personal hygiene and its relationship to fecal-oral transmitted disease can be explored in future research.

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SUPPORTIVE SUPERVISION IS ASSOCIATED WITH AVAILABILITY OF WORLD HEALTH ORGANIZATION INFECTION PREVENTION AND CONTROL CORE COMPONENTS IN HEALTH FACILITIES IN SOUTHWESTERN UGANDA

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Core components for infection prevention and control (IPC) support recommended IPC practices, which can reduce nosocomial infections and antimicrobial resistance. Quality improvement, including supportive supervision, promotes adherence to IPC, which can be challenging in resource-limited settings. We assessed the ability of supportive supervision to improve the availability of the World Health Organization (WHO) core components for IPC at health facilities in southwestern Uganda. We employed a before and after study design that included a baseline assessment of the availability of the WHO IPC core components followed by supportive supervision activities for targeted areas for improvement. We conducted a second assessment and determined differences in the availability of the core components between assessments. A score less than 70% was inadequate, a score between 70 and 85% was intermediate, and a score greater than 85% was adequate. Re-assessment occurred at 23 (21%) of 111 health facilities. The number of facilities that were <70% for each core component stayed the same or decreased at each facility type, but there was an increase from five to six health center III facilities scoring <70% for personal protective equipment (PPE). Conversely, the number of facilities that scored >85% for each core component stayed the same or was increased at each facility type, but there was a decrease from 4 to 2 health center III facilities scoring >85% for instrument processing. There was an increase in the median (interquartile range [IQR]) overall score from baseline to follow-up assessment for all facilities (65 [54-72] vs 75 [68-73], p=0.0001). Supportive supervision activities were associated with improved availability of the core components of IPC at health facilities in southwestern Uganda. PPE availability remained inadequate across visits and should be prioritized in health care facilities in the study area.

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A SEMI-AUTOMATED SCOPING REVIEW OF MICROPLASTIC CONTAMINATION IN FOOD AND WATER BANGLADESH PERSPECTIVE

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Microplastic are fragments of plastic debris that are less than five millimetres usually generated from the breakdown of consumer products and industrial waste. Everyday millions of metric tons of industrial waste are disposed in the environment. The health impact of microplastic in food and water is yet to be fully understood. Plastic trash accounts for 60-80% of all marine litter and is one of the fastest-growing segments of urban garbage. The microplastic pollution is higher in LMICs. Bangladesh is recognized as a nation with a plastic pollution crisis. The objective was to explore the existing knowledge by analysing scientific abstracts relating to the research on microplastic pollution and its effect on human health. We conducted a literature search in the indexed databases using the keywords “Microplastic AND (food OR water) AND Bangladesh”. We then processed the text of abstracts and converted these into a data where a row contained an abstract and each column a unique word across all abstracts. The frequency of words is recorded. Fitted a Latent Dirichlet Allocation (LDA) model to find common sub-themes across the abstracts. We found 121 abstracts based on the search. The first abstract was dated back to 2014 and it could be an indicator that research in microplastic is emerging recently. After initial processing we found 1262 unique words across all abstracts. Using LDA we found ten sub-themes. During the COVID-19 pandemic the amount of plastic pollution increased and it can be seen that one of the themes is concentrated, with the keywords, mask, pandemic, PPE etc. The marine and urban settings are the most affected areas. Fish and freshwater pollution is a key research domain. None of the themes showed any evidence of research relating to interventions in reducing plastic pollution or the assessment of the health impact of microplastics in food and water. The findings shows that there is a lack of research on the effect of the presence of microplastics in food and water on human health in Bangladesh. A rigorous research study is required to identify the level of knowledge, attitude and practices on the use of plastic products to develop interventions.

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TOILET FUNCTIONALITY AND CLEANLINESS STATUS IN HEALTHCARE FACILITIES IN DHAKA, BANGLADESH

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Lack of access to functional and clean toilets is a major public health concern in LMICs, including healthcare facilities (HCF), contributing to the spread of infectious diseases. Most recent sanitation assessments were conducted in sub-district level hospitals rather than larger hospitals in major cities. We conducted research in 10 government and 2 private hospitals to understand the availability, functionality, cleanliness, and toilet-user ratios in Dhaka. From Aug-Dec 2022, we conducted infrastructure assessments and collected information on toilet numbers and users from hospital daily registers. Given the heterogeneity of user numbers and structural complexity of different departments (inpatients vs. outpatient), we observed all toilets in selected hospitals. The number of toilet users was categorized into patients and their caregivers and hospital staff (doctor/nurse/cleaner). Cleanliness of the toilets was assessed using two parameters (clean/unclean) and associated criteria, and functionality was defined according to the WHO/UNICEF Joint Monitoring Programme definition for HCF. Amongst 2611 toilets, 2243 (86%) were directly observed, and more than 85% of toilets were functional. In government hospitals, 15% of toilets were not functional, and in private hospitals, 6% were nonfunctional. The main reasons for non-functionality were broken doors or locks (14%). Additionally, 84% (2200) of toilets were found clean in all hospitals. However, 16% of toilets were not clean in government hospitals, and 6% were not in private hospitals. An unacceptably high toilet:user ratio was observed with an average ratio of 1:51, whereas the national standard notes 1:6. The toilet:user ratio was higher in government hospitals (1:52) than in private hospitals (1:21), and the highest ratio was 1:395 for patients and 1:30 for staff. Overall, the study suggests that interventions are required to ensure adequate toilet facilities, maintenance, and cleanliness in hospital settings in Dhaka, which will require relevant leadership and resources to be allocated, including a significant augmentation of the number of toilets relative to users.

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ASSESSING FAECAL CONTAMINATION IN SOILS OF INFORMAL SETTLEMENTS- A COMPARATIVE STUDY OF TRADITIONAL SOIL TESTING AND INNOVATIVE BOOTSOCK TECHNIQUE

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Diarrhoeal transmission is commonly attributed to water, food, and sanitation (WaSH). However, recent research suggests that WaSH interventions must holistically consider the different pathways of the F-diagram. Soil transmission of diarrhoea, including through ingestion,

has been largely understudied despite evidence of high levels of microbes in soil environments. Gold standard soil sampling methods are unable to collect spatially representative data across community scales; requiring instead, the implementation of composite methods to increase our knowledge of direct soil transmission. Bootsock sampling, previously used for assessing diarrhoeal pathogens in poultry houses, was laboratory- and field-tested to collect surface soils within informal settlements for measuring E. coli concentrations. In the laboratory, a 5x1 m soil box was spiked with E. coli across the length of the walkway. E. coli was detected in 87% (n=24) of bootsock samples and 55% (n=20) of grab samples from the same uniformly inoculated transect. Paired bootsock and grab samples were also collected from 11 informal settlements in Suva, Fiji. In the field, 73% (n=33) of bootsock and 75% (n=79) of grab samples had detectable concentrations of E. coli. Bootsock estimations of E. coli levels were consistently higher than paired grabs. These findings demonstrated that bootsock results were comparable to those of the gold standard methods in measuring bacteria. Furthermore, a post-hoc power analysis also showed that a lower number of bootsock samples were needed to measure the same mean E. coli transect loads as grab samples. In this study, we demonstrated that alternative composite sampling methods, such as bootsock sampling, was able to consistently measure higher and more spatially representative levels of E. coli across the same transect. The successful optimisation and application of this method will increase the accuracy of faecal pollution and exposure assessment in contaminated settings. This would, in turn, add more information to our collective knowledge of soil transmission and risk, and thus, result in the development of better mitigation strategies.

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PREVALENCE OF PATHOGENIC MDR ESCHERICHIA COLI IN FAECAL SLUDGE TREATMENT PLANTS AND ADJACENT HOUSEHOLD DRINKING WATER OF ROHINGYA CAMPS, BANGLADESH

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Extended-spectrum β-lactamase (ESBL) producing pathogenic E. coli are responsible for high rates of community acquired infections and are linked to high mortality rates, increased healthcare costs and longer hospital stays. The contamination of drinking water is one of the primary routes of ESBL E. coli transmission in the community. This study aimed to investigate the prevalence, characterization of major ESBL and pathogenic genes, antibiotic susceptibility patterns and biofilm formation capability of ESBL producing E. coli in treated and untreated faecal sludge and adjacent household drinking water samples of Rohingya camps, Cox's Bazar, Bangladesh. A total of 127 ESBL E. coli isolates were obtained of which 87 from faecal sludge and 40 from adjacent household drinking water samples. In regards to ESBL gene presence, blaCTX-M was the most prevalent, being present in 44.5% of the isolates, followed by blaTEM and blaSHV in 18.6% and 2.3% isolates respectively. The genes blaTEM and blaSHV were detected only among faecal sludge isolates, which also harbored a higher percentage of blaCTX-M. With respect to pathogenicity, a total of 9.3% and 9.9% were found to be ETEC and EAEC, which are pathotypes of diarrheagenic E. coli. Both ETEC and EAEC were found among fecal sludge samples, whereas only EAEC was present in only drinking water. In the case of extra-intestinal pathogenic genes, a total of 3.2% of the isolates were found to be ExPEC. In regards to antibiotic susceptibility patterns, 99.2% of the isolates were found to be multi-drug resistant. Strong biofilm formation was observed at 25°C and 37°C for 33.9% and 3.9% of isolates respectively. Contaminated household drinking water can be an important mode of transmission of ESBL E. coli, and the prevalence of ESBL E. coli in faecal sludge might be a point of origin for spreading in the community. The continued exposure of the Rohingya individuals to these organisms may explain the high rates of diarrheagenic diseases within the region.

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ASSESSING THE IMPLEMENTATION OF WASH INTERVENTIONS IN A COASTAL DISTRICT WITH HIGH DIARRHOEA BURDEN, GHANA, 2022

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WASH interventions have significantly reduced diarrhoeal diseases globally. However, marginal declines have been recorded in some coastal settlements in Ghana where WASH interventions Were initiated over 20 years ago. As communities vulnerable to climate change consequences, there was the need to identify implementation challenges to build resilience and improve WASH. We assessed the WASH implementation gaps in Anloga, a coastal district in Ghana.We conducted a process evaluation of WASH interventions implementations (provision of water, and sanitary facilities) in the district. We used the USCDC 4-level socio-ecological model assessing the problem from intrapersonal, interpersonal, community, and societal levels. We conducted 30 household interviews, four community focus group discussions, 10 in-depth interviews with community leaders and four key informant interviews with district staff. We observed newest structures for accessibility. We transcribed and identified gaps using thematic analysis.Most individuals (18/30) had no knowledge of the history of WASH structures around them and had not received education on its use. Community members reported being only engaged for labour during construction. Both community leaders and members confirmed receiving a one-time education at commissioning of interventions. Most community leaders(7/10) said implementation engagements were done with selected leaders. Leaders(8/10) reported community's main role in implementation as labour provision. All district staff (4/4) mentioned that community leaders were the main people engaged throughout the process and implementation of interventions were subject to availability of district funds. We found that inadequate education on intervention, poor information flow, and lack of extensive engagement led to poor utilisation. We recommend the district adapts an all-inclusive implementation approach to ensure community ownership and appropriate use. Also, periodic supervision of interventions by the district with short educational talks would remind community members of relevance of interventions available to them.

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DETECTION OF SARS-COV-2 AND ENTERIC PATHOGENS IN MEGACITY DHAKA WASTEWATER: FINDINGS FROM AN ENVIRONMENTAL SURVEILLANCE PLATFORM

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Environmental surveillance has proved to be a valuable tool to monitor trends of infections with SARS-CoV-2 and enteric pathogens in the population. Dhaka city, the capital of Bangladesh, faces considerable challenges with unimproved sanitation and poor fecal sludge management. In this city, 80% of areas are not connected to centralized sewers, and household toilets are directly connected with open drains. We conducted wastewater surveillance from October 2022 to February 2023 on open drains/canals of seven zones of Dhaka North (non-sewer area) and four sewage pumping stations of Dhaka South to monitor temporal and spatial trends in vaccine-preventable enteric (Group A Rotavirus, Salmonella typhi, and Vibrio cholerae) and respiratory (SARS-CoV2) infections. 180 wastewater samples (119 from open drains/canals and 61 from pumping stations) were collected and quantified through multiplex qPCR. High proportions of wastewater samples tested positive for Rotavirus (96%), V. cholerae (56%), SARS-CoV-2 (54%), and S.typhi (43%). A higher proportion of samples from open drains/canals were positive for S.typhi, V.cholerae, and SARS-CoV-2 (58%, 61%, and 69% correspondingly) compared to samples from pumping stations (13%, 41%, and 31% correspondingly). The median log10 concentration of Rotavirus gene copies/Liter was 8.7 (range=4.7-10.4), V. cholarae was 6.2 (range=4.5-7.8), SARS-CoV-2 was 4.8 (range=3.9-6.5), and S.typhi was 5.8 (range=4.3-7.6). V.cholerae (50% to 65%) showed an increasing temporal trend in positivity from October 2022 to January 2023, while the detection of the other three pathogens had no obvious temporal patterns. Environmental surveillance is a useful tool for monitoring temporal and spatial trends of existing and emerging infectious diseases and supports evidence-based public health measures. Historical evidence for SARS-CoV-2 suggests a strong correlation between clinical cases and the presence of pathogens in wastewater. Findings also suggest that wastewater surveillance could play a crucial role where clinical case detection and reporting are not optimal due to scarce resources.

6402

FINDINGS OF ENVIRONMENTAL SURVEILLANCE FOR SARS-COV-2 AND ENTERIC PATHOGENS TRIGGER FUTURE PATH: LEARNING FROM A MEGACITY AND HUMANITARIAN SETTINGS IN BANGLADESH

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Environmental surveillance data have been recognized as a valuable supplement to epidemiological case data, especially in understanding the burden associated with enteric diseases. In low-income countries like Bangladesh, environmental surveillance can detect and quantify selected pathogens from wastewater and can be a useful and low-cost public health tool when limited epidemiological data are available. icddr,b conducted environmental surveillance in Dhaka city and Cox's Bazar (refugee camps and the municipality) with technical support from the Institute of Epidemiology Disease Control and Research. Wastewater samples were collected from open drains and sewage pumping stations that captured nearly one million people across 32 square kilometers. Transect walks, scoping visits, and GIS tools were used in 28 locations of Dhaka city, and finally, 11 sites were selected. In contrast, transect walks, stakeholder meetings, STRAVA mapping were used in 18 locations of Cox's Bazar, and 12 were finalized for wastewater sampling. Laboratory method optimization was completed with the development of the standard operating procedures for the detection of the Rotavirus, Salmonella typhi, Vibrio cholera, and SARS CoV-2 genetic markers by multiplex qPCR. Weekly samples across 23 sampling sides over 17 weeks provided insights on the presence/absence of the pathogens, as well as total viral concentration, enabling analysis of spatiotemporal trends. Multisectoral collaboration between the research team, government, and multinational stakeholders was established from the project onset. It will enable data-sharing health authorities to empower a more targeted and rapid public health response during outbreaks and infectious disease spikes. Environmental surveillance data will be compared to clinical data and analyzed in the context of climate variability to validate findings, explore changing patterns over time, and identify intervention points.

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HOUSEHOLD COPING STRATEGIES DUE TO WATER INTERMITTENCY: A MIXED-METHODS STUDY IN NORTHWESTERN ECUADOR

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While global access to improved water systems has increased, access to reliable piped water remains a concern. Intermittent water supply (IWS) systems are characterized by services being unavailable for hours or days at a time. How households cope with these two types of IWS are not well known. We collected data on household water supply and coping strategies (2019 – 2021) in response to IWS among three communities of different sizes and diverse access in northwestern Ecuador. We classified piped water service frequency (days/week) as low (<3), medium (3-5) and high (>5), and water service duration (hours/day) as low (<4), medium (4-8) and high (>8). We assessed the association between frequency and duration of piped water and household coping strategies using logistic models and complemented this analysis with in-depth qualitative interviews of residents. Intermittency patterns differed by community. Most households in the town of Borbon received a medium frequency and duration of water, the intermediate town of Maldonado received a high frequency but low duration of water, while the village of Timbire received a high frequency and high duration of water. Accordingly, communities responded differently to water intermittency. Compared to Timbire, households in Borbon and Maldonado were more likely to purchase bottled water, treat their domestic water, and store water. Compared with Borbon, households in Maldonado were more likely to purchase bottled water and treat their domestic water. Regardless of the community, households that received ≥5 days of water service had lower odds of purchasing bottled water for drinking and treating domestic water, but higher odds of using multiple drinking water sources. Households that received ≥8 hours of water service had lower odds of treating their domestic water source. Although being discontent with the water service was a recurrent theme during interviews, community members preferred the predictability of a high frequency, low duration water service. Household coping strategies depended on water supply characteristics, but all coping strategies incurred substantial financial and labor costs.

6404

DENGUE SEROEPIDEMIOLOGY RELATED TO DEFORESTATION RATES IN RURAL VILLAGES OF THE PERUVIAN AMAZON COMMUNITIES

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Dengue fever, the most common arboviral disease in humans, has increased globally due to climate change and human activities. In Peru, more than half of its population is at risk of dengue infection, and its aggressive and precary urban expansion in the Amazon region could exacerbate dengue incidence. In this study we explore the relationship between deforestation, as a proxy of urban expansion, and dengue seropositivity in Peruvian Amazon communities. We conducted a cross-sectional analytical study in 19 communities of Indiana and Belen districts in Loreto, Peru. Socioeconomic and human behavior questionnaires were applied to individuals in each randomly selected household, which was geo-referenced. Dried blood spots were collected for serological analysis. Deforested area data was extracted in a buffer of 5 km of each community using the Hansen Global Forest Change collection from 2000 to 2021. Seropositivity was stratified by age groups. Finally, a population weighted linear regression model adjusted by age groups was used to explore the relationship between deforestation rates and seropositivity in each community. A total of 1114 individuals were analyzed across both districts. Our findings showed a total seropositivity of 59.1% (range from 41.4% to 85.7%). The mean annual forest lost area rate (km2/year) was 0.46 (SD= 0.15). Seropositivity in age groups between 0 to 5, 6 to 10, 11 to 15, 16 to 20, and 21 or more years old were 26.5%, 37.4%, 49.4%, 56.4%, and 78.0%, respectively. The weighted regression model reveals that the annual forest lost rate (km2/year) is positively associated (β= 0.33; 95% CI= 0.16 - 0.51) with an increase in seropositivity at community level after adjusting for age trends. The results of this study highlights that, even in rural communities, higher dengue seropositivity levels were found. Finally, this study provides evidence that higher rates of annual deforestation rates, controlled by age (time of exposure), were correlated with an increase in dengue seropositivity at community level, highlighting the impact of rural communities' growth speed on dengue seropositivity.

6405

SPATIOTEMPORAL MODELLING TO INVESTIGATE THE IMPACT OF CLIMATE AND EXTREME WEATHER EVENTS ON ARBOVIRUS TRANSMISSION IN BRAZIL

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Brazil experiences large-scale annual outbreaks of dengue, chikungunya and zika virus infections, which are transmitted to humans by Aedes mosquitoes. The transmission of these three arboviruses is highly seasonal and their distribution is heterogeneous in space and time. There is evidence that dengue is expanding into previously protected regions in the north and south of Brazil, and previous analyses have demonstrated that transmission is associated with population demography, environmental temperatures and precipitation, with long-term hydrometeorological events such as drought and extreme wet periods also influencing the relative risk of dengue in Brazil. A key limitation of previous analyses is that they are often performed at coarse spatiotemporal resolution, for example using monthly dengue incidence data at the state or microregion level, or at the local level but for sub-national analyses. In this work, we aim to generate new evidence of the relative importance of demographic, socioeconomic, climatic and hydrometeorological factors in driving the observed seasonal transmission dynamics measured by dengue, chikungunya and zika virus incidence across Brazil at fine-scale temporal and spatial resolution. We analyse weekly case notification timeseries of chikungunya (between 2015-2020), zika (2015-2020) and dengue virus (2012-2020) at the municipality level (n = 5572) using spatiotemporal mixed-effects regression models, with climate predictors such as the range, average, and extremes of daily environmental humidity, temperature, and precipitation across different time periods, and long-term hydrometeorological events. We also explore the importance of socioeconomic factors, demography, land-use, human mobility and importation risk, and El Niño-Southern Oscillation (ENSO). Our results suggest that minimum humidity, long-term periods of extreme wetness and ENSO anomalies are important factors associated with increased human infections of all three arboviruses, thus highlighting the health impact of extreme weather conditions driven by changing climate on arbovirus transmission in Brazil.

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PRIOR ZIKA VIRUS INFECTION INCREASES RISK OF SUBSEQUENT SYMPTOMATIC INFECTION BY DENGUE VIRUS SEROTYPES 2 AND 4 BUT NOT SEROTYPES 1 AND 3

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The 4 dengue virus serotypes (DENV1-4) and the related Zika virus (ZIKV) are major concerns worldwide. We have shown that primary (1°) ZIKV infection increases risk of symptomatic and severe disease caused by DENV2 in our long-standing Nicaraguan pediatric cohort. Further, we found prior DENV immunity differentially modulates secondary disease: enhancement of DENV2, protection vs DENV1, and protection and enhancement of DENV3, depending on antibody level and disease outcome. We hypothesized that prior ZIKV infection may have similar associations with secondary dengue by serotype. In 2022, DENV4 circulated for the first time, along with DENV1-3, enabling us to test these hypotheses for all 4 serotypes. We used ZIKV and DENV inhibition ELISAs, ZIKV NS1 BOB assay, and clinically confirmed case data to define prior infection histories. All analyses used linear mixed models adjusted for age and sex. Compared to naïve individuals, 1° ZIKV infection significantly increased probability of symptomatic dengue and Dengue with Warning Signs/Severe Dengue. Stratifying by serotype, 1° ZIKV infection increased disease risk with DENV4 (probability = 3.74% [2.5, 5.59] vs Naïve, prob = 1.31% [0.82, 2.08]) but not DENV1. Children with one prior DENV infection before ZIKV and vice versa (ZIKV-DENV) were also at increased risk of subsequent disease caused by DENV4 but not DENV1. We re-ran models across 18 years of cohort data and found flavivirus (FV)-immune individuals had a significantly higher risk of dengue disease overall, compared to naïve

individuals. By serotype, this effect was significant for DENV2 and DENV4, but not DENV3, while FV-immune individuals were at lower risk of DENV1. Pre-existing anti-DENV antibodies increased risk of dengue caused by DENV2 across all titers and DENV3 and DENV4 at low titers. Conversely, low titers showed no association with DENV1 disease, while high titers were protective vs DENV1 and DENV3. In sum, we show prior ZIKV infection, like prior DENV infection, increases disease caused by certain DENV serotypes. Considering serotype-specific effects is essential when assessing the safety and efficacy of ZIKV and DENV vaccines.

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INVESTIGATING THE POTENTIAL OF DENGUE AND ZIKA VIRUS TO ESTABLISH A SYLVATIC TRANSMISSION CYCLE IN THE NEOTROPICS THROUGH A MODELING LENS

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Dengue (DENV) and Zika (ZIKV) virus are maintained in sylvatic cycles between non-human primate (NHP) hosts and arboreal mosquitoes in Africa and Asia. DENV was introduced to the Americas centuries ago, while ZIKV was introduced within the last decade. Despite its long residence in the neotropics, there is no evidence that DENV has established a sylvatic cycle there, but whether ZIKV will do so is an open and urgent question. Key determinants of sustained transmission in a novel environment are the replication of a virus within novel hosts and its transmission to vectors. We aimed to analyze parameters of DENV and ZIKV sylvatic transmission dynamics through statistical and mathematical modeling approaches. Recently, we used Aedes albopictus to infect novel hosts (squirrel monkeys, Saimiri boliviensis boliviensis) with sylvatic strains of DENV and ZIKV. We monitored host viremia and transmission to mosquitoes over the course of infection. Individuals infected with DENV showed low levels of virus replication, but we were able to fit a mechanistic within-host compartmental model to ZIKV viral dynamics in squirrel monkeys. We estimated the within-host basic reproduction number R0 to be 3.7 (median, 95% highest density interval [2.3 ; 5.1]), consistent with previous estimates in rhesus macaques using needle delivery of the virus. Lastly, we coupled viral dynamics with dose-response relationships within-vector, and estimated the probability to produce a saliva-positive Ae. albopictus upon bite on a ZIKV-infected squirrel monkey to be above 50% between days 3 and 5 post-infection. Transmission could be further enhanced if vectors are more likely to feed on infected than uninfected hosts. We therefore assessed the effect of host sex, temperature, weight, and viral load, as well as virus species, mosquito infection status, and time of feeding, on the proportion of mosquitoes taking a blood meal. None of these were significantly associated with Ae. albopictus feeding behaviour, in contradiction with recent results in mice. Nonetheless, our results suggest that a neotropical ZIKV sylvatic cycle may be imminent.

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INVESTIGATING THE VECTOR COMPETENCE OF A SCOPE OF MOSQUITO SPECIES IN THE TRANSMISSION OF GETAH VIRUS

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Getah virus (GETV) is an important Alphavirus of the Togaviridae family. Its genome is made up of a single-stranded positive sense RNA and it is transmitted by mosquitoes. Although no known clinical symptoms in people, GETV has been linked to epidemics in animals. Serological proof of GETV exposure and the threat of zoonotic transmission, however, makes GETV an important arbovirus in the field of veterinary medicine. With inadequate investigations into the vector transmission of GETV, there is very little information on the variables influencing the spread and the sporadic outbreaks of GETV infections. As a result, we assessed the GETV's host range in both in vitro and in vivo models. Cell lines derived from selected species of mosquitoes with medical importance were assessed by plaque assay to determine their susceptibility and replication under in vitro laboratory conditions. Conversely, quantitative Real Time Polymerase Chain Reaction and a plaque assay was carried out to evaluate the susceptibility and transmission potential of mosquito species to GETV infection in vivo. All examined mosquito-derived cell lines were GETV-susceptible with detectable cytopathic effects. The highest replication titres of GETV were recorded in C6/36 and NIID-CTR cell lines derived from Aedes albopictus and Culex tritaeniorhynchus mosquitoes, respectively. Comparisons of the infection, dissemination and transmission rates across species varied significantly with Cx. tritaeniorhynchus colony being the most effective species in GETV vector competency. This study is also the first account of An. stephensi and Ae. albopictus capability to transmit GETV under laboratory conditions, highlighting the potential risks of GETV transmission in nature, especially in unidentified potential vectors of GETV transmission in endemic regions where these vectors are prevalent.

6409

EXPOSURE TO WEST NILE VIRUS AND STRAIN-SPECIFIC DIFFERENCES SHAPE TRANSMISSION BY CULEX PIPIENS UNDER CLIMATE CHANGE

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Arthropod-borne viruses are associated with over 140 human diseases. The most widespread arboviruses belong to the flavivirus family, which includes West Nile virus (WNV), Zika virus, dengue virus, and several others. Across the globe, temperature is increasing and such increases influence the distribution and prevalence of vector-borne disease transmission. Life history traits of both the mosquito and pathogen have been utilized in modeling vector-borne diseases, thus far, models for WNV have identified species and vector population-specific differences. Previous studies have demonstrated that exposure and infection with WNV can influence mosquito longevity, fecundity, and blood-feeding behavior, yet trait-based R0 models have historically been generated using data from unexposed mosquitoes. The purpose of this study is to determine the interactions among temperature, infection status, viral strain, and WNV transmission in order to create more accurate predictive models of WNV transmission under climate change. Culex pipiens were fed a blood meal containing genetically distinct strains (WN02 or NY10) or a noninfectious blood meal. Following feeding, lifespan, biting rate, ovipositing, vector competence, and pathogen development rate were recorded at constant temperatures ranging from 10°C to 33°C and a mean cycling around 25°C. Bodies and legs of dead females were harvested to determine infection and dissemination rates of exposed mosquitos and qPCR was used to quantitate viral load. These data were used to generate thermal performance curves in conjunction with previously published life-history data, which were then used to inform R0 models. Our results demonstrate that WNV infection significantly influences the relationship between temperature and Cx. pipiens life-history traits, and that these relationships are strain-specific. Consideration of infection status and viral genetics, therefore, is necessary to improve models of WNV transmission under climate change. These results have broader implications for understanding the role of heterogeneity in vector-borne disease modeling.

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IDENTIFICATION OF ZIKA VIRUS GENES INVOLVED IN MOSQUITO TRANSMISSIBILITY

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Zika virus (ZIKV) is a flavivirus mainly transmitted by Aedes aegypti mosquitoes that recently emerged across the Pacific region and Latin America, causing large human outbreaks associated with birth defects and neurological disorders. Phylogenetic analyses show that ZIKV genetic diversity can be divided into an African lineage and an Asian lineage. Although to date, human outbreaks have exclusively been associated with strains from the Asian lineage, a growing body of evidence points towards higher transmissibility of ZIKV strains from the African lineage. To elucidate the viral genetic determinants underlying differential transmissibility between African and Asian ZIKV strains, we used a combination of viral reverse genetics and mosquito transmission assays in vivo. We constructed a set of six chimeric ZIKV strains from two parental strains with different levels of transmissibility by swapping the genome fragments encoding structural proteins, non-structural proteins or untranslated regions. We compared the in vivo transmissibility of the chimeric viruses in mosquitoes experimentally exposed to an artificial infectious blood meal. We detected viral genomes in mosquito head and infectious viruses in saliva and calculated transmission prevalence as the proportion of virus-positive head with a virus-positive saliva. We found that replacing the genome region encoding structural proteins of the low-transmissibility Asian strain with the same region from the high-transmissibility African strain significantly increased transmission prevalence. The reciprocal replacement resulted in the opposite pattern. Swapping the genome fragments encoding the structural proteins also resulted in significant changes in viral growth kinetics in mosquito cells in vitro. We concluded that the difference in mosquito transmissibility between African and Asian ZIKV strains is due to genetic variation in the viral structural proteins. Future work will provide mechanistic insights into these data using a mathematical model of within-mosquito infection dynamics and extend the results in a mouse-to-mosquito ZIKV transmission assay.

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CRYPTOSPORIDIUM PARVUM: THIOREDOXIN REDUCTASE ACTS AS THE PRIMARY REGULATOR OF GLUTATHIONE AND THIOREDOXIN REDOX PATHWAYS AND IS A TARGET FOR DRUG DISCOVERY FOR CRYPTOSPORIDIOSIS

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Cryptosporidium parvum (Crypto) is a protozoan parasite that causes cryptosporidiosis, a highly contagious disease with nearly 30% of the global population potentially exposed to the parasite. The options for treatment are severely limited; only a single drug (Nitazoxanide) is currently approved by the FDA and it is not fully effective in the young, elderly, or immunocompromised patients. Auranofin, which is clinically used for rheumatoid arthritis and in clinical trials for cancer and other infectious diseases, was shown to be active against Crypto in vitro. Auranofin is thought to function, in part, through inhibition of thioredoxin reductase (TrxR). While TrxR has numerous functions, some of its most important are regulating cellular redox balance and preventing damage caused by reactive oxygen species generated by the host immune response. In humans, TrxR and glutathione reductase (GR) are responsible for regulating thioredoxin (Trx) and glutathione (GSH) dependent pathways, respectively. No GR is present in the Crypto genome. We hypothesize that TrxR is the primary regulator of both Trx and GSH in Crypto and that its inhibition would disrupt both pathways and be lethal. To test this hypothesis, C. parvum (Cp)TrxR and CpTrx proteins were expressed and characterized. CpTrxR was found to have Trx reducing activity, but no GR activity. However, the combination of CpTrxR and CpTrx had high levels of GR activity. An IC50 was determined to be 2.4 nM for auranofin against CpTrxR. These results indicate that CpTrxR is an essential protein for both TrxR and GR activities, meaning that this protein acts at the primary regulator for both Trx and, subsequently, GSH pathways. We have identified crystallization conditions and successfully determined the structure of CpTrxR in complex with auranofin. These findings are significant in providing a foundation for future structure-guided drug development studies and redox biochemistry for improved cryptosporidiosis treatment.

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PROGRESS IN DEVELOPING METHIONYL-TRNA SYNTHETASE INHIBITORS FOR CHAGAS DISEASE

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The protozoan parasite, Trypanosoma cruzi, infects 6-8 million people primarily in Latin America. Antiparasitic drugs for chronic T. cruzi infection (Chagas disease) are inadequate due to bad side-effects and poor efficacy. T. cruzi has a single methionyl-tRNA synthetase (MetRS) which is essential for protein synthesis. We are developing inhibitors of the T. cruzi MetRS as therapeutics for CD. The MetRS inhibitors were initially developed against the T. brucei MetRS guided by crystal structure of that enzyme bound to inhibitors. Over 550 MetRS inhibitors synthesized by our group have been screened against mammalian-stage T. cruzi cultures establishing structure activity relationships. Nearly 150 compounds have been identified with EC50 values <10 nM. Most compounds are highly selective with cytotoxicity (CC50) values on mammalian cells of greater than 20,000 nM. An exemplary compound was tested in an in vitro washout assay (16-day exposure at 25X the EC50) and shown to have trypanocidal activity (with no outgrowth in the 60 day observation period) comparable to the clinical drug, benznidazole. Work has focused on two areas for lead development: 1) optimizing pharmacological properties to maximize exposure of free compound in mammalian models, and 2) maximizing the therapeutic window to avoid potential toxicity to mammalian cell mitochondrial function. A subset of lead compounds is being tested in the murine chronic T. cruzi infection model with results to be presented. MetRS inhibitors represent a promising class of compounds for treating Chagas disease.

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METABOLOMIC ANALYSIS REVEALS A NOVEL IMMUNOMODULATORY ROLE OF LYSOPHOSPHATIDYLCHOLINES IN IMMUNIZATION WITH A GENETICALLY MODIFIED LIVE ATTENUATED PARASITIC VACCINE

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Leishmaniasis is a spectrum of diseases caused by the blood borne protozoan parasites belonging to several different Leishmania species. Currently, there are no FDA-licensed vaccines against human leishmaniasis. Centrin-deleted Leishmania major (LmCen-/-) parasites were developed as a vaccine candidate for leishmaniasis using CRISPR/Cas9 gene-editing technology. Preclinical research has demonstrated the safety of LmCen-/- parasites in animal models and significant efficacy against sand fly-mediated infections with parasites causing either cutaneous or visceral disease. Substantial variations between the LmCen-/- and LmWT infections were seen in the immunological properties of the innate and adaptive responses. Since neutrophils are the first innate cells to arrive at the site of infection, it is hypothesized that metabolic reprogramming occurring in these cells could mediate the immune mechanisms of the protection using LmCen-/- and LmWT parasite strains. C57Bl/6 mice were intradermally infected with LmWTmCherry or LmCen-/-mCherry parasites. At 48h post-infection, 2.5-3x106 parasitized and non-parasitized neutrophils were sorted by flow cytometry and quenched immediately. Untargeted

metabolomic analyses were performed on the neutrophil populations using mass spectrometry. Three analytical runs per sample were performed. Mass spectrometric analyses showed that neutrophil populations isolated from ear draining lymph nodes of mice infected with LmCen-/-contained higher levels of lysophospatidylcholines (LPC), a class of metabolites that are derived from phosphatidylcholines, compared to neutrophils isolated from naïve or LmWT infected mice. The role of LPCs in immune regulation of neutrophils are further being explored using a LPC receptor antagonist in in vitro and in vivo studies. These investigations will shed light on immune defense processes and aid in the discovery of novel biomarkers for vaccine-induced immunity.

6414

NEW TRYPANOSOME GENOMES DEMONSTRATE THE CO-EVOLUTIONARY RELATIONSHIP BETWEEN ENERGY SOURCE AND SURVIVAL STRATEGY

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African (Salivarian) trypanosomes persist in the host bloodstream where they are exposed to the full force of the mammalian immune system. However, Trypanosoma cruzi (Stercoria) can invade host blood cells and tissues allowing the parasite to hide from the immune response. Fundamentally, these environments differ greatly in terms of the metabolic stress experienced by the parasite. The intracellular environment is rich in triacylglycerides, a frequently targeted energy source by pathogenic microbes, and extracellular parasites have access to soluble sugars, amino-acids and lipids. We predict that by assessing the metabolic capabilities between groups of trypanosomes it may be possible to link these traits with survival strategy. Further, it may be possible to predict the survival strategy of novel or understudied parasites based on this information. In this study we present three novel trypanosome genomes and one reassembled genome that allow us to investigate the genomic basis for differences in metabolic capability between trypanosomes with different survival strategies. We show that loss of genes in fatty acid metabolism pathways may have facilitated the switch to an extracellular lifestyle in the Salivaria. We also demonstrate that metabolic information, along with other genomic information, can allow us to make predictions about the survival strategy of understudied trypanosome species and give insight into the evolutionary history of these important pathogens of humans and livestock.

6415

FACING ADVERSITY: CHAGAS DISEASE TREATMENT TOLERABILITY AND ADVERSE EVENTS AT AN ACADEMIC SAFETY-NET HOSPITAL IN NEW ENGLAND

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Anti-trypanosomal therapy is generally recommended for individuals under age 50 with the indeterminate form of Chagas disease to prevent progression to cardiac or gastrointestinal (GI) disease. However, benznidazole (BNZ) and nifurtimox (NTX) carry a substantial risk of adverse drug reactions. We performed a cross-sectional retrospective chart review of treatment tolerability among patients with confirmed Chagas disease referred to Boston Medical Center from June 2017 to June 2021. Ninety patients with confirmed Chagas disease were evaluated, of whom 17 (18.9%) had contraindications to treatment. Fifty-eight patients started on therapy, with dosing and monitoring co-managed by an infectious diseases physician and pharmacist. Following initiation of BNZ as first-line therapy, 53 patients (91.4%) had at least one adverse event, of which GI side effects (27/58, 46.6%), rash (26/58, 44.8%), and symptoms of potential peripheral neuropathy (16/58, 27.6%) were most common. Rashes led to treatment discontinuation in 14 patients (24.1%) and met criteria for grade 3 severity in 9 patients (15.5%). Adjunctive therapies for rash included topical and systemic steroids and systemic antihistamines. Concern for peripheral neuropathy led to treatment cessation for 8 patients (13.8%). GI side effects occurred in 27 patients (46.6%), were relatively mild, and commonly managed with famotidine. Adverse events necessitated cessation of BNZ for 18 patients (31.0%), of whom 12 went on to receive NTX. NTX was associated more frequently with GI side effects (10 patients or 83.3%). Ultimately, a total of 53 patients (91.4%) received at least one month and 42 patients (72.4%) completed at least 60 days of either BNZ or NTX. Multiple strategies were used to prevent and alleviate adverse events; co-management with a multi-disciplinary team was essential to assist patients in tolerating therapy. Even so, most patients experienced some adverse events, of which rash and peripheral neuropathy were most concerning. These findings underscore the grave need for expanded safe and effective treatment options for patients living with Chagas disease today.

6416

INTRA-SPECIES GENETIC CLASSIFICATION OF ENTEROMONAS SP. DETECTED FROM HUMAN AND ANIMAL HOSTS IN INDONESIA

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Due to its non-pathogenic characteristic, Enteromonas sp. has been rarely studied, despite its widespread prevalence in both human and animal hosts, especially in low-hygiene tropical areas. As a result of such neglect, only a few genetic references of Enteromonas sp. are available in the GenBank, and the intra-species genetic diversity remains unrevealed. In this study, we aimed to address the genetic classification of Enteromonas sp. among humans and animals through a molecular epidemiological study conducted in Wainyapu village, where humans and animals live closely, in Sumba Island, Indonesia. Stool samples were collected from 2013 to 2016. The total DNA was extracted from the stools for the Polymerase Chain Reaction (PCR) screening of the 18S small subunit ribosomal RNA (18S rRNA) gene locus Enteromonas species. All the PCR amplicons confirmed approximately 1,400 base pairs of DNA sequences. The prevalences of Enteromonas sp. were 33.9% (73/215) in humans and 25.2% (68/270) in animals, including unique DNA haplotypes of 61 in humans and 90 in animals. On the reconstructed phylogenetic tree, we observed at least four clusters among the intra-species genetic diversity of Enteromonas species. Haplotypes from goats, rodents, and buffalos were clustered separately from other clusters indicating the presence of animal-specific groups. The human-derived haplotypes were grouped into another cluster at the same Operational Taxonomic Unit (OTU) level as the animal-specific ones. Among the human-derived haplotypes, three sub-clusters were also observed. The molecular taxonomy of minor intestinal protozoans, especially commensal types like Enteromonas sp., is essential to investigate and understand human gut microbiota dynamics. The classification proposed in this study will pave the way for investigating the roles of Enteromonas sp. in host gut homeostasis.

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CHEMICAL AND GENETIC INVESTIGATIONS ON LEISHMANIA DEXD/H-BOX PROTEINS AS POTENTIAL DRUG TARGETS AGAINST LEISHMANIASIS

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Leishmaniases, ill controlled and neglected diseases, constitute major public health problems. Besides the limited repertoire of obsolete 'drugs', current challenges also include high costs, toxicity, adverse effects, and emergence of drug resistance. Thus, identification of novel drugs constitutes a global research priority. Our objective is to validate members of the Leishmania DExD/H-box protein family, particularly DEAD-box proteins, also known as a rich source of drug targets in humans, as potential Leishmania drug targets, using chemical and genetic validation approaches. First, biochemical and genetic expression in yeast of the Leishmania infantum initiation factor 4A (LieIF) have shown its potential as a drug target. Then, we identified, through in silico modelling and virtual screens of small molecules, different ligands, which were screened on the ATPase activity of this protein. This allowed the selection of 6-aminocholestanol as LieIF inhibitor; this molecule presented an anti-Leishmania activity against promastigotes and intracellular amastigotes, which confirmed 6-aminocholestanol as a selective inhibitor and confirmed the chemical validation of LieIF as a drug target. Thus, we expanded our interest to other members of the DExD/H- box protein family. Our second target was encoded by L. infantum LINF_080005700 (LINF08), which has been identified as a close member to the Ded1/DDX3 protein by phylogeny and in silico search of conserved sequence motifs within sequence alignments of a large collection of DEAD-box proteins from various organisms. We interestingly demonstrated peculiar enzymatic characteristics of the recombinant protein so far not described for DExD box proteins; we have also demonstrated using CRISPR technology its nuclear localization both in promastigotes and axenic amastigotes. We are currently investigating its essentiality, which would genetically validate it as a drug target. To conclude, this study delivers two promising drug targets against leishmaniases that deserve further investigation for the development of novel therapeutic drugs.

6418

EFFICACY OF MOXIDECTIN VS. IVERMECTIN COMBINATION TREATMENTS FOR BANCROFTIAN FILARIASIS IN COTE D'IVOIRE: PRELIMINARY 24 MONTH RESULTS

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Lymphatic filariasis (LF) remains endemic in much of Africa despite many years of annual mass drug administration with ivermectin (IVM) and albendazole (ALB). Moxidectin (Mox) is a macrocyclic lactone that is superior to IVM for long-term clearance of onchocerciasis microfiladermia. To determine whether Mox combination therapy might also be superior for LF, we are conducting a phase III, open label, randomized trial in Côte d'Ivoire to compare the standard mass drug administration regimen of annual IVM+ALB (IA) vs. a single dose of Mox+ALB (MoxA) and Mox+DEC+ALB (MoxDA) vs. IVM+DEC+ALB (IDA) in persons with Bancroftian filariasis. The primary study endpoints are Mf clearance at 12 (IA vs. MoxA) or 24 (IDA vs. MoxDA) months post-treatment, as assessed by 1ml filtration of night blood. Secondary endpoints include decrease in circulating filarial antigen (CFA) (based on semiquantitative reading of filarial test strips, FTS) and clearance of adult worms nests in men as assessed by scrotal ultrasound. Enrolment for the study began in August 2020, and to date we have 24-month efficacy data for 66 of 121 (54%) participants infected with >40 Mf/mL of blood at baseline. At 24 months 9 of 19 (47%) participants in the IA arm (after two annual doses) had undetectable Mf compared to 13 of 14 (93%) participants in the single dose MoxA arm (p=0.006). There was no difference in Mf clearance between single dose IDA and MoxDA (81% vs 88% respectively, p=0.576). Adult worm nests were cleared in 2 of 11 (18%) men after IA and 7/8 (88%) of men after MoxA. Sixty percent of men (3 of 5) cleared their worm nests after IDA compared to 100% (9/9) after MoxDA (p=0.171). There was no difference in reduction of CFA between IA and MoxA (11% vs 36%, p=0.08) at 24 months, however more people in MoxDA compared to IDA (53% vs 19%, p=0.041) had reduction in CFA. These preliminary data strongly suggest that MoxA is superior to IA and comparable to IDA and MoxDA for clearance of W. bancrofti microfilaremia and inactivation of adult worm nests at 24-months. Additional 24-month data will be available after August 2023. Additional studies are needed to determine whether MDA with MoxA can accelerate LF in Africa.

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EFFICACY AND SAFETY OF ALBENDAZOLE 400 AND 800 MG ON HYPERMICROFILAREMIC LOIASIS: PRELIMINARY RESULTS OF A PHASE IIB, RANDOMIZED, SINGLE-BLIND CLINICAL TRIAL IN NORTHERN GABON

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Albendazole (ALB) is used safely for the reduction of Loa (L.) loa microfilaremia. However, there is no official recommendation. This molecule could be used routinely in onchocerciasis outbreaks in case of coendemicity with loiasis, in order to make hypermicrofilaremia carriers eligible for mass treatment with ivermectin. The purpose of this study is to compare the efficacy and safety of two ALB treatment regimens in the management of hypermicrofilaremic loiasis. The study was conducted in the Woleu-Ntem region of northern Gabon. Socioeconomic, demographic and clinical data as well as parasitological results were collected on a standardized form. Patients were to be divided into 3 groups: 2 groups of hypermicrofilaremia (≥8000 mf/mL) treated with 400 mg and 800 mg for 30 days and a control group consisting of patients with low microfilaremia (<8000 mf/mL) treated with ALB 400 mg for 30 days. Microfilaremia and adverse events were investigated and monitored weekly until day 30. Of 1363 individuals screened for loiasis, 72 were included and followed for 30 days on daily ALB administration. The control group consisted of 38 patients with microfilaremia less than 8000 who received ALB 400 mg. Of the remaining 34 patients with microfilaraemia greater than 8000 mf/mL, 16 received ALB 400 mg and 18 received 800 mg. L. loa microfilaremia and eosinophilia were measured at day (D) 0, 2, 7, 14, and D30. Clinical data were monitored daily before each ALB dose administration. Microfilaremia decreased at D30 in 82.3% of hypermicrofilaremic subjects to below 8000 mf/mL. No serious adverse events were recorded; 30.0% had clinical manifestations after ALB, and for 20.0%, the main adverse event recorded was pruritus. No difference between the two groups of hypermicrofilaremic patients was observed in the reduction of microfilaremia and the occurrence of clinical manifestations. In conclusion, treatment of hypermicrofilaremic loiasis with ALB dosed 400 mg and 800 mg for 30 days, significantly reduces microfilaremia and can be used for eligibility of microfilariae carriers for mass treatment with ivermectin.

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DEVELOPMENT OF AN ELISA TO DETECT ANTIBODY TO ONCHOCERCA VOLVULUS INFECTION USING A MAMMALIAN EXPRESSED RECOMBINANT ANTIGEN OV16

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The World Health Organization (WHO) recommends serological assessments to document onchocerciasis elimination. National onchocerciasis programs are hindered by the lack of diagnostic tests that meet WHO target product profile (TPP) criteria. One of the tests used by onchocerciasis programs, an ELISA based on the Ov16 antigen expressed in bacteria, has had several challenges when performed in endemic country laboratories. Ov16 produced in bacterial expression systems may have different conformation than the native antigen, may lack posttranslational modifications like glycosylation, and infected individuals may have antibodies to bacterial proteins that are difficult to remove in the Ov16 purification process; any of which could result in decreased assay performance. In addition to the issues related to bacterially expressed protein, the current ELISA takes 7 hours to complete, lacks standardized quality controls and is not available as a commercial kit. We sought to overcome the challenges of the current assay with a new ELISA utilizing a mammalian-expressed protein and decreased time to final result. We engaged a commercial company to express Ov16 in a Chinese Hamster Ovary mammalian expression system and purified the antigen using GST-tag and sizing column chromatography. The resulting 47-kDa purified protein, Ov16m, was used to optimize the ELISA. Using pre-coated and blocked plates, the total assay time was 1.5 hours. We also added a standard curve using a humanized IgG4 monoclonal anti-Ov16 antibody to improve assay comparability. Both sera and dried blood spots (DBS) were used to test the performance of the assay in receiver operating characteristic analysis. The sensitivity and specificity of the assay using 94 negative and cross-reactor sera and 134 Onchocerca volvulus positive sera, confirmed by skin snip microscopy or PCR, were 92% and 100%, respectively. In addition, 39 confirmed positive and 170 confirmed negative DBS were tested, yielding 100% sensitivity and 100% specificity. This Ov16m ELISA satisfies WHO TPP requirements and may be useful for informing programmatic decisions for onchocerciasis elimination.

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LABORATORY EVALUATION OF ONCHOCERCIASIS RAPID DIAGNOSTIC TESTS (RDTS)

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Reliable diagnostic tests are needed to support onchocerciasis programs, especially in low prevalence settings. Recently two target product profiles (TPPs), one for disease mapping and one for stopping mass drug administration (MDA) were developed. The TPPs outline performance characteristics required for new tests, including clinical sensitivity (F60% for mapping and ≥89% for stopping) and specificity (≥99.8% for both). Two antibody detection rapid diagnostic tests (RDTs) developed by DDTD were independently evaluated at CDC. Test A, previously described in 2022, contained Ov16 in one band. Test B included four antigens in two bands: Ov16 and Ov33.3 (band 1) and OvOC10469 and OvOC3261 (band 2); both bands must be visible for a positive result. Tests were performed according to manufacturer instructions using two independent readers. A panel of serum samples (n=146) from persons who were skin snip positive for Onchocerca volvulus by microscopy or PCR was used to evaluate sensitivity. A specificity panel included subpanels of Mansonella perstans and/or Loa loa (n=26), Wuchereria bancrofti (n=50), Plasmodium falciparum and/or P. vivax (n=16), Schistosoma mansoni (n=40), Strongyloides stercoralis (n=9), Rheumatoid factor/Type 1 diabetes (n=20) and North Americans with no history of international travel (n=50). Sensitivity and specificity of Test B were 90.4% and 94.3%, respectively. The two tests were then directly compared on a subset of 20 positive and 150 negative samples, Test A was 90% sensitive and 97% specific, and Test B was 85% sensitive and 92% specific. Both tests met the TPP sensitivity requirements for mapping or stopping MDA but not the specificity requirements. While the specificity issues may arise in part from the choice of biomarkers, it should be noted that nearly all problematic samples were M. perstans+/O. volvulus– but from an O. volvulus endemic country. Based on these data, development of an improved version of Test B is underway. In addition, the results show that to validate any new test for onchocerciasis, there is a need for M. perstans and L. loa samples from areas where O. volvulus exposure can be rigorously ruled out.

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WB5, A NOVEL BIOMARKER FOR MONITORING EFFICACY AND SUCCESS OF MASS DRUG ADMINISTRATION PROGRAMS FOR WUCHERERIA BANCROFTI ELIMINATION

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The success of mass drug administration (MDA) at reducing the prevalence of lymphatic filariasis (LF) in endemic countries has led to an increased need for diagnostic targets designed to monitor for recrudescence and ongoing transmission. While diagnostic targets exist for detecting Wuchereria bancrofti [Wb] and Brugia malayi [Bm] infections, additional targets may increase the sensitivity of these tests. For Wb at least, new biomarkers (in conjunction with Wb123) may be needed to supersede the current WHO recommendations which fail to reflect microfilariae (mf) clearance. Hence, diagnostic tools that reflect the presence/clearance of mf or early infection could be instrumental for not only MDA stopping decisions but also for monitoring. To this end, bioinformatic analyses coupled with stage-specific expression data for Wb and/or Bm resulted in the identification of 12 targets that were: 1) present in Wb and/or Bm; 2) have very little to no homology with proteins from other filariae; and 3) were enriched in the mf or L3 stages. Screening of these 12 antigens by a Luciferase Immunoprecipitation System (LIPS) assay for IgG with serum from Wb-infected (n=170) and uninfected individuals (n=60) identified a single antigen, termed Wb5, that was specific for Wb infections only. Recombinant Wb5 proteins were generated in multiple expression systems for use in a variety of IgG4-based immunoassays. Preliminary screening indicated a very high degree of correlation ($p<0.0001$) between the data derived from LIPS and those determined by more standard immunoassays. To assess if Wb5 could provide additional sensitivity to assays already using IgG4 antibodies to Wb123, head-to-head comparisons were performed using serum from 381 samples (231 Wb-infected; 150 controls). Using IgG4 based immunoassays at 100% specificity, Wb5 and Wb123 had individual sensitivities of 60.2% and 75.3%, respectively, while a combination resulted in 81.0% sensitivity. Moreover, kinetic studies of patients that were treated and followed up longitudinally demonstrated a sharper decline in Wb5 titers compared to Wb123, thus paving the way for Wb5 as a complementary tool to Wb123.

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PROTEIN INVENTORY OF ONCHOCERCA VOLVULUS NEOPLASMS IDENTIFIED BY DEEP VISUAL PROTEOMICS

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The nematode Onchocerca volvulus is the agent of river blindness and targeted by WHO for elimination. The main strategy for elimination is mass administration of ivermectin to endemic populations. The drug is microfilaricidal, but weak macrofilaricidal effects have been reported after many rounds of treatment. A small fraction of adult O. volvulus contain pleomorphic neoplasms, and their development is more common after

ivermectin. We analyzed 428 female worms by histological evaluation of paraffin embedded nodule sections as part of a trial of ivermectin combination treatments. Neoplasms were present in 5.6% of these worms. The purpose of this study was to compile protein inventories of adult worm tissues to identify protein profiles associated with neoplasms. We used digital image analysis of histological sections, laser capture microscopy and highly sensitive mass spectrometry analysis (ThermoScientific, Eclipse). Neoplasm tissue from three female worms was analyzed, and compared with normal tissues from the body wall, uteri and intestine of these worms and also tissues from a healthy female without neoplasm. Unlike healthy females, females with neoplasms did not show any signs of embryogenesis. A protein was called present, if supported by 2 peptides and found in at least 2 of the 3 biological replicates. In worms with neoplasms, we detected 151 proteins in the body wall, 215 proteins in the intestine, 47 proteins in the uterus and 1577 proteins in the neoplasms. The uterus of the healthy female with intact embryogenesis had a high number (1710) of proteins detected that was similar to that of neoplasms. A majority of the 20 most abundant proteins detected in neoplasms was highly conserved, and only two proteins were nematode specific. Proteins that were found in neoplasms but not in the other analyzed tissues included peroxiredoxins, proteases, and proteins related to signal transduction, and ribosomal or proteasome activity. In conclusion, we have successfully used deep visual proteomics to analyze the proteome of individual O. volvulus tissues in nodule sections and identified proteins that are overexpressed in neoplasms.

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ASSOCIATION BETWEEN ALTERED COGNITION AND LOAISIS: FIRST EVIDENCE FROM A CROSS-SECTIONAL STUDY IN A RURAL AREA OF THE REPUBLIC OF CONGO

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Individuals with high Loa loa microfilarial densities are at risk of developing severe encephalopathy after administration of antiparasitic drugs. Recent epidemiological data suggest an increased mortality and morbidity in L. loa infected individuals and a systematic review of atypical cases of Loa loa revealed that many organs appear to be affected by the parasite, including the brain. Apart from these findings, loiasis is still considered benign and studies are mandatory to evaluate the possible neurological morbidity associated with loiasis. We conducted a cross-sectional study to assess cognitive alteration in a population living in a rural area endemic for loiasis in the Republic of Congo. Fifty individuals with high L. loa microfilarial densities (MFD) were matched on sex, age and residency with 50 individuals with low MFD and 50 with no MFD. MoCA (Montreal Cognitive Assessment) tests and neurological ultrasounds were performed for all participants. For the main analysis, individuals with MoCA scores below 23/30 were considered to have altered cognition. Altered cognition was analyzed by L. loa MFD, sociodemographic characteristics and neurological ultrasound results. Mean MoCA score was 15.6/30 (range : 3/30 -28/30). Individuals with more than 15,000 microfilariae per milliliter of blood (mean predicted score:14.0/30) are more than twenty times more likely to have an altered cognition, compared to individuals with no microfilaremia (mean predicted score: 16.3/30). Duration of schooling were strongly associated with better MoCA results. Extracranial and intracranial atheroma were not associated with L. loa MFD with respectively 7 (14.9%) and 13 (13.7%) individuals with atheroma in microfilaremic and amicrofilaremic individuals. Loaisis microfilaremia is probably involved in cognitive impairment, especially when the MFD are high. These results add to the evidence that the burden of loaisis is highly underestimated and highlight the urgent need to better understand loaisis-induced neurological morbidity.

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DEVELOPING NOVEL FLATWORM ION CHANNEL LIGANDS TO TREAT NEGLECTED TROPICAL DISEASES

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Praziquantel (PZQ) is the mainstay for treatment of parasitic flatworm infections. After ~40 years of clinical usage, a putative target for PZQ was identified: a transient receptor potential ion channel in the melastatin subfamily (TRPMPZQ). This channel is conserved across all profiled parasitic flatworm species, and in vitro potency at each ortholog mirrors the known clinical sensitivity of each parasite. Notably, Fasciola spp. are insensitive to PZQ mirroring the lack of activation of Fasciola spp. TRPMPZQ in vitro. It was discovered that there are residues in the binding pocket of TRPMPZQ responsible for the observed differential sensitivity, and this knowledge prompted the development of molecules that could tolerate this variation. Given the increasing resistance of Fasciola spp. to triclabendazole, the discovery of new fasciolicidal targets is timely. Therefore, for proof-of-principle the decision was made to interrogate the druggability of F. hepatica TRPMPZQ (Fh.TRPMPZQ). Employing a target-based screen of >600,000 small molecules against both Sm.TRPMPZQ and then Fh.TRPMPZQ, a series of chemotypes that activate both channels were identified, and the pharmacophore shown to be most potent at Fh.TRPMPZQ was selected for further development. A library of molecules was synthesized to interrogate structure-activity relationships around the core of this molecule resulting in S55, a new molecule with submicromolar potency at both channels. When applied ex vivo to Schistosoma mansoni, S55 produced rapid contraction of the flatworm with concomitant tegument damage, phenocopying PZQ. Likewise, S55 produced an identical phenotype on freshly excised triclabendazole-sensitive and triclabendazole-resistant F. hepatica. S55 was non-toxic in HepG2 assays and is active and well-tolerated in vivo. Given these results, the data show that there is differential druggability among flatworm TRPMPZQ orthologs and demonstrate that Fh.TRPMPZQ is a druggable target that warrants further exploration.

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NOVEL INHIBITORS OF THIOREDOXIN GLUTATHIONE REDUCTASE WITH SCHISTOSOMICIDAL ACTIVITY

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Over 200 million people are infected with schistosomiasis resulting in more than 200,000 deaths annually. Schistosomiasis control strategies rely almost exclusively on mass drug administration (MDA) using praziquantel (PZQ) monotherapy, which is ineffective against juvenile worms. There are currently no available alternatives to PZQ, and few drugs or vaccines are in the clinical pipeline. Of immediate concern are results from MDA campaigns finding that PZQ cure rates are often less than 50%, and the possibility of emergence of PZQ resistant parasites is inevitable. Our aim is to develop new compounds that are effective against different developmental stages and species of the schistosome parasite. We have shown that S. mansoni thioredoxin glutathione reductase (TGR) is essential for worm survival in the mammalian host and druggable. Compounds targeting TGR identified to date are irreversible and/or covalent inhibitors with unacceptable side effects. To identify TGR inhibitors for clinical use, small molecule fragments obtained by X-ray crystallography screening were ligated and partially optimized as first-in-class non-covalent inhibitors of TGR. A first cryo-EM structure of TGR demonstrated that these inhibitors bind at a secondary

site adjacent to the NADPH binding site, blocking enzyme function. All compounds are found to be reversible via jump dilution experiments. These compounds display schistosomicidal activity against cultured worms equal to or better than praziquantel and superior to thresholds set by the WHO. Most importantly, several novel TGR inhibitors demonstrated efficacy against schistosome infections in mice, including treatment targeting juvenile worms, significantly outperforming praziquantel. These findings open a new avenue for the design of non-covalent inhibitors of TGR for the treatment of schistosomiasis.

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HIGH SENSITIVITY BUT LOW SPECIFICITY OF FEMALE GENITAL SCHISTOSOMIASIS SYMPTOMS AND RISK FACTORS DIAGNOSTIC TOOL ON GENITAL LESIONS ASSOCIATED WITH FEMALE GENITAL SCHISTOSOMIASIS IN ADOLESCENT GIRLS AND WOMEN IN MASWA DISTRICT, TANZANIA

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Female Genital Schistosomiasis (FGS) is a clinical feature of urogenital schistosomiasis caused by S. haematobium. Chronic FGS affect the women's reproductive system and even cause irreversible changes. The Liberia Ministry of Health developed the symptoms and risk factors checklist to help healthcare workers at primary healthcare facilities in endemic areas to identify and manage FGS. However, the sensitivity and specificity of the tool were not known. In that view, we hypothesized that the FGS checklist would have high sensitivity and specificity for diagnosis of FGS in women compared to colposcope and hence would improve early diagnosis of FGS among women in Tanzania. A community-based cross-sectional study was conducted among sexually active women at Maswa District. Women with informed consent, who produced 10mls of urine for urine filtration test were recruited and underwent thorough speculum examination by trained gynaecologists using a portable digital colposcopy to capture images of the cervix and vagina. A total of 347 adolescent girls and women aged 18-45 years were screened between October and November 2022. The mean age of women was 30 years (±0.414). Majority of women were aged 25-34, 153/347(44.09%), 186/347(54.07%) contacted fresh water bodies and 313/347 (90.20%) of the women had never used praziquantel. Among the 177 women who underwent a thorough colposcopy examination, the overall prevalence of genital schistosomiasis was 15.82% (28/177). Common FGS features detected were 14/28 (50%) homogenous yellow sandy patches, and 7/28(25%) abnormal blood vessels. The prevalence of urogenital schistosomiasis was 3.48% (13/345) among the study participants. The sensitivity, specificity, positive and negative predictive values of symptom and risk factor diagnostic tools were 85.71%, 8.72%, 15.00% and 76.47% among women who underwent gynaecological examination. Through this observational study, this diagnostic tool has shown high sensitivity but low specificity in diagnosing FGS. Studies with longer follow-ups and larger samples are needed to assess its validity in diagnosing FGS in endemic areas.

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OPTIMISATION OF THE DNA DIPSTICK AS A RAPID EXTRACTION METHOD FOR SCHISTOSOMA JAPONICUM IN INFECTED MICE SAMPLES AND SPIKED HUMAN CLINICAL SAMPLES

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Schistosomiasis remains a public health issue and the need for accurate and affordable diagnostics is crucial in the elimination of the disease. While molecular diagnostics is highly effective, it is expensive, with the main costs been associated with DNA extraction. The DNA dipstick is a rapid, affordable and simple DNA purification method that allows DNA to be extracted from diagnostic samples within 30 seconds. We aimed to optimise the DNA dipstick method for samples from mice and egg-spiked human samples. Urine, blood and faeces were collected from mice exposed to Schistosoma japonicum infection at weekly intervals from Day 0 to Day 42. Urine and faecal samples were collected from volunteer, uninfected humans and spiked with S. japonicum eggs. All samples were subject to several optimisation procedures and DNA extracted with the DNA dipstick. Amplification of the target DNA was carried out using LAMP and visualised using agarose gel electrophoresis and flocculation. The DNA dipstick successfully identified S. japonicum from infected mice and human clinical samples spiked with cracked eggs or genomic DNA from S. japonicum. The DNA dipstick combined with LAMP has huge potential in providing cost-effective, simple and accurate detection of schistosomiasis infection in endemic regions.

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ACCEPTABILITY OF GENITAL SELF-SAMPLING FOR THE DIAGNOSIS OF FEMALE GENITAL SCHISTOSOMIASIS IN HARD-TO-REACH COMMUNITIES

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Female genital schistosomiasis (FGS), caused by the waterborne parasite Schistosoma haematobium, is a debilitating gynaecological disorder that is difficult to diagnose. The 2022 WHO guideline on the control and elimination of human schistosomiasis anticipates that a screen-and-treat approach will be a useful programmatic strategy in certain contexts. We investigated the acceptability of a home-based genital self-sampling strategy for screening in two districts in Ghana. From October 2021 to January 2022, 250 non-pregnant, sexually active women were recruited from the Tain and Yeji Districts after community engagement and documentation of voluntary consent. Women were recruited using lot quality assurance sampling and trained to provide self-sampled cervicovaginal swabs and urine specimens for parasitological analysis. Women were subsequently invited to the community health centre for repeat sampling after a week. The mean age was 26.3±7.6. The prevalence of S. Haematobium ova by urine microscopy was 9.6%. Most participants rated self-sampling to be "very easy" or "easy" (82.4%: n=206), and "painless" (70.4%: n=176) and were confident that the sample was collected as they had been directed (81.2%: n=203). In addition, most women were willing to take another sample for FGS screening in future (96.8%: n=242) and were willing to recommend self-sampling to a close friend or family member by sending a customized text message (89.6%: n=224). Preference for sampling strategy was based on concerns of convenience, privacy and the need for supervision. Key informant interviews uncovered negative partner sentiments regarding genital screening programmes at health facilities in study communities. The self-sampling strategy can be successfully implemented for women in hard-to-reach communities as a patient-centred diagnostic strategy for FGS to improve screening coverage and promote healthcare equity. Opportunities to integrate self-sampling strategies into community health and extension services exist and should be explored in order to accelerate action towards schistosomiasis elimination targets.

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EXPANDING FEMALE GENITAL SCHISTOSOMIASIS LEARNING AND APPLICATION THROUGH AN ONLINE TRAINING FOR MIXED CADRES OF HEALTH CARE WORKERS IN FRANCOPHONE AFRICA

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Female Genital Schistosomiasis (FGS), a tropical disease caused by a parasitic worm (Schistosoma haematobium), is estimated to affect up to 56 million women and girls. It is a leading neglected issue in sexual and reproductive health in sub-Saharan Africa. Women and girls with FGS suffer physiological and social consequences from the infection which is associated with a three-fold increase in the risk of HIV acquisition. Most research on FGS focuses on epidemiology and treatment options. However, little attention is given to effective methods for awareness and education on FGS in healthcare workers (HCWs) and communities. Addressing the FGS knowledge gap in endemic areas is imperative. HCWs are generally unfamiliar with the effects of parasitic diseases on women's reproductive and sexual health as it is not typically included in medical training. FGS is often misdiagnosed and left untreated as symptoms mimic sexually-transmitted infections. HCWs need the expertise and tools to identify and treat FGS. Exacerbating this knowledge gap in Francophone countries, the English language dominates scientific literature and training. Therefore, the scientific community in Francophone Africa is isolated from contributing to and using this knowledge, limiting the uptake of research for decision-making. To help address these gaps, we are implementing an interactive online training in French to increase health capacity for FGS in Francophone countries by (i) training HCWs on FGS and its manifestations and presentations, (ii) supporting HCWs to develop action plans to integrate FGS into their practice and establish a culture of awareness in their local context, and (iii) creating an independent network of HCWs across Francophone Africa, linking them with a broader FGS network across endemic countries. Building a grassroots strategy advances economic and social well-being as it supports opportunities for communities to overcome health and education barriers. This presentation will share lessons from this experience developing a new cadre of Francophone FGS subject matter experts and review the local solutions detailed in the action plans developed.

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THE STATUS OF SCHISTOSOMIASIS AFTER A DECADE OF MASS DRUG ADMINISTRATION IN SIERRA LEONE

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In 2008, schistosomiasis (SCH) was found to be endemic in 14 health districts (HDs) of Sierra Leone. Endemic HDs were classified as low (≥1 and <10%) in the five coastal HDs; moderate (≥10 and <50%) in five HDs; and high (≥50%) prevalence in four HDs. Schistosoma mansoni is present in all nine high/moderate endemic HDs and S. haematobium in three HDs. Annual MDA began in 2009 to target school aged children (SAC) in six high/moderate endemic HDs and was scaled up in 2010 to all SAC and at-risk adults in the nine high/moderate endemic HDs. In 2016, a SCH impact assessment was conducted in the nine HDs; results showed an overall reduction in prevalence from 42.2% to 20.2%. MDA was subsequently revised to a sub-district (chiefdom) level treatment strategy. In 2022, after five rounds of MDA with effective SAC coverage, another school-based impact assessment was conducted in the same nine HDs. The sampling was statistically powered to estimate chiefdom prevalence; a total of 201 sites were selected using probability proportional to estimated population size of the chiefdoms with special consideration for large towns and small chiefdoms. In each site, a total of 24 children aged 5-14 years were tested. Fresh stool samples were examined by Kato Katz. Urine samples were tested by Haemastix with haematuria positive urines only tested by filtration technique. A total of 4,736 (male: 51%, female: 49%) and 4,618 (male: 51%, female: 49%) children were examined for S. mansoni and S. haematobium, respectively. Overall prevalence for S. mansoni was 16.3% (95% CI: 15.3-17.4), for S. haematobium was 2.0% (95% CI: 1.6-2.4), and for any SCH was 17.7% (95% CI: 16.7-18.8). The arithmetic mean intensity for S. mansoni and S. haematobium was 30.0 epg (95% CI: 24.8-35.2 epg) and 4.0 eggs/10ml (95% CI: 3.9-4.1 eggs/10ml), respectively. Of the 201 sites surveyed, 11 (5.5%) had high prevalence of S. mansoni versus 23 of 60 sites (38%) at baseline and 5 of 40 sites (12.5%) in 2016. Although prevalence remains high in a limited number of communities, SCH prevalence in Sierra Leone has overall reduced significantly. A more focused and intensive strategy could help reach Sierra Leone reach SCH control.

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DISCORDANT CIRCULATING AND MUCOSAL ANTIBODY RESPONSES ELICITED BY SARS-COV-2 INFECTION AND VACCINATION IN A LONGITUDINAL COHORT FROM BRAZIL

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The contribution of mucosal antibody responses to protection from SARS-CoV-2 infection and pathogenicity in humans remains understudied. We examined the systemic and mucosal immune responses elicited by varying exposures to infection and/or vaccination among a community-based cohort of urban slum residents from Salvador, Brazil, followed before and during the pandemic. We collected serum, nasal and saliva samples over the course of two sequential surveys (Survey 1, November 2020 to February 2021; Survey 2, July to October 2021) among 1,570 participants. We selected a stratified sample of 137 participants and examined the relationships of antibody responses within and between the serum, nasal, and salivary compartments. Of the 137 participants, 19 individuals were seronegative, 53 were vaccinated and had no serologic evidence of infection, 30 had experienced one infection, 14 had experienced two infections, and 21 had experienced both infection and vaccination. We found that 10/19 (52.6%, 95% CI 29.5-74.8%) individuals who were unvaccinated and seronegative had detectable antibodies in the nasal compartment, and 12/19 (63.2%, 95% CI 38.6-82.8%) had detectable antibodies in the salivary compartment. Furthermore, mucosal IgA responses remained detectable 6 months after infection. An unsupervised hierarchical clustering analysis identified discordance of antibody responses between the serum, nasal, and salivary compartments. Individuals with high serum neutralization activity against the ancestral, Gamma, Delta and Omicron variants exhibited increased and coordinated antibody response in their mucosal compartments compared to individuals with poor serum neutralization activity. Our findings suggest that measurement of serum antibody responses may underestimate the true prevalence of SARS-CoV-2 exposures and the degree of functionally relevant immunity in previously exposed populations. Various sequences of exposure to infection and vaccination can induce effective mucosal antibody responses and confer protection from infection and severe disease.

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DIFFERENTIAL PROTEOME EXPRESSION IN A DIVERSE POPULATION OF HOSPITALIZED PATIENTS WITH COVID-19

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The role of differential proteome expression in the pathogenesis of COVID-19 remains largely undefined, particularly in diverse racial/ethnic groups of hospitalized patients. As such, proteomic profiling of plasma was performed upon the initial phase of hospitalization (≤ 3 days) in a subset of COVID-19 patients (n=40) admitted to the University of New Mexico Hospital, matched according to age, sex at birth, race/ethnicity, time from admission, duration of symptom onset, and time since first PCR-confirmed infection. Patients were stratified as either (a) severe (n=20): defined as admission to the ICU and/or death, or (b) non-severe (n=20): defined as non-ICU requirements and survival. Proteomic analysis was performed using an aptamer-based technology for which 6,628 circulating proteins were quantified. There were 339 differentially expressed proteins (DEPs) at P<0.05 between the groups: 302 were up-regulated and 37 were down-regulated with a log2 mean fold-change between 3.29 to -1.08. Enrichment analyses revealed that the top-ranked pathway maps were Vascular Endothelial Cell Damage (FDR-adj. P=1.136x10-4) and Blood Coagulation (FDR-adj. P=1.370x10-4). Consistent with this finding, Blood Coagulation emerged as a top process network (FDR-adj. P=4.765x10-3). Canonical network analyses revealed IL6-HSP70-IL18R1-BAFF(TNFSF13B)-CCL2 as a central regulatory interaction with TRAF6 as the convergence hub (14 edges) and NF-kB as the divergence hub (13 edges). Collectively, these proteomic results in diverse populations illustrate that endothelial cell damage and coagulopathy are central pathogenic features of severe COVID-19 in which aberrant intracellular responses to protein folding are a substantial component.

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EXTENSIVE TRANSMISSION OF SARS-COV-2 BQ.1 VARIANT IN A POPULATION WITH HIGH LEVELS OF HYBRID IMMUNITY

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The SARS-CoV-2 BQ.1* variant spread globally in late 2022, yet there is limited data available regarding the transmission and disease severity caused by this variant. This study aimed to determine the incidence and severity of BQ.1* infection in a population with high levels of hybrid immunity. As part of a long-term cohort study, we conducted a prevalence survey during the BQ.1* wave between Nov 16th and Dec 22nd, 2022 in Salvador, Brazil. We performed interviews and collected nasal samples for SARS-CoV-2 antigen and RT-PCR testing and whole genome sequencing. Cumulative incidence was estimated by using RT-PCR positivity and cycle threshold values, together with external data on RT-PCR positivity following infection, to estimate daily probability of infection. Of 535 cohort participants, 54% had a documented SARS-CoV-2 exposure and 74% received COVID-19 vaccination prior to the survey. Among these, 79 (14.3%) had a positive SARS-CoV-2 test with BQ.1* identified in 90.7% of positive samples. The prevalence was highest (32.1%) in the week of Nov 23 – 29th, 2022. The cumulative incidence was estimated to be 56% (95% CI, 36 – 88%). Of 79 positive participants, 38 (48.1%) had a symptomatic illness and a lower proportion had fever (37% vs. 51%, p=0.221) and fulfilled the WHO COVID-19 case definition (47% vs. 70%, p=0.023) than cases identified from the cohort in prior Omicron waves. No participants required medical attention. Early exposure to SARS-CoV-2 during the pandemic was associated with a lower risk of infection during the survey (multivariate OR= 0.50, 95% CI=0.25 – 0.97). By reconstructing transmission dynamics from PCR prevalence data, we found that the BQ.1* variant disseminated widely (attack rate of 56%) despite high population-level hybrid immunity. The lower disease severity associated with BQ.1*, as compared with prior Omicron variants, contributed to significant under-reporting of infection. As observed for BQ.1* in this study, hybrid immunity may provide weak protection against future SARS-CoV-2 variants and may not prevent widespread transmission after their introduction.

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PERFORMANCE OF A NOVEL REALTIME-TIME PCR DEVICE FOR DETECTION OF SARS-COV-2, RESPIRATORY SYNCYTIAL VIRUS AND INFLUENZA VIRUSES FROM AUGUST 2022 TO JANUARY, 2023

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Real-Time PCR (RT-PCR) is the gold standard for the detection of respiratory viruses. Despite high sensitivity and specificity, RT-PCR method is sophisticated, expensive, time-consuming, laboratory-based and unsuitable for point-of-care (POC) use in resource-limited settings. We evaluated the novel Lab-On-An-Array (LOAA) digital real-time PCR (dPCR) analyzer for the detection of SARS-CoV-2, Respiratory Syncytial Viruses (RSV) and influenza viruses type A and B.A cross-sectional multi-centre hospital-based study was conducted between August 2022 to January 2023 in Ashanti and Savannah Regions of Ghana. Oropharyngeal swabs from 356 patients were tested for respiratory viruses by LOAA and RT-PCR simultaneously. Nucleic acids were extracted using Qiagen Viral Mini kit (QIAGEN Diagnostics GmbH, Germany). LOAA tests were done using LOAA dPCR analyzer and GenoplexorTM COVID-19/Flu/RSV Detection Kit (Optolane Technologies Inc, South Korea) while RT-PCR tests were done using Bio-Rad CFX96 and FluoroType SARS-CoV-2/Flu/RSV kits (Hain lifesciences, Germany). Sensitivity, specificity, accuracy, kappa (κ), positive, and negative predictive values (PPV and NPV) were assessed for LOAA using RT-PCR as the gold standard. Overall positivity rate for respiratory viruses was 106 (29.8%) for LOAA and 116 (32.6%) for RT-PCR. The sensitivity of LOAA to detect RSV was 87.8% (95%CI: 84.1-90.9), SARS-CoV-2 87.5% (95%CI: 84.1- 90.9), influenza B 80.7% (95%CI: 76.5-84.8) and influenza A 75.0% (95% CI: 70.5-79.5). Specificity for LOAA was ≥98.0%. The accuracy of LOAA was 98.9% for SARS-CoV-2, 98.0% for both RSV and influenza A, and 97.8% for Influenza B. The PPV for RSV (97.7%), SARS-CoV-2 (95.5%), Influenza B (92.6%), and Influenza A (69.2%). The NPV was ≥98.0% for all respiratory viruses. There was very good agreement for RSV (κ=0.91), SARS-CoV-2 (κ=0.91), influenza

B (κ=0.85), and substantial for influenza A (κ=0.71).LOAA showed strong diagnostic agreement and comparable accuracy with RT-PCR for detecting SARS-CoV-2, RSV, and influenza B infections and moderate agreement for influenza A in low-resource clinical settings.

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PATHWAYS & MORTALITY OF UNDER 5 CHILDREN IDENTIFIED AS SEVERE CASES WITH ROUTINE PULSE OXIMETRY USED INTO THE INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESS GUIDELINES AT PRIMARY HEALTH CENTERS IN WEST AFRICA, JUNE 2021 TO JUNE 2022

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The Integrated Management of Childhood Illness (IMCI) guidelines for children under5 is a symptom-based algorithm, adapted for resource-limited countries at primary health center (PHC) level. To improve the diagnosis & care-management of severe cases with hypoxemia, the AIRE project, UNITAID-funded, has implemented the routine Pulse Oximeter (PO) use into IMCI consultations at PHCs in Burkina Faso, Guinea, Mali & Niger. The purpose of this study was to describe the care pathway & mortality of children with serious illness. In 16 AIRE PHC research sites (4/country), all under5 children attending IMCI consultations with routine use of PO & classified as severe cases were enrolled in a prospective short cohort study with 14-Days of follow-up, with parental consent. From June 2021 to June 2022, 39,360 children attended IMCI consultations at the research PHCs. Among the 3,163 identified as severe cases, 1998 were followed of whom 463 (23.2%) were referred to district hospital (DH) while 1499 (75%) were treated at PHC & 36 (1.8%) were neither referred nor treated at PHC. The D14-mortality rate was at 4.7% (95/1998 - 95% CI: 3.9-5.8). It was significantly different among children managed at hospital level with 14.7% (68/463 - 95% CI: 11.5 -18.2) & those treated at PHC level with 1.3% (19/1499 - 95%CI: 0.8 -2.0). Among the 1998 followed, severe hypoxemia (SpO2<90%) was detected in 142 children of whom 117 (82.4%) were referred at DH vs 17 (12%) treated at PHC. Their D14-mortality rate was estimated at 26.1% (37/142; 95%CI: 19.1-34.1). In conclusion, unexpectedly, referral of severe case to hospital is not systematic even for hypoxemia for whom oxygen therapy was not available at PHC level. The D14-mortality rate remain high especially at hospital level. The proper management of severe case (transfer and oxygen therapy) remain challenges in West Africa.

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IMPACT OF PNEUMOCOCCAL CONJUGATE VACCINES ON PENICILLIN RESISTANT STREPTOCOCCUS PNEUMONIAE

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The use of Pneumococcal Conjugate Vaccine (PCV) has effectively reduced antimicrobial resistance in pneumococci. This study assessed the prevalence of penicillin resistance in carriage pneumococci from children under 2 years old pre-PCV (2006-2008) and after PCV13 (2018-2019) introductions. In this study nasopharyngeal swabs were collected from healthy children <2yo in Lima, Peru before PCV (n=999) and after PCV13 (n=996). We whole-genome sequenced all pneumococcal isolates from the carriers on an Illumina MiSeq. In silico serotype and antimicrobial susceptibility were predicted from the genomes using CDC analysis pipeline. Changes were indicated by odds ratio (OR) and 95% confidence interval using logistic regression. Logistic regression models were adjusted for sex, age, hospital, previous hospitalization, attending daycare, and the number of children at home. The pneumococcal carriage rate was 25% (253/999) in pre-PCV and 19% (193/996) in post-PCV13 period. The prevalence of penicillin-non-susceptible isolate did not change between pre-PCV and post-PCV13 periods (12% vs. 14%, p-value>0.05). However, the odds ratio of penicillin-resistant pneumococcal carriers due to PCV13 vaccine serotypes decreased from 10% to 3% (adjusted OR= 0.29, 95% CI 0.19-0.45; p value <0.001). Conversely, the odds of penicillin-resistant pneumococcal carriers due to non-PCV13 vaccine serotypes increased from 3% to 10% (adjusted OR= 4.64, 95% CI 2.85-7.54, p value <0.001). The PCV has reduced overall penicillin resistance in pneumococci from healthy children in Peru. However, penicillin resistance was observed to increase in pneumococci that are not targeted by PCV13.

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MULTIPLEXED ANTIGEN SPECIFIC ANTIBODY FC PROFILING FOR POINT OF CARE DIAGNOSIS OF TUBERCULOSIS

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Tuberculosis (TB) is a leading cause of infectious disease related deaths despite the existence of effective treatments. Lack of accurate yet rapid and inexpensive diagnostics contributes to a significant proportion of TB deaths. Key challenges in TB diagnostics include the heterogenous spectrum of disease, ranging from latent TB infection (LTBI) to active TB (ATB), and difficulty in obtaining and processing sputum samples, especially from children. Antibody (Ab) titer-based serological tests, which are used as a simple means to detect many infections, have failed for TB. Recently, we and others have observed that the inflammatory state of Mtb-specific Abs, driven by changes in Fc-glycosylation, differs across LTBI and ATB. Here, we report the discovery of a M. tuberculosis (Mtb)-specific Ab Fc profile based biomarker for TB to distinguish ATB from LTBI and a method for its point-of-care (POC) detection using an inexpensive, multiplexed and high throughput optical biosensing method. First, highly multiplexed bead-based Ab biophysical profiling (both Fab and Fc) was applied to sera from a set of ATB and LTBI patients. Antigen-coated barcoded beads were incubated with serum and probed with fluorescently-labeled isotype and subclass probes, tetramerized Fc receptors and lectins. Machine-learning based methods (LASSO-SVM) applied to the resultant high-dimensional dataset, revealed a minimal Ab Fc profile biomarker. Next, a POC detection method was developed where multiple TB antigens (Ag85A, PPD, Esat6, HspX) immobilized on laser cut PDMS microwells, are incubated with drops (<10μL) of TB patient serum. Horseradish peroxidase labelled Fc and lectin probes are added, followed by silver substrates to produce a quantitative and sensitive enzymatic metallization based optical readout which can be read out using a cellphone camera. Application of this to two geographically distinct cohorts of TB patients (South Africa and Vietnam, n=40), achieved a high diagnostic accuracy (AuROC~0.9). Thus, a non-sputum based Ab Fc profile biomarker for TB and a method for its inexpensive yet accurate POC detection from a drop of serum was developed.

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THE IMPACT OF NEXT-GENERATION DUAL-ACTIVE INGREDIENT LONG-LASTING INSECTICIDAL NET DEPLOYMENT ON INSECTICIDE RESISTANCE IN MALARIA VECTORS DURING A THREE-YEAR CLUSTER-RANDOMIZED CONTROLLED TRIAL IN TANZANIA

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Insecticide resistance among malaria vector species is now a pervasive problem, which threatens to jeopardize global disease control efforts. Novel vector control tools, including long-lasting insecticidal nets (LLINs) incorporating new active ingredients (A.I.s), with different modes of action, are urgently needed to delay the evolution and spread of resistance.During a four-arm cluster-randomised controlled trial in Tanzania, evaluating the effectiveness of three dual-A.I. LLINs compared to pyrethroid-LLINs (PY-LLINs), we measured longitudinal phenotypic and genotypic insecticide resistance profiles among 47,258 female Anopheles mosquitoes collected over 36 months. In the PY-LLIN arm, a significant increase in alpha-cypermethrin and permethrin resistance intensity and concomitant decline in mortality, following exposure to the synergist PBO, was observed in An. funestus s.l. (the predominant vector species complex) over 24 months. A similar phenomenon was apparent in the pyriproxyfen-PY LLIN arm over three years, with the greatest escalation in resistance intensity evidenced in the PBO-PY LLIN arm. The chlorfenapyr-PY LLIN arm had no significant effect on pyrethroid resistance, supported by minimal reductions in chlorfenapyr susceptibility. By comparison, An. funestus s.l. populations displayed limited sterility following pyriproxyfen exposure. Highly over-expressed detoxification enzymes presented dynamic patterns of selection throughout the trial. Phenotypic data strengthened trial epidemiological findings; chlorfenapyr-PY LLINs provided superior protection from malaria across multiple transmission seasons, with little impact on insecticide resistance. Rapid fifty-fold pyrethroid resistance intensification in the PBO-PY LLIN arm and pre-existing tolerance of vector populations to pyriproxyfen in the trial site may explain the poorer performance of these two interventions on malaria outcomes. Ongoing work is elucidating potential mechanisms driving cross-resistance between pyrethroids and novel A.I.s, to better inform pragmatic design of resistance management schemes.

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WHOLE GENOME SEQUENCING AND RNASEQ IDENTIFIES POTENTIAL MOLECULAR MARKERS OF INSECTICIDE RESISTANCE WITHIN THE ANOPHELES GAMBIAE SPECIES COMPLEX

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The Anopheles gambiae species complex represents the major malaria vector species across the African continent. Insecticide-based vector control is the single most important tool in combating malaria, with insecticide treated bed nets being the most important intervention. All bed nets contain insecticides from the pyrethroid class leading to widespread insecticide resistance to these chemistries. Despite the importance of tracking the evolution and spread of new and described resistance mechanisms, the number of markers to track insecticide resistance in endemic settings are minimal. Here, we use whole genome sequencing on seven insecticide resistant colony populations from West Africa, a foci of intense insecticide resistance. Within this study 157 individual female mosquitoes from insecticide resistance An. coluzzii, An. gambiae and An. arabiensis were analysed. The results reveal evidence of shared haplotypes between An. arabiensis and An. coluzzii at loci putatively involved in insecticide resistance. Of particular note is evidence of the 'new' kdr mutation I1527T in An. arabiensis which was confirmed using TaqMan analysis. Further, a clear haplotype spanning the GSTE cluster was shared between An. arabiensis and several An. coluzzii populations, including four non-synonymous SNPs in GSTE1 and GSTE8. To determine the impact of these SNPs on pyrethroid resistance, two colonies were generated differing in this haplotype and changes to resistance scored. Finally, the availability of RNAseq data for these populations also allowed elucidation of potential eQTL markers linked with resistance loci.

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EFFICACY OF DUAL-ACTIVE INGREDIENT LONG-LASTING INSECTICIDAL NETS RELATIVE TO STANDARD NETS, AGAINST HIGHLY PYRETHROID-RESISTANT ANOPHELES MOSQUITOES IN TANZANIA: AN EXPERIMENTAL HUT TRIAL

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The global fight against malaria vectors has been threatened by widespread insecticide resistance across multiple chemical classes. There is a need for new vector control tools with different modes of action to combat the issue of resistance. This study aimed to evaluate the bio-efficacy of Olyset Plus (combining PBO and permethrin), Interceptor G2 (chlorfenapyr and alpha-cypermethrin), Royal Guard (pyriproxyfen and alpha-cypermethrin) long-lasting insecticidal nets (LLINs), compared to a standard pyrethroid-only net (Interceptor) across their operational lifespan in experimental hut trials. a total of thirty nets were withdrawn from the community at 12, 24 and 36 months, as part of a large-scale cluster-randomized controlled trial. Hole size and number were recorded. A Latin square design was used to rotate net type and sleepers between huts. The following morning mosquitoes were collected, and mortality monitored every day up to 72 hours. Live, blood fed female Anopheles at 72 hours, collected from the huts with Royal Guard, Interceptor and untreated nets were dissected to assess the effect of pyriproxyfen on egg development. Interceptor G2 LLIN induced significant superior 72-hour mortality compared to standard LLINs at 12 months (43% vs 13%); 24-hour mortality was also higher with Royal Guard LLINs compared to standard LLINs (21% vs 13%), and marginally higher also with Olyset Plus (19%). Seventy-two-hour mortality was still slightly higher at 24 months for Interceptor G2 LLINs compared to standard LLIN (24% vs 11%). None of the other nets showed higher mortality at 24 months. The effect of the second active ingredient or synergist was not observed at 36 months for any of the LLINs. The effect of pyriproxyfen on Anopheles mortality was not observed at any of the time point. All dual active ingredient (dual-A.I.) LLINs performed better than standard Interceptor nets up to 12 months of field use.

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EVIDENCE SUPPORTING DEPLOYMENT OF NEXT GENERATION INSECTICIDE TREATED NETS IN BURKINA FASO: BIOASSAYS WITH CHLORFENAPYR AND PIPERONYL BUTOXIDE INCREASE MORTALITY OF PYRETHROID-RESISTANT ANOPHELES GAMBIAE

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Before deploying alternative insecticide treated nets (ITNs) on a large scale, it is crucial to characterize the resistance profiles of primary malaria vector species for evidence-based decision making. Anopheles gambiae (s.l.) were collected in 2020 from 15 sites located throughout Burkina Faso for synergist and WHO bottle bioassays with chlorfenapyr at a dose of 100µg/bottle. An. gambiae s.l. were found resistant to all pyrethroid insecticides in all sites. The piperonyl butoxide synergist (PBO) pre-exposure followed by deltamethrin restored full susceptibility in one site. The PBO pre-exposure followed by permethrin partially restored susceptibility in 12 sites. There was no significant increase in permethrin mortality after PBO pre-exposure in 3 out of 15 sites; while in Seguenega, Orodara and Bobo-Dioulasso there was a significant increase in mortality. Susceptibility to chlorfenapyr was confirmed in 14 sites. Based on these results, PBO+deltamethrin ITNs would likely provide greater protection than pyrethroid only nets. Since susceptibility in bioassays was not restored in most sites following pre-exposure to PBO, chlorfenapyr ITNs may likely provide greater protection as susceptibility was recorded to chlorfenapyr in nearly all sites. This study provides evidence supporting the 2019 mass distribution of next generation ITNs, such as Interceptor G2 nets and PBO nets, rather than pyrethroid only ITNs

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PHENOTYPIC RESISTANCE TO PYRETHROID ASSOCIATED TO METABOLIC MECHANISM IN VGSC-L995F RESISTANT-ANOPHELES GAMBIAE MALARIA MOSQUITOES

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The indiscriminate use of insecticides in agriculture and public health lead to a selection of resistance mechanisms in malaria vectors compromising vector control tools and strategies. This study investigated the metabolic response in the Vgsc-L995F Anopheles gambiae Tiassalé resistance strain after long-term exposure of larvae and adults to deltamethrin insecticide. We exposed, over 20 generations, Vgsc-L995F An. gambiae Tiassalé strain larvae to deltamethrin (LS) and adults to PermaNet 2.0 (AS) and combining exposure at larvae and adult stages (LAS) and compared to unexposed (NS) group. All four groups were subjected to the standard World Health Organization (WHO) susceptibility tube tests using deltamethrin (0.05%), bendiocarb (0.1%) and malathion (5%). Vgsc-L995F/S knockdown-resistance (kdr) mutation frequency was screened using multiplex assays based on TaqMan real-time polymerase chain reaction (PCR) method. Additionally, expression levels of detoxification enzymes associated to pyrethroid resistance, including CYP4G16, CYP6M2, CYP6P1, CYP6P3, CYP6P4, CYP6Z1 and CYP9K1, and glutathione S-transferase GSTe2 were measured. Our results indicated that deltamethrin resistance was a response to insecticide selection pressure in LS, AS and LAS groups, while susceptibility was observed in NS group. The vectors showed varied mortality rates with bendiocarb and full susceptibility to malathion throughout the selection with LS, AS and LAS groups. Vgsc-L995F mutation stayed at high allelic frequency level in all groups with a frequency between 87% and 100%. Among the overexpressed genes, CYP6P4 gene was the most overexpressed in LS, AS and LAS groups. Long-term exposure of larvae and adults of Vgsc-L995F resistant-An. gambiae Tiassalé strain to deltamethrin and PermaNet 2.0 net induced resistance to deltamethrin under a significant effect of cytochromes P450 detoxification enzymes. These outcomes highlights the necessity of investigating metabolic resistance mechanisms in the target population and not solely kdr resistance mechanisms prior the implementation of vector control strategies for a better impact.

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RNASEQ-BASED GENE EXPRESSION PROFILING OF THE CHLORFENAPYR -RESISTANT ANOPHELES GAMBIAE FROM CAMEROON HIGHLIGHTS DOWN-REGULATION OF MAJOR PYRETHROID RESISTANCE GENES

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Chlorfenapyr (CFP) has shown great promise at controlling pyrethroid-resistant malaria vectors, but its sustained use can be threatened by the evolution of CFP resistance. An understanding of how CFP interacts with other insecticides used in vector control and the molecular basis of CFP resistance is needed to achieve successful malaria control. Here, we assessed the resistance status of the major malaria vectors to CFP across Africa and performed RNA-seq to detect the major genes conferring CFP resistance. Resistance to CFP (100µg/ml) was detected in Anopheles gambiae populations from DRC (Kinshasa) (mortality rate: 64.3 ± 7.1%), Ghana (Obuasi) (65.9 ± 7.4%), and Cameroon (Mangoum ;75.2±7.7% and Nkolondom; 86.1 ± 7.4) whereas all An. funestus populations were fully susceptible. After RNA-seq, commun metabolic genes ussually associated with pyrethroid resistance (e.g: CYPs, GSTs···) were down-regulated in CFP-resistant samples compared to the susceptible lab-strain Kisumu. Carboxylesterases and transcriptions factors were among the predominant over-expressed genes in CFP-resistant mosquitoes with fixed mutations detected and reduced susceptibility observed in the resistant strain. Also, a negative association was observed between the L1014F-kdr mutation and CFP resistance with a greater frequency of homozygote-resistant mosquitoes among the dead after exposure compared to alive (OR=0.5; P=0.02).This study reveals a greater risk of CFP resistance in An. gambiae populations than in An. funestus although most pyrethroid-resistant individuals were more vulnerable to this insecticide. Ongoing functional validation will help to establish the contribution of carboxylesterases and other transcription factors or P450/GST's suppressors to CFP resistance and to design a DNA-based diagnostic tool for the rapid detection and monitoring of the resistant markers in the field. This will help preserve the efficacy of chlorfenapyr-based control interventions such as Interceptor G2 which is currently largely distributed across Africa for malaria control.

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INSECTICIDE RESISTANCE AND WHOLE TRANSCRIPTOME PROFILES OF ANOPHELES FUNESTUS POPULATION IN WESTERN KENYA

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Anopheles funestus is an efficient vector of Plasmodium falciparum malaria in Africa. The resurgence of An. funestus in western Kenya was partly attributed to insecticide resistance. However, there is a limited body of evidence on the molecular basis of pyrethroid resistance in western Kenya. Indoor resting An. funestus mosquitoes were collected by aspiration in Bungoma, Teso, Siaya, Port Victoria and Kombewa in western Kenya. The F1 progenies were exposed to deltamethrin (0.05%), permethrin (0.75%), DDT (4%) and pirimiphos-methyl (0.25%) following WHO guidelines for insecticide susceptibility test. A synergist bioassay using Piperonyl butoxide (PBO) (4%) was conducted to determine cytochrome P450s role in pyrethroid resistance. Illumina RNA-seq was performed on a pool of specimens which were 1) Resistant, 2) susceptible and 3) unexposed to unveil the molecular mechanisms of pyrethroid resistance. Pyrethroid resistance was observed in all the sites with a mortality rate (MR) ranging from 11% to 87%). Port Victoria had the highest level of resistance to permethrin (MR=53%, n=217) and deltamethrin (MR=11%, n=100) pyrethroids. Teso had the lowest level of resistance to permethrin (MR=70%, n=100) and deltamethrin (MR=87%, n=100). Resistance to DDT was observed only in Kombewa (MR=89%, n=100) and Port Victoria (MR=85%, n=100). A full susceptibility to pirimiphos- methyl (0.25%) was observed in all the sites. PBO synergist assay revealed high susceptibility (>98%) to the pyrethroids in all the sites except for Port Victoria (MR=96%, n=100). Whole transcriptomic analysis revealed that the main enzyme families associated with pyrethroid resistance are cytochrome P450s, GSTs, COEs, cuticular proteins and salivary gland proteins. The highly upregulated genes include P450s (CYP4H18, CYP4H17, CYP9J3, CYP4G16, CYP6Y1, CYP18A1, AFUN008357, CYP4D17, AFUN019401 and CYP4C25), GSTs (GSTE2, GSTE1, GSTE5, GSTU2, GSTU3 and GSTD6), and others (AFUN002514, AFUN010203, AFUN016508, AFUN000373 and AFUN001273). This study unveils novel insights into the molecular mechanisms underlying the pyrethroid resistance of An. funestus in western Kenya.

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THE THREE-DIMENSIONAL APPROACHES BY MULTIPLE CORRESPONDENCE ANALYSIS CAN DIFFERENTIATE LEPROSY DISEASE STATES AND HOUSEHOLD CONTACTS WITH HIGH ACCURACY

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The development of clinical leprosy is multifactorial; however, there are still gaps in our knowledge about risk factors and predictors of disease. Multiple Correspondence Analysis (MCA) is a statistical tool that can characterize associations between immunologic and sociodemographic parameters and the presence/absence of M. leprae infection. MCA works based on the reduction of dimensionality and considers each variable as a dimension of space. We conducted MCA on data from 101 participants from Minas Gerais, Brazil: 14 paucibacillary leprosy [L(PB)], 14 multibacillary leprosy [L(MB)], 42 household contacts of PB disease HHC(PB), and 31 household contacts of MB disease HHC(MB). Blood was collected for cytokine measurement and interviews were done to obtain demographic data. The MCA allowed for the disposition and association of laboratory and sociodemographic variables in the Euclidean space with two Dimensions representing more than 40% of the total variability of parameters (Dimension 1 [DM1 = 28.73%, x axis] and Dimension 2 [DM2 = 15.36%, y axis]. Cytokines production from M.leprae-stimulated culture allowed for better discrimination of the study groups, by showing defined clusters according to the operational classification of each group. The cytokine IFN-γ was more associated with (Dim2), as was the L(PB) group (y-axis associated). On the other hand, cytokines IL-4 and IL-10 were more related to (Dim1), in the same way as the L(MB) group, the x-axis associated group. Using these associations, the mathematical model then classified the individuals with an accuracy of 0.8317. The sensitivity and specificity for L(PB) (0.7778, 1.00); L(MB) (0.8333, 0.9550); HHC(PB) (0.8409, 0.9123); and HHC(MB) (0.8519, 0.8919) were respectively, established. By incorporating immunological and demographic parameters in an advanced model, MCA allowed for the classification of leprosy cases and contacts with high sensitivity and specificity. Consequently, this approach holds promise for using these statistical models for predicting disease and complementing clinical diagnosis.

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LEPTOSPIROSIS SEROPREVALENCE AND RISK FACTORS AMONG SLAUGHTERHOUSE WORKERS IN BURKINA FASO

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Leptospirosis is an occupational disease affecting risk groups that are exposed to animal reservoirs. Given the general lack of awareness of the disease and difficulties in its diagnosis, the epidemiological status of human leptospirosis in Burkina Faso has not been well defined. The objective of this study was to determine the seroprevalence and risk factors of leptospirosis among slaughterhouse workers in Burkina Faso. We have performed a cross-sectional survey of slaughterhouse workers from Ouagadougou and Bobo Dioulasso between March and April 2021. Questionnaires were used to collect information from these workers on socio-demographic characteristics, work activities, knowledge of zoonotic diseases, and risk behaviors. Blood was collected by venipuncture and serum samples were tested for leptospirosis using Enzyme-Linked Immuno Assay (ELISA): “SERION ELISA classic Leptospira IgG and IgM”, and Microscopic Agglutination Test (MAT). Of the 172 subjects investigated, 28 (16.28%) were found positive for leptospirosis using ELISA or MAT. The main Leptospira infecting serogroups were: Mini, Autumnalis, Canicola, Copenhageni, L. mayottensis (ND), Icterohaemorrhagiae, Pyrogenes/ Tarassovi (cross reaction), Panama, and Ballum. Risk factors included: residence in Bobo Dioulasso (Odds Ratio ajusté: ORa=2.53; 95% CI: 1.11-15.00; p = 0.02), working at the bleeding station (ORa=5.51; 95% CI: 1.19-29.5; p = 0.03), contact with feces and urine (ORa=2.50; 95% CI: 0.97-6.65; p = 0.04), and the practice of agriculture outside the slaughterhouse (ORa=4.28; 95% CI: 0.79-20.80; p = 0.05). However, working at the stunning station (ORa=3.57; 95% CI: 0.79-15.00; p = 0.08) had a higher risk of Leptospira seropositivity without statistical significance. These findings indicate that a significant proportion of slaughterhouse workers is being exposed to pathogenic Leptospira. Public-health interventions against leptospirosis are needed to target this occupational group.

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LEPTOSPIROSIS OUTBREAK AFTER HURRICANE FIONA, PUERTO RICO, 2022

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Leptospirosis is a bacterial disease endemic to Puerto Rico, which reported 51% of all cases nationally during 2016-2019 and historically reported increased cases after hurricanes. On September 18, 2022, Hurricane Fiona hit Puerto Rico, leading to major flooding. In response, we investigated leptospirosis cases and characterized temporal and spatial patterns. The Puerto Rico Department of Health expanded leptospirosis laboratory testing, increased messaging to providers, and used existing surveillance to investigate cases reported with clinical suspicion for leptospirosis. Confirmed cases had a positive PCR result for pathogenic Leptospira, probable cases only had a positive IgM result, and suspected cases had negative or no laboratory results. We compared cases in the 37 weeks before Hurricane Fiona (January 2-September 17, 2022) and during the 11 weeks after Hurricane Fiona (September 18-December 3, 2022). Before Hurricane Fiona, 173 leptospirosis cases were reported including 16 (10%) confirmed, 90 (52%) probable, and 67 (38%) suspected cases. After Hurricane Fiona, 743 cases were reported, including 31 (4%) confirmed, 84 (12%) probable, and 628 (84%) suspected cases; median age was 41 (interquartile range: 25-59) years, 486 (65%) were male, 375 (50%) were hospitalized, and 6 (1%) died. After Hurricane Fiona, the mean weekly number of confirmed or probable cases was 10.5, 3.6 (95% CI: 2.5-5.3) times higher than before (2.9 cases). Confirmed and probable cases were identified in 42/78 (54%) municipalities before Hurricane Fiona versus 47/78 (60%) municipalities after; 32 municipalities reported cases in both periods. For both periods, the four municipalities with the highest attack rates were western inland municipalities. We identified an outbreak of leptospirosis that lasted >2 months after Hurricane Fiona, using existing surveillance built after previous hurricanes. In endemic areas, health departments should reinforce leptospirosis surveillance and increase clinician awareness, particularly during hurricane season.

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OCULAR CHLAMYDIA TRACHOMATIS INFECTION MONITORING WITHIN DISTRICT-LEVEL TRACHOMA IMPACT AND SURVEILLANCE SURVEYS: RESULTS AND LESSONS LEARNED 2018-2021

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A World Health Organization (WHO) report has recently recommended monitoring for ocular Chlamydia trachomatis (Ct) infection within districts experiencing persistent trachoma. The Trachoma Control Program in Amhara, Ethiopia, has monitored ocular Ct since 2011 to provide prevalence data at the zonal and regional levels. Beginning in 2018, the Program has focused on collecting Ct data to generate district level estimates with the aim of better understanding infection patterns within trachoma persistent districts. Trachoma impact surveys (TIS) and trachoma surveillance surveys (TSS) conducted in the Amhara Region of Ethiopia as part of this study were population-based, multi-stage cluster random surveys. Persistent districts were defined as having ≥2 trachoma impact surveys (TIS2) with a trachomatous inflammation-follicular (TF) ≥5%. Following a household questionnaire, certified graders assessed participants for trachoma signs using the WHO simplified grading system. After grading, children ages 1-5 years were swabbed for infection. All samples were pooled 5 samples to 1 pool and tested using the Abbott Real Time PCR at the Amhara Public Health Institute. Between 2018 and 2021, Ct monitoring was included in 35 TIS and 4 TSS. Among the TIS districts, 34/35 were considered persistent districts (16 TIS2, 17 TIS3, 1 TIS5). A total of 17,534 children ages 1-5 years were swabbed in 1170 communities. Among TIS districts, the TF ranged from 4.1% to 42.6%, and the trachomatous inflammation-intense (TI) ranged from 0.05% to 6.6%. The mean, standard deviation (SD) and range of Ct infection among TIS districts overall was 6.0% (6.8), 0-34.4%, while among districts with TF ≥30% it was 15.2% (10.2), 7.1-34.4%. Among the 4 TSS, 2 districts had Ct infection, 1 district with TF <5% (Ct=1.2%) and 1 district with TF ≥5% (Ct=2.2%). Across all 39 districts, the correlation between Ct and both TF (r=.67) and TI (r=.72) was high. Considerable Ct infection was present among trachoma persistent districts in Amhara. The experience from Amhara demonstrated that with the proper systems and processes in place, monitoring Ct infection at a programmatic scale is possible.

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PHOTOGRAPHIC GRADING OF TRACHOMATOUS SCARRING AMONG ADULTS IN TRACHOMA ENDEMIC AMHARA REGION OF ETHIOPIA

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Trachomatous scarring has been shown to progress regardless of active Chlamydia trachomatis infection, indicating that drivers may be unrelated to ongoing transmission. Scarring prevalence has been associated with older age, and women are more likely to develop signs of severe trachoma such as entropion and trichiasis. This study aimed to characterize the magnitude of scarring in a trachoma endemic setting using a validated 5-point severity scale and to elucidate contributing factors to different stages of scarring. This analysis used conjunctival photographs collected during trachoma impact surveys conducted in 2017 within Amhara, Ethiopia. Photographs of left and right upper tarsal conjunctiva of adults (ages >15 years) in 10 survey districts were collected by a trained photographer. Two graders, trained at Johns Hopkins Hospital and masked to each other's scores, examined each photograph for signs of scarring to record eye-level data based on a 5-point severity scale. Concordant grades were aggregated to the participant level. Discordant grades were adjudicated by another experienced grader. Scarring scores were generated for 729 individuals and 19 individuals were excluded due to poor photograph quality. The mean age of the sample was 38 years and 62.8% were female. Overall, most cases (19.9%) fell within the highest level of scarring category (S4), categorized as scarring comprising more than 90% of the upper tarsal conjunctiva, compared to the prevalence of S3a and b (11%), S2 (8%), and S1 (18.8%). Scarring at every stage was observed among the youngest age group (15-19 years old). Older participants, particularly those over age 60 years, experienced a greater burden of scarring than their younger counterparts, with an S4 prevalence reaching 32.6%. While early stages of scarring were more comparable between women and men, the prevalence of severe scarring (S4) among women was 1.74 times the prevalence observed among men (CI: 1.14-2.7, p<0.01). The prevalence of trachomatous scarring, and its potential for progression to trichiasis, may prove a considerable barrier to achieving the elimination of trachoma as a public health problem.

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IMPACT OF PARTNERS IN SCALING UP THE PREVENTION OF BLINDNESS FROM TRACHOMA IN SOUTH SUDAN

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South Sudan has one of the region's most significant burdens of Neglected Tropical Diseases (NTDs). Out of the 17 NTDs identified by the World Health Organization (WHO), South Sudan harbors 13. Trachoma, an infectious disease caused by Chlamydia trachomatis, is one of the causative agents of preventable, irreversible blindness worldwide. The Ministry of Health (MoH) engaged and collaborated with partners in trachoma surveys, mass drug administration, and trachomatous trichiasis (TT) surgeries to eradicate trachoma. One of the strategies to eliminate trachoma is developing a system that can identify and manage incident TT cases and have the financial resources to implement these strategies. To show the results of the collaborative efforts of the MoH with partners in reducing the backlog of TT in some of the endemic areas, we reviewed the data collected in areas where activities had been conducted by Christian Blind Mission (CBM) project in Unity State (UNS) in Mayom county and Ruweng Administrative Area (RAA) in Abiemnom county, and the Ophthalmological Association of South Sudan (OASS) in Jonglei State (JS) in Old Fangak, Ayod, Akobo, and Waat counties). Out of the 9,632 patients who attended the trachoma program services, 59.5% (5,728) were from JS, 31% (2,988) from RAA, and 9.5% (916) from UNS. TT cases were 21.7% (2,094) of the screened cases, in which the majority, 49.7% (291), were from JS, 36.4% (762) from RAA, and 13.9% (291) from UNS. In addition, a total of 54.3% (2,272) underwent trachoma lid correction surgery, with 53.6% (1,055) in JS, 25.3% (576) in RAA, and 21.1% (479) in UNS. The number of males and females who received eyelid surgery was 74.5% (1,713) and 25.5% (579), respectively. Through collaborative efforts with partners, the MoH has reached a milestone in increasing access to TT surgeries to prevent corneal scarring and irreversible blindness in the affected regions. Urgent scaling up of the program is needed in the endemic/hyper-endemic states with the involvement of different partners, using integrated approaches, capacity building, and community initiatives to reach the global elimination targets for trachoma in South Sudan.

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AN RNA VACCINE FOR PLAGUE

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Plague is a dangerous zoonotic disease which can present in two forms: bubonic and pneumonic. The death rate is 50 to 70 % for the bubonic form and can reach 100 % for the pneumonic form if not treated properly. Despite the threat that this disease poses, no approved vaccine is currently available for prevention. Self-amplifying RNA vaccine for F1 and V antigen of Yersinia pestis were prepared, formulated in 20 % v/v alhydrogel and tested on mice model. Groups of OF1 mice (8/group) were immunized by the intra-muscular route with the saRNA vaccine at 1 µg (group 1 and 4) and 5 µg (group 2 and 5) using 2 immunizations (at day 0, then boost dose at day 28). Results were then compared to a positive control those immunized with a reference vaccine (group 6) and the negative controls which consisted of the injection of equivalent doses of irrelevant RNA in LNP (group 3 and 7) or 20 % v/v alhydrogel (group 8). Immunized mice were challenged with Y. pestis at day 56 (28 days post-boost) at doses of 180 or 1800 cfu and monitored for 14 days. Spontaneous deaths not related to vaccine dose-level and to plague were observed in group 1, 2 , 4, 7 and 8 (1death/group). RNA vaccine protected 5 of 7 mice at either 1µg or 5µg for both of the challenge doses compared to just 1 survivor in the negative control groups (group 3, 7 and 8) and to the reference vaccine which protected 7 out of 8 mice for the challenge at 1800 cfu. Post-mortem culture of the survivor's spleen on CIN agar and BHI broth were negative for Y. pestis. SaRNA vaccine showed protective effect against plague in these preliminary results giving this approach a potential for further development.

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A SALIVA-BASED, DNA-EXTRACTION-FREE APPROACH FOR THE MOLECULAR DETECTION OF STREPTOCOCCUS PNEUMONIAE

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Streptococcus pneumoniae is a common cause of severe diseases including meningitis, pneumonia, and sepsis. Pneumococcal carriage is a prerequisite for pneumococcal disease and surveillance is crucial for evaluating the performance of current vaccines and informing new vaccination strategies. In recent years, molecular methods have improved the sensitivity of pneumococcal carriage detection as compared to the gold standard culture-based method. However, nucleic acid extraction from samples collected is resource-intensive, limiting scalability for extensive surveillance particularly in low-resource settings. We previously developed a saliva-based PCR test for SARS-CoV-2, having identified that nucleic acid extraction can be omitted and replaced with a simple enzymatic lysis or heat treatment step without compromising the accuracy and efficiency of testing. Here, we compared pneumococcus detection in saliva samples collected weekly from an observational longitudinal study in childcare centers in New Haven (CT, USA), using our standard protocol (culture-enrichment followed by DNA extraction) and a DNA extraction-free protocol (addition of proteinase K then incubation at 95°C for 5 min). The presence of pneumococcus was determined by qPCR detection of pneumococcal genes, piaB and lytA, when Ct values <40 for both targets. A total of 754 saliva samples were collected from 92 children (median age 3.65 years; IQR:2.46-4.78). Pneumococcus was detected in 356 (47.2%) samples by the extraction-free protocol and in 367 (48.7%) samples by the culture-enrichment protocol. There was a substantial agreement (Cohen's kappa: 0.62) and a high Ct-value correlation (r=0.92) between the two methods, though the extraction-free protocol reported lower bacterial loads (ΔCt -3.16, $p<0.05$). Our findings suggest that this DNA-extraction-free protocol offers a cost-effective alternative to the resource-intensive culture-enrichment method for pneumococcal carriage detection and offers a sustainable approach for pneumococcal carriage surveillance particularly in resource-limited settings.

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PNEUMOCOCCAL CARRIAGE IN THE SAHEL REGION OF BURKINA FASO BEFORE A 13 VALENT PNEUMOCOCCAL CONJUGATE VACCINATION CAMPAIGN

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Burkina Faso introduced 13-valent pneumococcal conjugate vaccine (PCV13) among infants in 2013 and subsequently achieved more than 90% three-dose coverage nationally. PCV13 coverage in the Sahel region has been substantially lower due to an ongoing security crisis, resulting in reduced access to health services and an increased number of internally displaced persons. In 2022, a PCV13 catch-up campaign was conducted among children aged 9-59 months in the Dori and Gorom-Gorom districts of the Sahel region. We conducted a cross-sectional, age-stratified

pneumococcal carriage study in Dori to describe vaccine-type (VT) carriage before the catch-up campaign. Healthy individuals were recruited into five age groups: 1 month to less than 1 year, 1 year, 2-4 years, 5-14 years, and more than 15 years. We collected nasopharyngeal swabs (participants of all ages) and oropharyngeal swabs (participants age more than 5 years). Each swab was immediately placed in a cryotube containing skim milk, tryptone, glucose, and glycerol, vortexed, and frozen at -80°C until laboratory analysis. Pneumococcal carriage was determined by culture and isolated pneumococci were serotyped by polymerase chain reaction. For this analysis, any serogroups containing PCV13 serotypes were considered VT strains. We evaluated preliminary overall and VT carriage and serotype distribution by age group. Among 1080 participants, overall pneumococcal carriage was 60%; carriage was highest among children 1 year of age (77%) and lowest among participants more than 15 years (32%). VT carriage ranged from 14% (31/217) to 17% (37/215) in the age groups less than 15 years and was 7% (14/213) in participants more than 15 years. Among 691 pneumococcal isolates from all ages, the most common VT were 6A/6B/6C/6D (9%) and 19F (4%); the most common non-VT were 11A/11D (6%) and 21 (6%). These results will serve as the baseline for assessing the impact of the catch-up campaign through future carriage studies and will help inform future strategies to reduce VT carriage in settings with low vaccine coverage and disrupted health services.

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PNEUMOCOCCAL CARRIAGE AND CHANGES IN SEROTYPE DISTRIBUTION AFTER A SWITCH FROM PCV10 TO PCV13 IN CHILDREN IN A RURAL SITE IN MATIARI, PAKISTAN

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In 2021, the 10-valent Pneumococcal conjugate vaccine (PCV10) was replaced with the 13-valent in Pakistan's Expanded Program on Immunization. We aim to study the effect of the switch from PCV10 to PCV13 on the nasopharyngeal carriage in the same population carriage in children under 2 years of age in Pakistan. Children< 2 years were randomly selected from a line listing in two rural union councils of Matiari, Sindh, Pakistan. Nasopharyngeal swabs were collected using standard WHO guidelines by trained staff and were processed at Infectious Disease Research Laboratory at The Aga Khan University, Karachi using culture on sheep blood agar. Whole genome sequencing (WGS) was performed on culture-positive isolates. Analysis was done using Pathogenwatch. The serotypes were then classified as either vaccine type (VT) or non-vaccine type (NVT). Of the 200 children enrolled, pneumococcal isolates were detected in 140 (70%). However, WGS could only be performed in 100 isolates. The proportion of children who had received all 3 doses of PCV13 was 55.0%. Overall carriage remained similar when compared to the pre-PCV13 data from 2018 (70% vs 72.8%). PCV13-specific serotype carriage decreased from 16.6% in 2017/18 to only 5% in the current survey. Thus, we saw a rapid decline in PCV13-specific serotype 18 months after switch to PCV13 from PCV10 with modest vaccine coverage. Most of this decline could be attributed to decrease in serotype 19A. Epidemiology of the prevalent serotypes in a population is extremely useful to guide vaccine introduction in a country.

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ANTIBIOTIC USE AMONG ADULT PATIENTS WITH SEVERE ACUTE RESPIRATORY INFECTION IN TERTIARY LEVEL HOSPITALS ACCORDING TO THE WHO ACCESS, WATCH, AND RESERVE (AWARE) CLASSIFICATION IN BANGLADESH

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Acute respiratory infections, often caused by viruses, are a leading cause of antibiotic use contributing the exponential growth of antimicrobial resistance. To promote rational antibiotic use, the world health organization (WHO) introduced Access, Watch, and Reserve (AWaRe) classification system. We investigated antibiotic use among adult patients with severe acute respiratory infection (SARI) according to the AWaRe classification in Bangladesh. We analyzed data for adult (≥18 years) SARI patients collected during January 2013-December 2022 from the hospital-based influenza surveillance platform at nine tertiary-level hospitals in Bangladesh. Surveillance physicians identified inpatients meeting the WHO-SARI case definition and recorded patient demographics, and antibiotics received during hospitalization. Surveillance tested nasopharyngeal swabs for influenza by rRT-PCR. We used descriptive statistics to summarize the data. We enrolled 17,358 adult SARI patients [median age: 45 years (IQR: 30-60); 64% male]. Of them, 3,045 (18%) had influenza. Of enrolled patients, 14,989 (86%) received at least one antibiotic and 22% received >1 different course of antibiotics. Around 2,547 (84%) patient with lab-confirmed influenza received antibiotics. Most of the antibiotics prescribed were from Watch group (12,149; 81%) followed by Access group (4,791; 32%) and none received Reserve group of antibiotics. The most frequently used antibiotics were ceftriaxone (7,427; 40%), followed by amoxicillin+clavulanic acid (3,823, 21%), azithromycin (2,757, 15%), clarithromycin (1,470, 8%) and cefuroxime (645, 4%). Among these frequently used antibiotics all were from Watch group except amoxicillin+clavulanic which is not recommended by WHO for clinical use. Over four of five adult SARI patients received antibiotics despite a confirmed viral etiology indicating irrational antibiotic use. Predominant use of Watch group antibiotics is also concerning. Strengthening hospital antimicrobial stewardship programs can reduce inappropriate antibiotic use and help mitigating antimicrobial resistance.

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PREVALENCE OF SOIL-TRANSMITTED HELMINTH CO-INFECTION AMONG PERSONS WITH TUBERCULOSIS

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Tuberculosis (TB) remains an enduring threat to human health. In 2021, 10.6 million individuals developed active TB and 1.6 million died of TB. When we map the global distribution of TB, the parts of the globe that light up are overwhelmingly in tropical and sub-tropical areas. Intestinal parasitic infections are also concentrated in these regions and the geographic overlap is striking. An estimated one billion people are infected with soil-transmitted helminths. As such, the probability of intestinal parasitic infections in persons with latent and active TB is high. Very few studies have described the prevalence of parasitic infections in persons with TB (PWTB). A key limitation of these studies is that they used stool microscopy which may have underestimated the prevalence of parasitic infections. The prevalence of intestinal parasitic infections among PWTB in India has not been well documented. The TB LEOPARD study was designed to assess the prevalence of parasitic infections among PWTB in Puducherry and rural areas of Tamil Nadu in India. This study is currently in the recruitment phase. We present preliminary data from this study. Fresh stool samples from 38 persons with TB were collected. After sonication of the stool

specimen, we extracted DNA and conducted multiplex polymerase chain reaction testing for Ascaris lumbricoides, Strongyloides stercoralis, Trichuris trichuria, Necator americanus, and Ancylostoma duodenale. We found that 14 (39.4%) participants tested positive for at least one helminth infection and 3 (7.8%) tested positive for 2 helminths. The most common parasite detected was Necator americanus which constituted 78.4% of the heminth infections. These preliminary data are intriguing as the prevalence of helminth infections considerably exceeds the expected rate of helminth infection (20-30%) for the general population. Future studies should assess the significance of asymptomatic carriage of helminths among PWTB given the potential impact of parasitic infections on the immune response to TB. Additionally, the value of systematic screening and treatment of helminths for PWTB in India should be assessed.

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ASSESSING PROGRESS TOWARDS THE WORLD HEALTH ORGANIZATION TARGET OF ZERO CATASTROPHIC COSTS DUE TO TUBERCULOSIS BY 2035

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When the total of household expenditures and lost income due to tuberculosis (TB) exceeds 20% of pre-illness annual household income these costs are termed 'catastrophic' because it is unlikely that it will allow treatment completion to be affordable. The World Health Organization End TB strategy prioritizes the target of zero catastrophic costs. Costs due to TB have been assessed by repeatedly surveying patients throughout treatment about their recent costs; or by asking patients once at the end of treatment to recall all costs due to TB over more than 6 months since their illness began. There is little evidence comparing these strategies. The optimal approach depends on how long patients with TB can reliably remember their costs. To address this important research question, 174 patients newly diagnosed with TB recalled their recent pre-diagnosis costs due to TB to have been USD$=437 (IQR=95-1450). Then, 6 months later, without being reminded of their previous answers, patients again recalled these pre-diagnosis costs to be median USD$=660 (IQR=100-1880). Between both assessments, the Spearman correlation coefficient was 0.68, ($p<0.001$). The costs due to TB during treatment were median USD$782 (IQR=210-3200). Pre-illness annual household income was median USD$=15,960 (IQR=10,200-24,000). Thus, if pre-diagnosis costs due to TB were assessed recently at the time of diagnosis then catastrophic costs due to TB affected 34% of households (95% confidence interval, CI=27-42, 60/174). This was not significantly different (P=0.5) if pre-diagnosis costs due to TB were assessed later at the time of treatment completion then catastrophic costs due to TB affected 38% of households (95% CI=31-45, 66/174). Thus, patients with TB can usually reliably recall costs due to TB for many months, and catastrophic costs due to TB can be reliably assessed with a questionnaire applied only once at the end of treatment.

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THE EPIDEMIOLOGICAL SHIFTS OF DRUG-RESISTANT TUBERCULOSIS IN SABAH, EAST MALAYSIA DURING THE COVID-19 PANDEMIC: A 6-YEAR REVIEW OF THE GAINS AND LOSSES FROM 2016 TO 2021

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As the world's oldest pandemic, TB has been the world's leading cause of death by a single infectious agent, usurped only by Covid-19 in 2020 and 2021. In 2019, TB incidence in Malaysia was at 92 per 100,000 people, with an "upper-moderate" categorization. These cases were not evenly distributed, with the eastern-most state of Malaysia, Sabah, reporting 135 cases per 100,000 in the same period, qualifying as an endemic region. There is an evidence gap on the burden of multidrug-resistant TB (MDR-TB) in Sabah, we aim to describe the epidemiology and clinical characteristics of MDR-TB to inform public health measures. All cases of TB between 2016 to 2021 from the state TB registry was reviewed, with a focus on MDR-TB. The impact of Covid-19 was evaluated by designating 2016-2019 as pre-Covid, and 2020-2021 as Covid years. Factors under investigation include age, citizenship, and other indicators. A descriptive analysis of characteristics and logistic regression of variables associated with poor MDR-TB treatment outcomes was done using R software. Sabah reported an average of 5027 TB cases annually pre-Covid, declining by 10.3% to 4508 per year during Covid. Within study period, there were 97 MDR-TB cases, with median age of 38 years, and 33% of these being non-citizens (n=32). The proportion of notified MDR-TB cases in Sabah was 0.27% of all TB cases pre-Covid, but rose to 0.47% of all TB cases reported during Covid years. A marked increase in MDR-TB cases means the actual burden remains unknown. The proportion of MDR-TB cases treated successfully decreased from 60% to 24% between pre-Covid and Covid periods (OR=3.45, $p<0.01$); in this time, proportion of non-citizens who successfully completed MDR-TB treatment decreased from 47.4% to 10.0% ($p>0.05$). Improving adherence to MDR-TB treatment and adequate management of side effects could reduce likelihood of poor outcomes. While the proportion of MDR-TB in Malaysia and the state of Sabah remains relatively low compared to endemic countries, vigilant surveillance is needed to detect, isolate, and treat new cases to prevent future outbreaks.

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MALARIA IN CAMEROON: A RETROSPECTIVE ANALYSIS

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The Cameroon National Malaria Control Programme (NMCP) sought to understand the epidemiological situation and to assess the impact of malaria control interventions deployed over the period 2015 to 2020. Using DHIS2 data and programmatic data from the NMCP, key malaria indicators - on incidence, mortality rate, case management and preventative interventions were analyzed at the regional and district level, disaggregated by demographic group. The impact of seasonal malaria chemoprevention (SMC) was also assessed using differences in differences analysis to compare districts receiving SMC to adjacent districts not receiving SMC. Malaria incidence had an upward trend with the Centre region seeing the greatest increase, with higher incidence in pregnant women across all regions compared to other groups. Mortality decreased over the study period at the national level, however some regions still had more than 100 deaths per 100,000 in the under 5's, namely the North, Extreme North and Adamoua. For case management there was a large improvement in testing rates in health facilities increasing to over 80% in most districts by 2020 with test positivity rate increasing to above 50% in most districts. Treatment of simple malaria with first-line ACT was over 50% nationwide by 2020, and the proportion of severe malaria cases receiving third-line treatment quinine increased, with second-line treatment artemether decreasing. In terms of the impact of SMC, the 2016 and 2017 campaigns had a statistically significant impact, decreasing under 5 incidence, however this effect was not seen in later campaigns. The results highlight the efforts of the NMCP to reduce the malaria burden across the country and the heterogeneous epidemiology of malaria across regions. Focus on protecting vulnerable groups such as pregnant women and children under 5 from malaria illness must continue. SMC has had a positive impact in reducing malaria illness in the under 5's and there should be more research to assess factors that could be limiting the effectiveness of SMC in later years as there could be scope to expand the geographical reach of the intervention or expand to the over 5's.

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QUANTIFYING THE IMPACT OF MALARIA IN PREGNANCY ON MATERNAL ANEMIA AND ITS ASSOCIATED BURDEN ACROSS AFRICA

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Plasmodium infection during pregnancy causes maternal anemia but quantitative estimates of the burden of malaria on maternal anemia are lacking, in part because the impact of untreated infections cannot be ethically measured. To address this gap, we used individual-level data on hemoglobin (Hb) concentrations and malaria PCR status at enrolment into 4 recent trials of alternative approaches to malaria prevention in pregnancy, involving 12,608 women in seven countries (Burkina Faso, The Gambia, Ghana, Kenya, Malawi, Mali, and Tanzania). We developed a Bayesian inferential framework to account for the various exclusion criteria of the trials, using data on gestational age at enrolment as a proxy measure for the length of time an infection was left untreated to capture Hb dynamics up to the end of the second trimester (T2). We estimate that among primigravid women, reductions in Hb associated with malaria infection increase throughout gestation, reaching a reduction of 1.24 [95% Credible Interval (CI) 1.13, 1.36] g/dL at the end of T2. Accounting for concomitant declines in Hb throughout gestation in non-infected women, we estimate that, in primigravidae with ongoing infection, the risk of malaria-associated severe anemia (Hb < 7 g/dL) increases from 2.2% [95% CI 1.1-3.5] to 14.3% [95% CI 10.8-17.9] between the ends of the first trimester (T1) and T2. The impact of malaria upon Hb in multigravid women varied by transmission intensity, with the impact similar to primigravidae in areas of lower prevalence but increasingly diminishing in areas of higher transmission, following well-understood patterns in acquisition of pregnancy-specific malaria immunity. Using modelling, we estimate that among women who have experienced infection in one previous pregnancy, the reduction in Hb concentration associated with ongoing infection at end of T2 is 0.38 [95% CI 0.21, 0.55] g/dL, and no reduction in Hb concentration in any subsequent pregnancies. Using this framework, we will extrapolate the associated burden across Africa using estimates of fertility and malaria endemicity collated by the Malaria Atlas Project and the World Health Organization.

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A GLOBAL MALARIA CASE-MANAGEMENT MODEL CASCADE WITH AN INTERACTIVE TOOL FOR POINT-OF-CARE CONSUMPTION ANALYSIS

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Quality malaria case management is essential for preventing severe disease and death, both from malaria and other severe illness. In preventative intervention mix planning, consensus has emerged that data-driven decision making - supported by models - is necessary for optimal allocation of resources. But limited evidence exists on the (relative) impact of each component of the post-infection care cascade on population-level outcomes. This work represents a step towards treating post-infection intervention policy planning with the same rigour as preventative interventions. Here we present an interactive online tool, using which policy-designers can easily explore the impact of case-management policy initiatives on coverage and consumption of malaria drugs and diagnostics. Retaining the ease of 'back of the envelope' calculations, our tool captures nuances including community-based positivity rates and the age structure of symptomatic malaria. For such scenario analysis to be worthwhile one must first estimate the status quo in absolute terms. We have developed a complete case-management modelling framework which produces estimates for each step in the logical flow through the health-system: an individual developing symptoms; seeking medical advice; receiving a diagnostic test; and, finally, being treated with an antimalarial. The natural conditionality here poses challenges to quantifying coverage - both routine and survey data suffer from increasingly small sample sizes, variations in interpretation, and recall biases. Our framework is statistical, leveraging multiple sources of data including cross-sectional surveys and a comprehensive literature review, and provides baseline estimates of point-of-care malaria commodity consumption across 75 malaria-endemic countries reflecting an estimated 448mil RDTs consumed in public-sector clinics in 2021, and 314mil ACTs, of which 75% were consumed in malaria-endemic Africa.

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MALARIA AS A RISK FACTOR FOR COVID-19 IN WESTERN KENYA AND BURKINA FASO (MALCOV)

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It is unknown whether malaria affects COVID-19 severity or duration. We conducted a cohort study in newly diagnosed COVID-19 patients of all ages in western Kenya and Burkina-Faso. Participants were screened for SARS-CoV-2 using rapid antigen tests. Patients co-infected with Plasmodium falciparum malaria were treated with 3-day artemether-lumefantrine or pyronaridine-artesunate. COVID-19 disease progression was assessed daily by Flu-Pro+ questionnaires until day 14 by mobile phone or at clinic visits. Nasal swabs and blood samples were taken on days 1, 3, 7, 14, and 28. SARS-CoV-2 and viral load were assessed by RT-PCR. All analyses were adjusted for enrolment age, disease severity, and viral load. From February 2021 to January 2022, 708 COVID-19 patients were enrolled; 139 (20%) had malaria. Malaria patients were younger: 43/139 (31%) were aged <15 yrs vs 31/569 (5%) without malaria (P<0.0001). SARS-CoV-2 clearance in the first week was slower among malaria patients (aHR=0.59 95% confidence interval 0.45-0.76, p<0.001). By day 7, 71/131 (54%) and 319/481 (66%) had cleared SARS-CoV-2 in the malaria and non-malaria group (adjusted RR=0.90, 0.78-1.04, p=0.2) and this was 118/132 (89%) and 418/468 (89%) by Day-14 (aRR=0.98, 0.79-1.21, p=0.90). There were no differences in viral load on Day-7. Patients with malaria were more likely to have moderate-to-severe disease at enrolment (all ages: 70% vs 60%, aRR=1.25, 1.09-1.41, p<0.001; <15 years: aRR=1.61, 0.97-2.95,

p=0.085; >=15 years: aRR=1.23, 1.06-1.39, p=0.002), but the time to clearance of moderate-to-severe symptoms (aHR= 1.04, 0.85-1.28, p=0.7) and duration of any symptoms were similar (aIRR=1.01, 0.89-1.16, p=0.8). Overall, 3 (2.0%) and 7 (1.2%) patients with and without malaria had to be hospitalised, and 2 (1.3%) and 3 (0.5%) died. Patients co-infected with SARS-CoV-2 and P. falciparum malaria were more likely to have moderate-to-severe disease at enrolment. SARS-CoV-2 clearance was slower in malaria patients, but malaria did not affect COVID-19 disease progression or the duration of illness after successful antimalarial treatment of malaria.

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PREVALENCE OF MALARIA INFECTION AND COVERAGE OF KEY CONTROL INTERVENTIONS AMONG SEASONAL MIGRANT WORKERS AT FARM SITES AND SURROUNDING RESIDENT POPULATIONS IN NORTHWEST AMHARA REGION, ETHIOPIA

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In many malaria-endemic countries, population mobility presents a key challenge to malaria elimination efforts due to the potential importation of infection. In Amhara Region, Ethiopia, the expansion of large-scale agricultural development in lowland areas attracts close to half a million seasonal migrant workers annually, mainly from highlands where malaria transmission is low. These groups are at a higher risk of malaria due to poor living conditions, and behavioral and occupational factors at farms. A cross-sectional study was conducted to estimate the prevalence of malaria infection and coverage of key interventions among seasonal migrant workers and the surrounding resident population in the Delello farm site, Metema District, northwest Amhara Region in October 2022 following the major rainy season. Through multistage cluster sampling, 1,900 seasonal migrant workers from 32 farms and 1,001 residents from 15 hamlets were randomly selected and tested for malaria using rapid diagnostic tests (RDTs). Dried blood spots (DBS) were collected for molecular analysis. Half (50.4%) of participants in the resident population were male, compared to 96.8% of the seasonal migrant workers. Malaria infection prevalence by RDT was 19.5% [95% CI: 17.8-21.4] in seasonal migrant workers, and 8.5% [95% CI: 6.9-10.4] in the resident population. Only 8.0% [95% CI: 6.9-9.3] of seasonal migrant workers and 74.2% [95% CI: 71.4-76.8] of the resident population owned mosquitoes net, and 6.5% of seasonal migrant workers and 68.4% [95% CI: 64.9-71.6] of the resident population slept under a net the previous night. The proportion of households covered with indoor residual spraying in the last 12 months was 76.1% [95% CI: 70.2-81.1] among the resident population, whereas seasonal migrant workers slept in un-sprayable structures or worked outdoors at night. These results indicate high malaria prevalence and low coverage of vector control interventions among seasonal migrant workers and suggest the need for targeted interventions to reduce the malaria burden in these populations and the potential importation of infection in low-transmission areas.

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MALARIA SEROEPIDEMIOLOGY IN VERY LOW TRANSMISSION SETTINGS IN THE PERUVIAN AMAZON

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Peru is on track to malaria elimination, due to control programs such as the Zero Malaria Plan (2017) and the National Malaria Elimination Plan (2022). However, measuring malaria exposure in low transmission areas remains essential to gain insight in these contexts and achieve elimination. This study aims to determine malaria exposure and associated risk factors according to distance to facility as a proxy for access to care in two very low transmission areas of Loreto. A cross-sectional analytical study was conducted in 38 communities in Indiana and Belen districts. Standardized questionnaires were applied to capture socio demographic and behavioural information, households were geo-referenced and blood samples were collected for serological and molecular analysis. Local Getis-Ord Gi* statistic was performed to identify clusters of households with high (hotspots) or low (coldspots) seroprevalence. A total of 4000 individuals were analyzed across both districts. Our findings show an overall malaria seropositivity of 9.3% (95%CI: 8.4%-10.2%). We also found a seropositivity level to any exposure (recent or historical) of 2.5% (95%CI: 2.0%-3.0%) and 7.8% (95%CI: 7.0%-8.7%) for P. falciparum and P. vivax, respectively. The seropositivity trend in P. Vivax changed in the [40-50) age group ($\beta 1 = 0.04$, $p = 0.003$), while in P. Falciparum occurred in the [50-60) age group ($\beta 1 = 0.004$, $p = 0.010$). Moreover, distant and extra distant villages were more exposed to any malaria (recent or historical) than those classified as proximate (DSCFdistant = 16.29, p<.001; DSCFextra distant = 18.86, p<.001) and moderate (DSCFdistant = 10.48, p<.001; DSCFextra distant = 12.53, p<.001). The spatial analysis showed that cold spots were located mostly in the center of Belen district, while hot spots were located on the border, and hot spots were located near the Amazon river in Indiana. Higher concentrations of malaria exposure were found in more distant communities. This information may be useful for the redesign of control strategies focused on distant subpopulations to improve malaria surveillance and continue on the path to elimination.

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CAUSES OF DEATH AMONG INFANTS AND CHILDREN ENROLLED THROUGH THE CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) NETWORK

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Globally, 2.8M deaths occur yearly among children aged 1-60 months (53% of all deaths in children <5 years). Detailed characterization of childhood deaths could inform interventions to improve child survival. The Child Health and Mortality Prevention Surveillance (CHAMPS) Network conducts childhood mortality surveillance in sub-Saharan Africa and South Asia using innovative postmortem minimally invasive tissue sampling (MITS). We describe the causes of child deaths across CHAMPS sites in 7 countries. From 2016 to 2020, 632 MITS (331 in 1-11 months; 301 in children 12-59 months) were completed on decedents. Expert panels determined locally the underlying, intermediate, and immediate conditions in the chain of events leading to death, based on histopathology, microbiological diagnostics, clinical data, and verbal autopsies. The six most common underlying causes of death were malnutrition (104; 16.5%), HIV (75, 11.9%), malaria (71, 11.2%), congenital birth defects (64, 10.1%), lower respiratory tract infections (LRTI; 53, 8.4%) and diarrheal diseases (46; 7.2%). Infection was present in the causal chain in 549/632 (87%) of deaths with Klebsiella pneumoniae (155/549, 28.2% of all infectious deaths; 82% considered nosocomial) Plasmodium falciparum (122/549; 22.2%) and Streptococcus pneumoniae (109/549; 19.9%) being the commonest pathogens contributing to infectious deaths. Cytomegalovirus (57; 10.4%) or Acinetobacter baumannii (39; 7.1%; 35/39 [89.7%] considered nosocomial), also played important roles. Expert panels considered 78% (494/632) of all deaths preventable and 4% (26/632) preventable under certain conditions. CHAMPS results show that, in high-mortality settings, infectious diseases continue to cause most deaths in infants and children, often in conjunction with malnutrition. Results highlight opportunities for action to prevent fatalities and reveal common interactions of various etiologies in the path towards death. The previously unrecognized significance of pathogens such as Klebsiella pneumoniae and cytomegalovirus highlights the need to focus on them to improve child survival.

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INFANT MORTALITY AND GROWTH FAILURE AFTER ORAL AZITHROMYCIN AMONG LOW BIRTHWEIGHT AND UNDERWEIGHT NEONATES

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Biannual mass azithromycin distribution has been shown to reduce all-cause child mortality, with the largest effects in children aged 1 to 11 months, who have the highest mortality rates. Low birthweight (birthweight <2500 grams, g) and underweight (weight-for-age Z-score, WAZ, < -2) infants have higher risk of poor outcomes compared to their well-nourished peers. Interventions to improve growth and reduce mortality must not interfere with breastfeeding. If effective, azithromycin could represent an easily implementable intervention for infants. We evaluated the role of azithromycin for reducing mortality and improving growth outcomes in low birthweight and/or underweight infants in Burkina Faso. Infants aged 8-27 days of age weighing ≥2500 g at enrollment in Burkina Faso were randomized 1:1 to a single, oral dose of azithromycin (20 mg/kg) or matching placebo. Birthweight measurements were extracted from each child's government-issued health card. We evaluated mortality and anthropometric outcomes in four subgroups: 1) both low birthweight and underweight at enrollment; 2) low birthweight-only; 3) underweight-only; 4) neither low birthweight nor underweight. Of 21,832 enrolled infants, 21,320 (98%) had birthweight measurements and included in this analysis. Of these, 747 (3%) were both low birthweight and underweight, 972 (5%) were low birthweight-only, 825 (4%) were underweight-only, and 18,776 (88%) were neither low birthweight nor underweight. Infants who were both low birthweight and underweight receiving azithromycin had lower odds of underweight at 6 months compared to placebo (OR 0.65, 95% CI 0.44 to 0.95), but the treatment group by subgroup interaction was not statistically significant (P=0.06). We did not find evidence of a difference between groups for other outcomes in any subgroup. In conclusion, azithromycin may have some growth-promoting benefits for the highest risk infants, but we were unable to demonstrate a difference in most outcomes in low birthweight and underweight infants. As a secondary analysis of a trial, this study was underpowered for rare outcomes such as mortality.

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EFFECT OF A SINGLE DOSE OF PROPHYLACTIC AZITHROMYCIN TO INFANTS ON FECAL CARRIAGE OF ENTEROPATHOGENS IN PAKISTANI INFANTS

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Azithromycin (AZ), a macrolide, is recommended by the World Health Organization (WHO) for mass drug administration (MDA) in low-middle-income countries (LMICs) for treatment of infections. MDA-AZ improves child survival and may have a role in improving infant growth outcomes. Concerns about antimicrobial resistance gene (ARG) carriage and enteropathogen burden remain even in antibiotic naïve infants. The study aimed to assess AZ impact on ARG carriage and enteropathogen burden in 8-week-old infants. Mumta study was a 1:1:1 randomized controlled trial of malnourished lactating women (LW) and their infants (n=957 dyads). Interventions were lactation counseling (LC) only, LC and balanced energy protein (BEP) sachet for the mother, and LC, BEP with one dose of AZ to the infant at day 42 of birth. Fifty infants from each arm were randomly selected for biomarker and microbiome analysis at day 56 of birth. Enteropathogen burden and ARG carriage were assessed using a customized TaqMan Array Card (TAC). There was no difference between enteropathogen burden in healthy infants who received AZ and those who did not. Enteropathogen count in infants was strongly associated with mothers (p<0.001) even at 8 weeks after birth, regardless of place, mode of delivery and exclusive breastfeeding. In our study of 150 infants, 91.3% of infants were positive for ARG CTX-M type extended-spectrum β-lactamases. The prevalence of fluoroquinolone resistance genes with the gyrA mutation was 66.7%, and the parC mutation was 45.3%. There was no difference between ARG carriage between infants who received AZ and those who did not. Factor analysis of TaqMan data showed three distinct factors: the Campylobacter family, E. coli family, and ARGs (CTX-M, gyrA, and parC types). Enteropathogen count was predicted by an increase in three infant EED biomarkers MPO, LCN-2 and CALPR, and CRP. In conclusion, we show early vertical transmission of enteropathogens in infants, with substantial antimicrobial carriage irrespective of AZ use. Our study lends insight into mechanistic pathways for AZ action in low-resource malnourished settings.

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EVALUATING THE ACCURACY OF INTERVA-5 AND INSILICOVA ALGORITHMS IN DETERMINING THE LEADING CAUSES OF MORTALITY IN INFANTS AND CHILDREN UNDER-5 IN WESTERN KENYA

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Verbal autopsy (VA) guides public health priorities in communities where physician certification of deaths is largely unavailable. VA has been frequently validated against physician coding of causes of death (CoD), but none have done so with CoDs rigorously determined from multiple data sources, including minimally invasive tissue sampling (MITS) and post-mortem laboratory and pathology testing. Child Health and Mortality Prevention Surveillance (CHAMPS) investigates causes of death in children under 5 using MITS, post-mortem laboratory and pathology testing, VA, and clinical and demographic data in seven countries. The CHAMPS Determination of Cause of Death (DeCoDe) expert panel analyses all available data, and ascertains the immediate, underlying and other antecedent causes of death. We compared results of the VA algorithms InterVA-5 and InSilicoVA to the CHAMPS-Kenya site DeCoDe CODs in children 1 to 59 months of age. InterVA and InsilicoVA had closer agreement with each other than with DeCoDe. The highest agreement across three systems was for malaria as a cause of death (Kappa=0.29 [CI:0.17-0.41]). Both VA systems indicated that gastroenteritis and 'other causes' were in the top five causes of death (24.3% and 15.3% respectively) but had low agreement on meningitis (15.8% and 5.0%), which wasn't detected by DeCoDe in any cases. DeCoDe indicated malnutrition was responsible for 26.6% of deaths, while the VA algorithms indicated this as causing 2.7% and 3.2% of deaths. Both InterVA-5 and InsilicoVA underestimated malnutrition, malaria, sepsis and HIV disease. InterVA-5 overestimated diarrheal diseases and InsilicoVA overestimated respiratory infections including pneumonia. The VA algorithms performed suboptimally in determining the leading causes of mortality, likely because they cannot accurately differentiate between conditions with similar symptoms and because recall bias may confuse results where no medical records exist. Our findings underscore the importance of maintaining gold standard surveillance systems in countries where VA is widely relied on and to use rigorous results to validate and refine VA algorithms.

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IDENTIFYING RISK FACTORS FOR MATERNAL NEAR MISS AMONG RURAL PREGNANT WOMEN ADMITTED TO A TERTIARY PUBLIC HOSPITAL IN BANGLADESH: A CASE-CONTROL STUDY

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Maternal near miss (MNM) refers to women who experienced complications during pregnancy, childbirth, or within 42 days of termination and narrowly escaped death. The Child Health and Mortality Prevention Surveillance (CHAMPS) network is conducting health and demographic surveillance in Baliakandi, a rural sub-district of Bangladesh and tracking each pregnancy and its outcome. We studied risk factors and pregnancy outcomes of MNM in women from Baliakandi admitted to Bangabandhu Sheikh Mujib Medical College Hospital (BSMMCH), a tertiary-level hospital. We conducted an unmatched case-control study using WHO clinical and laboratory criteria for MNM to identify cases and randomly selected women from Baliakandi who gave birth without experiencing significant morbidity at BSMMCH in 2022 as controls using a 1:1 ratio. We examined demographic, obstetric, and treatment-related characteristics using multivariate logistic regression controlling for age, education, and parity. HDSS 2022 data recorded 5930 pregnancy outcomes in Baliakandi; 219 got admitted to BSMMCH, 62 experienced MNM, and controls shared similar demographic profiles to cases. Hypertensive disorders (60%) and obstetric hemorrhage (32%) were common admission complaints of MNM cases compared to 2% hypertensive disorders and 5% obstetric hemorrhages in controls. No antenatal care (ANC) (adjusted odds ratio [aOR]: 3.23, 95% CI: 1.73 - 6.38) and >4 hours delay in seeking care from the onset of the complaints (aOR: 1.89, 95% CI: 1.10 - 3.37) was associated with a higher risk of MNM. No significant association with age and parity with MNM was found. Most (88%) MNM cases and half (58%) of controls were referred from other healthcare facilities. MNM was significantly associated with increased risk of stillbirth (aOR: 5.8, 95% CI: 2.27 - 16.95, p: <0.001) and cesarean delivery (aOR: 2.07, 95% CI: 1.01 - 4.30, p: 0.04). Implementing interventions that address reduction of first-step delay, improvement of quality antenatal care and establishment of effective referral systems in low-resource settings is crucial to decrease MNM events, improve maternal health, and increase child survival.

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ANTENATAL CARE SERVICES IN BENIN AND TANZANIA, 2021-2022: AN EQUITY ANALYSIS STUDY

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Antenatal care (ANC) improves maternal and neonatal outcomes, yet access to ANC and quality of care (QoC) may be inequitable due to sociocultural factors and monetary and time costs. Examining drivers of ANC disparities may identify those amenable to policy change. We conducted an ANC equity analysis of public facilities in Tanzania, where services are free, and in Benin, where there is cost-recovery. Using data from representative household surveys in the catchment of 40 clinics per country, we assessed total ANC visits in last pregnancy, QoC indicators (e.g., blood pressure (BP) and urinalysis), and wait times, disaggregated by education and wealth quintiles. We used indices of inequality, concentration indices, and Oaxaca-Blinder decompositions to determine the distribution, direction, and magnitude of inequalities and the contributing factors. We assessed out-of-pocket (OOP) expenses associated with ANC visits relative to income. Wealthier individuals had more ANC visits than poorer ones at every education level in both countries, with the wealthiest and most educated having two visits more than the poorest, least educated. In Benin, individuals who attend ANC receive similar care regardless

of socioeconomic status; BP was measured for 98% of women in the highest and lowest wealth quintiles. In contrast, in Tanzania, there are wide disparities in QoC received by education or wealth; 83% of the wealthiest women had BP measured versus 64% of poorest. In Tanzania, wealthier and more educated clients spent 27 fewer minutes at ANC. In Benin, OOP expenses are 2.7% of annual income for women in the lowest wealth quintile compared to 0.8% for the highest; cost recovery is the primary cost. In Tanzania, the values are 3.1% and 0.5%, respectively; transportation is the main cost. We identified inequities in total ANC visits, favoring wealthier, more educated individuals. In Benin, removal or reduction of cost-recovery could improve ANC access. In Tanzania, ensuring healthcare staff have necessary training and supplies will help ensure uniform and high-quality care, while community health services could address the transportation cost barrier.

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COSTING OF A COMBINATION INTERVENTION (KYATEREKERA) ADDRESSING SEXUAL RISK-TAKING BEHAVIORS AMONG VULNERABLE WOMEN IN SOUTHWESTERN UGANDA

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In Uganda, women engaged in sex work (WESW) have an HIV prevalence of 31.3% and account for 18% of all new HIV infections in the country. This marginalized population is at the intersection of multiple vulnerabilities. The Kyaterekera intervention is targeted at WESW in Rakai and the greater Masaka regions in Uganda and combines a traditional HIV risk reduction (HIVRR) approach with a savings-led economic empowerment intervention and financial literacy training (FLT).We estimated the economic costs of the Kyaterekera intervention from a program provider perspective using a prospective activity-based micro-costing method. All program activities and resources used were identified, measured, and valued across the two study arms: 1) control arm (7 clusters, 186 women) receiving a traditional HIVRR intervention; 2) treatment arm (12 clusters, 356 women) receiving a matched individual development savings account (IDA) and FLT on top HIVRR. Estimated costs were summed per each arm and divided by the participant numbers to calculate the per-participant cost by arm. All costs were adjusted for inflation, discounted at an annual rate of 3%, and presented in 2019 US dollars.The total per-participant cost of HIVRR and HIVRR+IDA+FLT arms was estimated at $323 and $1,435, respectively, using the treatment-on-the-treated (TOT) sample. When calculated based on the intent-to-treat (ITT) sample, the per-participant costs were reduced to $183 and $588, respectively. The key cost drivers were the capital invested in IDAs at opening and through matched contributions and the personnel and transportation costs for program operations, linked to WESW's higher mobility and the dispersed pattern of hot spot locations.This is the first study to estimate the costs of a combined HIVRR and economic empowerment intervention for WESW in Uganda. The findings contribute to a dearth of evidence on the economic costs of implementing a targeted intervention for this marginalized population in resource-constrained settings and sheds light on the scale of potential investment needed to better achieve the health equity goal of HIV prevention strategies.

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THE COLLABORATIVE CROSS REVEALS A SINGLE LOCUS REQUIRED FOR PROTECTIVE IMMUNITY AGAINST HIGHLY VIRULENT TOXOPLASMA GONDII STRAINS

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We employed an unbiased forward genetics screen to determine new requirements for immunity to Toxoplasma gondii against a highly virulent strain of T. gondii, the causative agent of human toxoplasmosis. To detect immunity QTLs generated by vaccination or natural infection with a low-virulent strain, we screened the available panel of 59 lines of the Collaborative Cross (CC), a highly diverse genetic panel of inbred mice captures ~90% of the genetic variation within the Mus musculus species. We challenged immunized mice with a highly virulent French Guyana strain, GUY-DOS, capable of evading immunological memory responses in some but not all founder CC lines. We found one highly significant Quantitative Trait Locus (QTL) in a small region on chr11 that correlated with survival to GUY-DOS secondary infections in vaccinated or naturally infected animals. The chr11 QTL accounts for 70% of the total phenotypic variance in the CC. The protective effects to GUY-DOS in the CC mice were related to PWK/PhJ (Mus m. musculus) and CAST/EiJ (M. m. castaneous) alleles but not those from common laboratory mice (M. m. domesticus) at this locus. The number of mutations and GO enrichment of genes in the chr11 QTL indicates that the most probable candidate in the region corresponds to Tcf7, a known regulator of CD4+ T follicular and CD8+ T central memory lymphocytes. A further evaluation revealed enhanced central memory CD8+ T cells and higher frequencies of TCF-1+ in CD8+CD44+ lymphocytes in resistant CAST/EiJ and PWK/PhJ compared to susceptible C57BL/6J mouse genetic backgrounds. To test the genetic effect of the chr11 QTL, we applied the same infection model to congenic B6.PWD-chr11.1 mice and observed complete protection against challenge with the highly-virulent strain VAND but partial protection to GUY-DOS, suggesting that chr11 7-60 Mb from the M. m. musculus genetic background promotes immunity to atypical strains in a strain-specific manner. Furthermore, we utilized a Tcf7 deficient mouse line (Tcf7 P45-/-), whereby TCF1 expression is reduced but not abrogated, and observed that vaccinated Tcf7 P45-/- mice succumbed to a challenge with the Type I RH T. gondii strain, typically non-lethal in vaccinated C56BL/6J mice. Together, these results show the contribution of Tcf7 in immunity to T. gondii and reinforce the importance of Tcf7/TCF-1 regulation in vaccination against T. gondii and other parasitic diseases.

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EXPLORING NATURALLY ACQUIRED IMMUNITY TO PLASMODIUM FALCIPARUM IN A GENOTYPIC ANALYSIS OF A LONGITUDINAL COHORT STUDY

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We genotypically profiled six thousand samples from a longitudinal cohort study in Kalifabougou, Mali to characterize malaria infection dynamics with unprecedented clarity. In this cohort which spanned May 2011 to January 2012, about half of the subjects were infected with Plasmodium falciparum at enrollment into the cohort, across all ages (3 months-25 years old). To better understand the distribution and prevalence of polyclonal infections, particularly as they relate to naturally acquired immunity (NAI) development, we generated Illumina amplicon sequencing data from 464 subjects in this cohort. We estimated complexity of infection (COI), the

number of genetically distinct clones within a sample and found that over 50% of the P. falciparum positive samples (1210 of 2315 samples) were polyclonal, regardless of subject age. This finding is consistent with previous findings from this cohort showing similar times to first PCR-detectable infection, regardless of age, suggesting that NAI does not reduce rates of infection or the clonality of infection. We also compared the time to the first new infection across multiple subject groups. We found that subjects who were already infected with parasites at study enrollment, before the transmission season, acquired a new infection more quickly during the transmission season itself than those who were uninfected at baseline, suggesting that ongoing blood-stage infections may not protect against superinfection. As this pattern was also unchanged with subject age, as well as with stratification by number of new infections, as a proxy for heterogeneity in exposure, the rate of superinfection establishment does not appear to be impacted by NAI. Future work will screen for elusive signs of immunity at a molecular level, including analyses of allelic exclusion, spontaneous infection resolution, and duration between infection onset and presentation of symptoms. This work highlights the utility of longitudinal amplicon sequencing data to provide a deeper look at molecular signatures, suggesting that both COI and rates of superinfection establishment are not molecular signs of naturally acquired immunity.

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INVESTIGATION OF THE RELATIONSHIP BETWEEN NATURALLY ACQUIRED ANTIMALARIAL ANTIBODIES AND THE DURATION AND CLEARANCE OF ULTRA-LOW DENSITY PLASMODIUM VIVAX INFECTIONS

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Subclinical Plasmodium spp. infection is attributed to the acquisition of non-sterilising antimalarial immunity, particularly antibodies. The spontaneous clearance of subclinical peripheral Plasmodium spp. parasitemia, including P.vivax, occurs frequently in low transmission settings. Subclinical Plasmodium spp. infections contribute significantly to ongoing malaria transmission, therefore understanding the role of antibody mediated immunity in the spontaneous clearance of parasitemia is essential to the broader understanding of the epidemiology and transmission potential of P.vivax. We sought to identify IgG responses associated with subclinical P.vivax infection and clearance of peripheral parasitemia. IgG to a suite of 30 P.vivax antigens was determined by Luminex assay in participants of a nested cohort study of subclinical Plasmodium spp. infection in Laos (n=202) and Cambodia (n=150). Participants were sampled monthly for 12 months (n=3041), and Plasmodium spp. infections detected by high-volume ultrasensitive qPCR. Mixed effects regression models were used to determine the association between antigen specific IgG levels and spontaneous clearance of peripheral P.vivax parasitemia. Over 12 months, a total 610 subclinical Plasmodium spp. infections were detected, including 293 P.vivax infections. Spontaneous clearance of peripheral P.vivax infection was observed in 79% and 67% of participants and the median time to clearance of peripheral P.vivax parasitemia was 93 and 68 days in Laos and Cambodia, respectively. Anti-P.vivax IgG responses were higher in participants with detectable P.vivax infection compared to those free of P.vivax during the study period, for all 30 antigens investigated. Individual antigen-specific IgG responses were not associated with clearance of peripheral P.vivax parasitemia. Future investigations will include analysis of multi-antigen responses and time to clearance of peripheral P.vivax parasitemia. These findings will further our understanding of acquired immunity in the maintenance, clearance and ultimately the transmission and epidemiology of P.vivax infections.

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NEW INSIGHTS INTO SCHISTOSOMIASIS MANSONI PATHOGENESIS: EVIDENCE FOR BACTERIAL TRANSLOCATION, INFLAMMASOME ACTIVATION, AND UPREGULATION OF PROINFLAMMATORY CYTOKINES IN HEPATOSPLENIC PATIENTS

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IL13 drives schistosomiasis fibrogenesis, but growing evidence suggests that IL1β and IL17 contribute to severe disease. Our aims were to evaluate the immune response in patients with schistosomiasis and determine if liver fibrosis is associated with bacterial translocation, inflammasome activation, and Th17 response. Plasma samples from controls (n=30) and patients with acute (n=22), hepatointestinal (n=40), and hepatosplenic (n=26) schistosomiasis mansoni were collected. ELISA was performed for IL1β, IL5, IL6, IL10, IL13, IL17, TNFα, IFNγ, CCL11, and CCL17. Snap-frozen liver biopsies from controls (n=6) and hepatosplenic patients (n=36) were also included. Real-time PCR was performed for genes related to bacterial translocation, inflammasome activation, immune response, and fibrogenesis. Liver fibrosis was assessed by ultrasound (WHO protocol). Patients with acute schistosomiasis had higher levels of IL1β, IL5, IL6, IL10, IL13, IL17, TNFα, CCL11, and CCL17 than hepatointestinal patients or controls. Hepatosplenic patients had higher IL13, IL5, IL1β, TNFα, and CCL11, but lower CCL17 levels than hepatointestinal patients or controls. IL-5, IL-13, IL-1β, TNFα, and CCL11 positively correlated with the degree of fibrosis, while CCL17 levels were negatively correlated. Hepatosplenic patients had increased liver expression of markers of bacterial translocation (16S rRNA, LPS binding protein), inflammasome activation (NLRP3, Caspase 1, IL1β, IL18), Th1 (IL12p35, TNFα), Th2 (IL5, IL13, GATA3, CCL11, CCL17), Th17 (IL17A, IL17RC, IL17RC, IL23, IL23R, IL6), Treg (IL10, TGFβ), myofibroblast activation (αSMA, Vimentin) and collagen deposition (type I, III and VI). Bacterial translocation, inflammasome activation, Th2, and Th17 cytokines correlated with myofibroblast activation, collagen deposition, and fibrosis staged by ultrasound. Liver fibrosis in hepatosplenic schistosomiasis is associated not only with Th2 response

but also with NLRP3 inflammasome activation and Th17 immune response, probably exacerbated by bacterial translocation. Dual targeting of IL13/IL17 may benefit patients with severe disease.

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IMMUNE RESPONSE KINETICS IN NEUROCYSTICERCOSIS OVER TIME POST INFECTION USING AN ANIMAL MODEL

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Neurocysticercosis (NCC) is an infection of the central nervous system (CNS) caused by the metacéstode helminth Taenia solium. In NCC, brain lesions depend on the host-immunoinflammatory response interaction. However, it is not clear how is the inflammatory response in the early stage and throughout the infection process over time. We generated a rat model for NCC in which activated T. solium oncospheres were inoculated intracranially. 10 groups were used: 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 months post-infection (MPI). It was shown that in parenchymal cysts of 1 MPI more than 60% of the area around the cyst present macrophages organized in palisades without fibrosis, and from 3 MPI the presence of macrophages with fibrosis begins to be observed, as the post-infection time progresses this fibrosis increases, being 40% around the cyst for the 3 MPI, in the 4 with 70% and 80% in groups of 6 MPI. Picrosirius Red staining shows that the predominant type of collagen in the fibrotic tissue for 3 MPI is type III, with green fibrosis being observed; then, as the post-infection time progresses, the presence of red/yellow type I collagen is observed with greater predominance. On the other hand, a striking characteristic of meningeal and ventricular cysts is the presence of a higher percentage of moderate to severe inflammation score of 30% around the cyst compared to parenchymal cysts with only 10% around the cyst. The microglial cells of the groups of 1 to 2.5 MPI are found forming a layer of cells around the cyst and mainly with ameboid/phagocytic morphology. While in cysts from 3 MPI was located both in the fibrotic tissue that borders the cyst and continuous to this tissue are the astrocytic cells; microglia morphology was rod-shaped for the 3 to 4 MPI; in those of the 6 and 12 MPI, the microglia had a branched/debranched hypertrophic and dystrophic morphology. Concluding that the type of cellular infiltrate, macrophages, the formation of fibrosis and glial cells participate in the modulation of the host's immune response throughout the post-infection time in NCC.

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TRANSCRIPTOMIC IDENTIFICATION OF BIOMARKERS FOR CHAGAS DISEASE PROGRESSION

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Chagas disease affects approximately 8 million individuals worldwide. Of those infected, 20-40% will go on to develop chronic Chagas cardiomyopathy (CCC) and ultimately heart failure. There is currently no way to predict which patients will develop CCC, and the mechanisms underlying CCC progression are poorly understood. This study aims to discover biomarkers of disease progression by using whole blood samples that were obtained from individuals prior to disease progression (stage A). These individuals were evaluated yearly for any electrocardiogram (EKG), echocardiogram, or symptomatic changes suggestive of CCC. We then randomly selected patients who went on to develop EKG changes to stage B heart failure (asymptomatic progressors), those who went on to develop reduced ejection fractions and symptoms of stage C heart failure (symptomatic progressors), and age and sex matched non-progressors that remained in stage A. We performed RNA-sequencing on these blood samples to investigate differential gene expression, immune cell composition and HLA type. For symptomatic progressors compared to non-progressors, we identified various differentially expressed genes (DEGs) and significantly enriched biologic processes. These pathways included muscle morphogenesis, regulation of cell-cell adhesion, and defence response to intracellular pathogens. Notably, for very early-stage progression to asymptomatic disease compared to non-progressors we also identified DEGs related to immunologic and remodelling functions, and significant increases in memory B cells, M2 macrophages and eosinophils. No significant difference was detected in HLA type with disease progression. Overall, these findings indicate RNA transcripts detected in the blood of Chagas patients can differentiate those individuals who will go on to progress in CCC from those who will not, and suggest that there are notable physiologic changes that precede clinically detectable CCC progression. Our findings may help inform screening strategies for risk of disease progression and to develop novel therapeutic strategies that target these early dysregulated genes.

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REDUCTION OF SEXUALLY TRANSMITTED INFECTIONS FOLLOWING AZITHROMYCIN MASS DRUG ADMINISTRATION FOR TRACHOMA IN NAURU

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Sexually transmitted infections (STIs) are a major public health problem globally, particularly in low-and middle-income countries (LMIC). STIs are common in the Western Pacific region, including Nauru. The strategy of syndromic STI management, relying on clinical findings alone without laboratory confirmation, has long been endorsed by the World Health Organization but misses more than 80% of asymptomatic infections, especially common during pregnancy. Screen and treat strategies are not currently affordable or feasible at scale in LMIC. In areas where trachoma or yaws are endemic, mass drug administration (MDA) with azithromycin might offer an alternative approach to the population control of STIs as well as Neglected Tropical Diseases (NTDs). In Nauru, we evaluated the impact of an azithromycin-based MDA for trachoma control on bacterial STIs in a population aged 18-29 years, by conducting a before and after community survey pre and post MDA with 8-month follow-up to determine long-term impact on genital infections. The study enrolled 381 participants at baseline and 360 post-MDA. At baseline C. trachomatis infection was diagnosed in 21.7% of participants (95% CI 17.6% - 26.3%) T. vaginalis and M. genitalium were also common (21.2% and 10.9%, respectively) as well as N. gonorrhoeae 2.7% (95% CI 1.3% - 4.9%). Eight months following azithromycin MDA a reduction in prevalence was observed in all STIs except for T. vaginalis. The relative reduction in the prevalence of C. trachomatis was 34.6% (95% CI 25.7 - 45.2) and that of N. gonorrhoeae was 66.7% (95% CI 56.9 - 76.1). This study is the first to investigate the reduction of STIs using azithromycin-based MDA in the general population, not restricted to the female population and/or pregnant women. The significant decrease in STI prevalence seen in this study 8 months after azithromycin MDA is encouraging in island populations such as this, where populations are less mobile. Azithromycin MDA is a well-established and safe intervention which has been successfully adopted for NTD control. Prospective evaluations of MDA strategies specifically targeting common STIs should be undertaken.

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THE SECONDARY EFFECTS OF IVERMECTIN MASS DRUG ADMINISTRATION DESIGNED FOR MALARIA ON ECTOPARASITIC INFESTATIONS IN MOPEIA, MOZAMBIQUE: A CLUSTER-RANDOMIZED CONTROLLED TRIAL

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Ectoparasitic diseases such as scabies are severely neglected, despite the existence of effective treatments. There is limited data on their prevalence in Africa, and no published reports assessing the prevalence of scabies in Mozambique at scale. Ivermectin Mass Drug Administration (iMDA) is currently being studied as a potential malaria vector control tool. Given the substantial overlap between populations at risk of malaria, scabies and headlice, and the known efficacy of ivermectin against scabies and headlice, it is likely that in co-endemic areas there will be collateral benefits. During a cluster randomised controlled trial (BOHEMIA), which aimed to assess the effect of iMDA against malaria, we monitored the prevalence of scabies, headlice and bedbugs. The intervention consisted of a single dose of 400 mcg/kg ivermectin given monthly to eligible humans or humans and livestock in 3 consecutive months during the rainy season. The control group received albendazole (humans only). 39 of 100 total clusters were randomly selected and monitored for ectoparasitic infestations (scabies, headlice and bedbugs) among the three study arms. Cross-sectional surveys took place in adults and children at 3 months after the first dose (1,341 participants) and in untreated children under 5 (382 participants) at 6 months. Scabies and headlice diagnosis were determined by a questionnaire and examination of exposed skin/scalp by non-experts after intense training. Bedbug infestation was based on a short questionnaire. The baseline prevalence of scabies, headlice and bed bugs were 10.14% (95%CIs 8.58-11.88), 9.80 (95%CIs 8.23-11.55) and 16.70 (95%CIs 14.15-19.52), respectively. A semi-blinded and unadjusted analysis suggests a reduction in scabies prevalence of up to 88% (RR 0.12 (95%CI 0.06-0.25) after 3 months and up to 87% (RR 0.13 (95%CIs 0.04-0.41) in untreated children after 6 months. For headlice, the data suggests a reduction of up to 74% (RR 0.26 (0.13-0.49)) and no effect in untreated children after 6 months. The data suggests no significant effect on bed bugs at any time point. A full unblinded analysis will be available during the meeting.

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ASSESSING THE PREVALENCE OF SOIL TRANSMITTED HELMINTHS AND TUNGIASIS DURING LYMPHATIC FILARIASIS SURVEILLANCE IN THE COASTAL REGION OF KENYA

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The World Health Organization encourages Neglected Tropical Diseases (NTD) programs to employ integrated approaches to disease surveys for NTDs with similar epidemiology for efficient resource utilization and to avoid duplication of efforts. During Lymphatic Filariasis (LF) treatment, albendazole is co-administered with diethylcarbamazine and, as such soil-transmitted helminths (STH) are secondarily treated. A cross-sectional survey conducted in Kilifi and Kwale counties in 330 randomly selected schools to establish if LF transmission is ongoing assessed the impact of LF treatment on STH. The survey also collected relevant WASH data and assessed the prevalence of Tungiasis, which is known to occur widely and is prevalent among school-age children. 17,602 children aged 6-7 years were tested for circulating filarial antigen using the rapid filariasis test strip. All those positive were further tested for microfilaria using microscopy. For STH and Tungiasis, 60 children per school of ages 10-14 years were randomly selected, 12 children from each of grades 4 to 8. All sampled children were asked to provide stool samples for STH testing. Their feet were further washed, dried, and carefully examined for the presence of Tunga penetrans fleas. They were also interviewed on individual WASH characteristics. LF positive results were only reported in two sub-counties- Rabai 2/1,655; 0.12% (95%CI: 0.03-0.47) and Magarini 1/1,624; 0.06% (95%CI: 0.01-0.46). All three positive cases were negative by microscopy. For STH, the highest prevalence was in Msambweni sub-county (15.1%, 95%CI: 12.2-18.6). For Tungiasis, the highest median school prevalence was also recorded in Msambweni Sub-County (6.8%, 95%CI: 5.2-8.9). However, the highest intensity of infection was recorded in Kinango Sub-County with a median of 8.0 (IQR 2.8-8.0) embedded fleas. Schools with the highest prevalence of Tungiasis were in the same wards as schools with a high prevalence of STH. This study demonstrates that implementing integrated surveys for NTDs with similar epidemiology was feasible and enabled the evaluation of Tungiasis prevalence for the first time in Kenya.

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ESTIMATING THE BURDEN OF MALARIA-HELMINTH CO-INFECTIONS AMONG CHILDREN LIVING IN A SETTING OF HIGH COVERAGE OF STANDARD INTERVENTIONS FOR MALARIA AND HELMINTHS

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Concurrent infections of Plasmodium falciparum with Soil Transmitted Helminths (STH) and Schistosoma spp are still a major public health problem among children living in sub-Saharan Africa. We conducted two prospective studies among children living in urban and rural settings of Senegal, where control programs have been sustained, to determine the prevalence of malaria-helminth co-infection. We enrolled 910 children aged 1-14 years from Saraya and Diourbel districts of Senegal in June and November 2021. Finger-prick blood samples were obtained from the children for malaria microscopy and PCR methods. Stool samples were also collected. Kato-Katz and PCR methods were used to detect STH and S. mansoni, and Merthiolate-iodine-formalin test for other intestinal protozoans. Urine samples were analyzed using a filtration test, Point of Care Circulating Cathodic Antigens, and PCR methods for detection of S. haematobium. Continuous and categorical variables were compared across the two study sites and adjusted Odds ratios were used to explore risk factors for malaria-helminth co-infections. The overall prevalence of polyparasitism with P. falciparum, STH, S. haematobium and S. mansoni among children was 2.2% (20/910) while prevalence of P. falciparum-S. haematobium co-infection was 1.1% (10/910); P. falciparum-S. mansoni 0.7% (6/910) and P. falciparum with any intestinal protozoan 2.4% (22/910). Co-infection was slightly higher among 5-14-year-old children (17/629,2.7%; 95% CI:1.43-3.97) than 1-4 years (3/281,1.1%; 95% CI:–0.12-2.32) and, in boys (13/567,2.3%; 95%CI:1.27-3.96) than girls (7/343, 2.1%; 95% CI:0.52-3.48). Children aged 5-14 years (aOR=3.37; 95% CI:0.82-13.77, p=0.09), who were boys (aOR=1.44; 95% CI: 0.48-4.36, p=0.51) and lived in Saraya (aOR=1.27; 95% CI: 0.24-6.69, p=0.77) had a higher risk of the co-infection. Living in houses with spaces between the walls and frequent contact with water were statistically significant risk

factors for malaria-helminth co-infection. These findings could help to develop and implement strategies that would lead to elimination of malaria and helminths in the study areas.

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INTEGRATED NEGLECTED TROPICAL DISEASES SURVEYS TO ASSESS IMPACT OF INTEGRATED MASS DRUG ADMINISTRATION IN VANUATU

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Soil transmitted helminths (STH), scabies and yaws are neglected tropical diseases (NTDs) endemic to Vanuatu. To control and eliminate these NTDs, the Vanuatu Ministry of Health, with the support of the non-profit organisation Bridges to Development, is implementing large-scale innovative integrated control programs including two rounds of mass drug administration (MDA) with albendazole, azithromycin and ivermectin, concurrent with active surveillance of yaws and leprosy. To monitor and evaluate the impact of this program, cross-sectional parasitological surveys will be conducted before and after MDA. A cross-sectional baseline prevalence survey was conducted in 92 villages across three provinces. In each village the aim was to recruit 100 residents of skin examination and 50 to provide stool samples. One day prior to the MDA, field teams visited selected households, sought consent, and provided a stool collection kit to be returned the following day. On the day of MDA, a nurse performed a skin examination for scabies, yaws and leprosy. The dual path platform (DPP) rapid diagnostic test (RDT) was used to confirm suspected yaws cases. Stool samples were tested for STH species using sodium nitrate flotation (SNF) technique and qPCR. At the time of writing this abstract, a total of 4815 individuals in 2 provinces participated in the baseline survey that took place in Tafea in November 2021 and Sanma in September 2022. A baseline survey is planned for Shefa in May 2023. In the first 2 provinces, the prevalence of any STH by SNF was 28.3%, Ascaris lumbricoides 16.7%, Trichuris trichuria 11.4%, and hookworm 12.1%. The prevalence of scabies was 14.0% in Tafea vs 2.6% in Sanma. Active surveillance of yaws and leprosy identified 15 cases of confirmed yaws (13 in Tafea and 2 in Sanma) and 6 cases of suspected leprosy. Our study suggests that there is a high prevalence of STH and skin diseases among Vanuatu population. The implementation of surveys integrated with MDA is a novel approach that allows more cost-efficient collection of data necessary to monitor and evaluate impact of the MDA.

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COMMUNITY DIALOGUE AS AN INNOVATIVE APPROACH TO IMPROVE THE EFFECTIVENESS OF NEGLECTED TROPICAL DISEASE (NTD) CONTROL PROGRAMS TO IMPROVE MASS DRUG ADMINISTRATION (MDA) COVERAGE FOR LYMPHATIC FILARIASIS IN BURKINA FASO

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Burkina Faso has implemented mass drug administration (MDA) for lymphatic filariasis (LF) for over 20 years in all 70 health districts (HD). Currently, 62 of the 70 districts have stopped treatment. However, LF transmission has persisted in 8 HDs despite multiple rounds of MDA with good, reported coverage and implementation of additional MDA quality improvement strategies since 2018. In order to identify the factors for the persistence of transmission, the National Neglected Tropical Disease Program (PNMTN) implemented a community dialogue in 2022 in the districts of Gaoua, Batié, Bogodogo, Ouargaye and Tenkodogo. A total of 52 villages were selected based on the following criteria: therapeutic coverage rate ≤65%, antigenic prevalence ≥2%, and accessibility from a security perspective. Data collection of the community dialogue was done through individual interviews and focus groups, which were then qualitatively analyzed by theme. In total, the dialogue was conducted in 47 of the 52 villages targeted (90.4%) due to the deteriorating security situation. The individual interviews involved 346 people, including head nurses (5.2%), community distributors (27.1%) and community leaders (67.6%); 15.3% of participants were women. A total of 92 people (47 women) participated in the focus groups. The main factors for the persistence of LF were determined to be non-adherence to treatment and missed opportunities for treatment. The reasons mentioned by participants were lack of knowledge about LF, insufficient social mobilization, visits to the home at inconvenient times by distributors, the delay in providing financial resources available to implementing actors and MDA conducted in the rainy season. Some recommendations from the community dialogue, including improved planning, social mobilization, training, supervision, and distribution, were implemented during an MDA two months later; reported therapeutic coverages increased by an average of 4% in all districts. The remaining recommendations will be implemented in 2023.

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CHARACTERISTICS OF NON-TREATED POPULATIONS AMONG SELECT NEGLECTED TROPICAL DISEASE (NTD) MASS DRUG ADMINISTRATION (MDA) CAMPAIGNS IN WEST AFRICA: RESULTS FROM MULTI-LEVEL MODELING USING COVERAGE EVALUATION SURVEYS

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Effective mass drug administration (MDA) is the cornerstone of preventive chemotherapy (PC) neglected tropical disease (NTD) programs. USAID's Act to End NTDs | West program supports Ministries of Health to eliminate or control five PC NTDs across 11 West African countries by assisting with MDAs and disease specific assessments. Coverage evaluation surveys (CES) are used to validate coverage shortly after MDA. Non-treated populations (MDA eligible people in endemic districts who do not participate in the treatment campaign) are of concern as they may enable ongoing transmission of infection. If these populations can be better characterized, programs can take more precise actions to identify and target them. Three-level (persons/households/villages) hierarchical models of non-treatment were built using Act | West CES data from six surveys (39,705 MDA-eligible respondents) conducted in 24 districts across Ghana, Niger, Senegal, and Sierra Leone. We employed a range of explanatory variables from the CES and using geospatial techniques, we estimated travel time between households and the closest health facility as an additional explanatory variable. The overall model results showed odds of non-treatment were higher among males compared to females in all age groups except under 5. The highest odds of non-treatment were observed in males compared to females in the age group 25-34 (OR=2.55, 95% CI = 2.08, 3.13). People living in household more than one hour away from the closest health facility had 1.7 times higher odds (95% CI = 1.25, 2.34) of non-treatment compared to those living closer. Not having prior knowledge of the MDA campaign was also a significant predicter of non-treatment (OR=6.45, 95% CI = 5.46, 7.62). Country-specific models indicated that the drug distribution platform and an individual's time living in the community were also significant covariates. Our findings suggest the most influential programmatic response could include implementing age and sex specific

MDA mop-up, increasing the information coming through the health system to raise awareness of MDA, and focused attention on facilities serving relatively remote areas.

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A SEMI-QUANTITATIVE DIPSTICK ASSAY IN SERUM FOR THE FOLLOW-UP OF PATIENTS WITH SUBARACHNOID NCC

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Neurocysticercosis (NCC) is one of the most frequent parasitic diseases in the human central nervous system. Clinical manifestations rely principally on cyst localization, being subarachnoid NCC (SANCC) the most severe clinical form of NCC. Taking leverage of the enormous quantities of antigens released into circulations in SANCC, we evaluated the utility of a dipstick assay based on monoclonal antibodies (mAbs) anti-T solium (TsW8 and TsW5) in serum samples of SANCC patients for the follow-up after antiparasitic treatment; and compared its performance with a standard Ag-ELISA using the same pair of mAbs . Fifteen patients were included, with a total of 45 samples collected over 3 months. Under the hypothesis that a low mAb concentration would only detect high levels of circulating antigen, whereas when antigen level decrease, it would only be detectable using high mAbs concentrations; we developed a dipstick format with two different mAb concentrations: TsW8 at 3mg/ml and 0.5 mg/ml. Our results demonstrated that initially all SANCC cases presented saturating antigen levels the new dipstick assay (3+++ intensity bands) and Ag-ELISA (Ag ratio ranging from 104.73 to 21.00). Second and third bled showed a drastic reduction in antigen levels, obtaining one (n=10) or absent (n=1) bands and negative antigen ratios ranging from 0.92 to 0.25. As shown, the presence and intensity of reactive bands in our dipstick assay correlated strongly with antigen levels measured by Ag-ELISA. This new dipstick assay is a cheap, practical and reliable tool for the follow-up of patients with the NCC type with the worse prognosis (SANCC) reflecting the efficacy of cysticidal treatment. Hopefully, subsequent work will assess whether this dipstick assay can be used with non-invasive samples such as urine and in rural cysticercosis endemic communities.

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OPTIMIZATION OF A PCR ASSAY TO DETECT URINARY PARASITE DERIVATE DNA IN PATIENTS WITH NEUROCYSTICERCOSIS

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Neurocysticercosis (NCC) is one of the main causes of epilepsy and other neurological morbidity in most of the world. Definitive diagnosis is based on technically demanding and costly imaging approaches that are impractical for routine screening or monitoring treatment effectiveness. Specific molecular diagnosis of helminth-derived cell-free DNA (cfDNA) in body fluids has shown promise as a tractable approach monitoring infection status through measuring parasite cfDNA fragments in blood or urine by PCR. In this study, we explored the utility of a PCR-based detection of T. solium cfDNA for diagnosis of NCC. First, we tested the difference in stability and yield of parasite cfDNA from urine samples stored/processed under different conditions (fresh urine extracted immediately after collection, fresh urine in filter paper, frozen urine at -20C and frozen urine at -80C). Urine stored at -80°C gave the highest DNA yield and, when combined with a new 30-minute extraction protocol, requires as little as 4 ml of urine for sufficient cfDNA for analysis. We also evaluated and standardized 15 different sets of primers using urine samples from 6 subarachnoid and 6 parenchymal NCC cases. Primer pairs that resolved the amplicons pTsol9 (116 bp), TsollTS (86 bp) and Tsol13(<100 bp) demonstrated that T. solium cfDNA could pass the glomerular barrier and be detected in urine. Cross reaction analysis with T. multiceps, the closest related brain parasite in humans, revealed that none of the primer pairs generated amplicons from T. multiceps DNA. For the urine samples tested, all three primers pairs detected T. solium cfDNA; however, the pTsol9 amplicon showed the highest intensity band after electrophoresis. In a second phase of this study, we will increase our sample size to better assess the performance of the cfDNA detection system. This molecular test, based on the detection of parasite-derived cfDNA, could serve to categorize populations with viable cysts as an initial screen prior to confirmatory diagnosis and could also function as a sensitive biomarker for monitoring treatment efficacy using a non-invasive sampling method.

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DETECTION OF TAENIA SOLIUM ANTIGENS IN PAIRED SERUM AND URINE SAMPLES FROM PATIENTS WITH NEUROCYSTICERCOSIS USING THE TSW8/TSW5 ANTIGEN ENZYME-LINKED IMMUNOSORBENT ASSAY (AG- ELISA)

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Neurocysticercosis (NCC) is a frequent parasitic disease of the human central nervous system and is caused by the accidental ingestion of Taenia solium eggs. NCC is endemic in most developing countries, estimating that the third part of epilepsy cases are attributable to this parasitosis. The diagnosis of NCC is based on radiological images due to the heterogeneous clinical manifestations, which principally depend on its localization within the CNS. Detection of circulating parasite antigen marks the presence of live parasites, but it is usually assessed in serum sampling, which is poorly accepted by patients. On the other hand, urine antigen detection has been lately shown as an alternative non-invasive sample to detect parasite antigens. However, the correlation between paired samples of serum and urine has not been assessed with TsW8/TsW5 Ag-ELISA. We evaluated the correlation between paired serum and urine samples of 172 NCC patients using a T solium monoclonal antibody based enzyme-linked immunosorbent assay TsW8/TsW5 Ag-ELISA expressed as optical density (OD) and OD ratios. Study samples included subarachnoid (n=51), parenchymal (n=18) and calcified (n=103) NCC cases. Correlation between LogOD (rho=0.79) and antigen ratio (rho=0.66) of all samples was statistically significant (p=0.000). When separated by type of NCC, positive correlations were found between the urine and serum LogOD and ratio of subarachnoid (rho=0.71/rho=0.53), parenchymal (rho=0.83/rho=0.79), and calcified (rho=0.66/rho=0.64) NCC cases. Our results showed a strong correlation between paired serum/urine samples, guiding our perspective to a less invasive form of diagnosis.

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PRESENTATION, COMPLICATIONS, AND OUTCOMES OF CYSTIC ECHINOCOCCOSIS IN CUSCO, PERU

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Cystic echinococcosis (CE) morbidity and mortality are associated with size, delayed care, and cyst complications. Data on CE outcomes are scant in endemic countries. We characterized the clinical presentation, complications, and outcomes of CE in two tertiary hospitals in Cusco, Peru. We reviewed available medical records from patients discharged with a diagnosis of CE between January 2009 and December 2019. Medical records of 489 patients with over 821 cysts were included, the median age was 23 years (IQR 29), 50% were female, and 40% were referred from another health center. The most common occupations were student (43%) and homemaker (21%). Lung (64%) and liver (42%) CE were the most common. Other locations included other intraabdominal organs, brain, and pelvis. Most liver (60%) and lung (54%) CE had a diameter larger than 10 cm. Most lung (76%) and 42% of liver cysts were complicated on admission. Common complications of lung CE were hemoptysis, vomica, and bronchial fistulas. Leukocytosis (21%) and eosinophilia (10.6%) were uncommon. Surgery was performed on 72% of lung and 45% of liver cysts. Twenty-three percent of patients had a second related hospital admission and 4.7% had a third one. Three patients died in the hospital and 23.6% had a discharge status of "worse or unchanged". Patients with lung cysts (OR=1.92; 95%CI 1.07-3.44) and those reporting contact with dogs (OR 1.53; 95%CI 1.15-2.05) were more likely to have more than one admission. Patients with complicated cysts on admission (OR=1.9; 95%CI 0.99-3.66) and those treated medically (OR= 5.5; 95%CI 2.21-13.67) were more likely to meet a composite outcome of death or "worse/unchanged" discharged status. Patients receiving post-surgical medical treatment (OR=0.43; 95%CI 0.22-0.82) and those referred from another health center (OR=0.22; 95%CI 0.12-0.42) were less likely to have the composite outcome. Advanced and complicated CE were common and associated with worse outcomes. Readmission and worse/unchanged discharge status rates suggest a large burden affecting patients and the health system. Early detection and treatment may decrease the disease impact in the Cusco Region.

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DEVELOPMENT OF A HIGHLY SENSITIVE QPCR ASSAY FOR DETECTION OF ECHINOCOCCUS MULTILOCULARIS AND FURTHER MAPPING THE EXTENT OF EUROPEAN-LIKE STRAINS IN NORTH AMERICA

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Echinococcus multilocularis (Em) is a severe invasive parasitic disease. Humans are exposed through eggs shed primarily in the stool of wild canids, the definitive host. Almost all human cases of Em have been reported in Europe and Asia, despite the fact that North American strains of Em were previously known to circulate in wild canids in the Northern US and Canada. With the recent reporting of several human and canid cases of Em in Canada and the US due to a more aggressive European-like strain, we sought to develop a highly sensitive qPCR assay for detection of Em in stool samples that could be used for high throughput screening. Using RepeatExplorer, the Em genome was mined for unique, highly abundant interspersed repeats. We then developed and compared 15 new Em qPCR assays against the 5 found in the literature. The most sensitive assays were tested for cross reactivity to E. granulosus, E. ortleppi, and E. vogeli. New Em assay 17S2 was 2-fold more sensitive than any previously reported assay, had a threshold of detection of 25fg (at 97.7% sensitivity) and was specific to Em. We then screened wild canid stool samples from across the US and Canada (n=261), specifically from Virginia, Maryland, Nebraska, and British Columbia. A total of 13 samples (5%) were positive for Em. Mitochondrial sequencing is underway to determine the haplotype of these isolates. One of the positive isolates from a red fox in a Washington, DC suburb had a European haplotype at the gene loci COB and NAD2. This highly sensitive and specific qPCR assay for the detection of Em can be used to identify the prevalence of wild canid infection. Understanding the true extent of European-haplotype Em in North American wildlife will help better understand the risk to human disease and inform preventative measures.

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EVALUATION OF ETIDRONATE IN CALCIFIED CYSTS IN THE PIG MODEL OF NEUROCYSTICERCOSIS

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Neurocysticercosis (NCC) is the most important factor associated with late-onset epilepsy in developing countries. Cysts in the brain go through a process of complete resolution or calcification and these calcifications would be associated with epilepsy and seizures. Bisphosphonates, such as etidronate, have been shown to have an effect in reducing the ectopic calcification process in soft tissues, which would probably cause a decrease in epileptic activity. The objective was to evaluate the calcification process in pigs treated with etidronate in a natural infection of neurocysticercosis. This was an experimental study consisting of fourteen pigs naturally infected with Taenia solium and treated with 15 mg/kg albendazole and 25 mg/kg praziquantel orally. Then the animals were divided into two groups, one treated with etidronate for 10 weeks orally (n=7) and the other control group without treatment (n=7). After 8 months, the necropsy was performed and calcifications were evident on CT scan and SEM. Inflammation and calcium deposits were assessed with H&E, Masson's trichrome, Alizarin Red, and Von Kossa stains. In naturally infected pigs, we assessed the likelihood of residual calcification calcification after 8 months in 240 cysts from ten NCC pigs treated with either antiparasitic drugs plus etidronate antiparasitic only. Etidronate was associated with a significantly lower risk (49% 67/137 vs 77.67% 80/103 RR:0.63 $p<0.05$). Calcifications in pigs receiving etidronate had a non-statistically significant reduction in density measured on CT as Hounsfield units (80.8 ± 15.5 vs 100.6 ± 31.4). On SEM, calcifications in pigs receiving etidronate demonstrated significantly lower proportions of weight (Wt%) of phosphorus (2.68 vs 4.19 $p=0.02$) and calcium (4.2 vs 8.21 $p=0.01$). Etidronate also prevented the aggregation of macrophages, which are associated with calcification. This study shows the evaluation of the calcification process in animals treated with etidronate, observing less calcification in these, serving as a basis for future drug treatments in neurocysticercosis.

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DYSREGULATED AUTOPHAGY LEADS TO AXONAL SWELLING IN NEUROCYSTICERCOSIS

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Neurocysticercosis is a central nervous system disease caused by infection with the larval stage of Taenia solium (cysticercus). We have published novel neuropathological findings in neurocysticercosis, such as axonal swellings, which other studies linked to seizures and cognitive decline, common symptoms in neurocysticercosis. As axonal swellings indicate an impairment in axonal transport and accumulation of cargos throughout the neurons, autophagy was proposed as a possible mechanism involved in axonal swelling formation. We aimed to understand the role of autophagy in the axonal swelling formations in neurocysticercosis. Using our rat model of neurocysticercosis, we analyzed secretory cysticerci antigens and different markers for autophagy, like Beclin-1, p62, and LC3B, in brain sections by immunohistochemistry. We found overexpression of autophagy markers, and this autophagy was dysfunctional where p62 was increased in the tissue surrounding the parasite, and neurons mainly overexpressed autophagy markers, unlike glial cells. Although microglia engulfed most parasite antigens, secretory cysticerci antigens were found within the neuron, which co-localized within autophagosomes. The results suggest an important role of autophagy in disease development in neurocysticercosis and may afford attention toward improved disease management.

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EVALUATION OF APOPTOSIS IN RESPONSE TO ANTHELMINTIC TREATMENT IN RAT BRAINS EXPERIMENTALLY INFECTED WITH ONCOSPHERES OF TAENIA SOLIUM

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An important cause of seizures, epilepsy and other neurological manifestations is the infection by Taenia solium, which is endemic in developing countries and currently a public health problem worldwide due to migration. In recent years, studies have increased trying to understand the pathogenesis of the disease and the host's inflammatory response using animal models. The unpredictable nature of the host's immune reaction in response to the presence of the parasite and the various pathological mechanisms that this reaction induces in the nervous system, make this a complex disease. When the cysticercus begins to degenerate due to it's development or in response to antiparasitic drugs, it triggers an exacerbated inflammatory response. This could cause damage to neuronal and glial cells, a central feature of neurodegenerative diseases, nevertheless; there are no studies in Neurocysticercosis that confirm this information. Recent evidence suggests that apoptosis process plays a key role in nerve cell death in acute and chronic diseases of the nervous system. In the present study, we proposed to evaluate whether the presence and subsequent inflammation caused by the cysticercus of Taenia solium would be associated with damage and death by apoptosis of neuronal and glial cells in an animal model. To achieve this, by the colocalization of biomarkers by immunofluorescence; The TUNEL technique and activation by Caspase-3, the presence of apoptotic cells will be determined in an animal model of NCC using laboratory rats. We found that colocalization of TUNEL essay and active Caspase-3 was performed, suggesting the presence of cell death by apoptosis, with an evident increase in rats infected with NCC, predominantly in those that were sacrificed 24 hours after treatment. In addition, an increase in immunoreactivity to the apoptotic marker Caspase-3 was demonstrated, with an increase predominant in NCC-infected rats sacrificed 24 hours after treatment. In addition, cellular colocalization of active Caspase-3 was demonstrated with GFAP and NeuN but not with Iba-1, suggesting that apoptosis mainly affects astrocytes and neurons but not microglia.

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LEAKY GUT MECHANISMS IN GIARDIASIS

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Giardia duodenalis is an intestinal parasite endemic worldwide and commonly transmitted via contaminated water. Infection in children under 2 is one of the top 5 infectious causes of childhood growth stunting. Growth faltering is a complex pathology facilitated by changes in the intestinal barrier and enzymatic deficiencies. This pathology is predictive of later delays in cognitive and motor development. However, while infection is widely associated with barrier damage in vitro, in animal models, and in patient studies, the mechanisms behind this process are not well understood. The Protease-activated receptor 2 (PAR2) has a prominent role in modulating intestinal tight junction permeability in Celiac disease. Co-culture of Giardia and Caco2 cells similarly results in altered tight junction morphology as revealed by staining for the tight junction-associated protein Zonula occludens 1 (ZO-1); these changes are reduced by treatment with a PAR2 antagonist. Effects of Giardia-induced PAR2 signaling on barrier function are being assessed further by measuring transepithelial electrical resistance (TEER) in Caco2 cells and PAR2+/- and PAR2-/- organoids cultured on transwell filters. Additionally, infected mice lacking PAR2 and fed a low-protein diet gain weight normally over time, while wildtype C57BL/6 animals under the same conditions arrest growth post infection. These data indicate that PAR2 signaling contributes to intestinal permeability defects and growth faltering. Identifying parasite factors that activate PAR2 will provide novel targets for development of pharmaceuticals and vaccines to improve child growth.

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DISRUPTION OF HUMAN LYMPHATIC EPITHELIAL CELL CONTACT INTEGRITY PROTEINS BY FILARIAL MIRNAS

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Parasitic filarial nematodes Wucheria bancrofti, Brugia malayi, and Brugia timori are the causative agents of the debilitating, yet neglected, infectious disease lymphatic filariasis. Adult worms reside in the human lymphatic system where they can survive and reproduce for 8-10 years. The worms can damage the lymphatics and cause lymphedema, however the mechanism by which this occurs is unclear. As filarial worms are in contact with lymphatic endothelial cells (LECs) we used an in vitro model to study interactions between the parasite and human LECs. Filarial worms have been shown to secrete microRNAs (miRNAs) that can be detected in the biofluids of infected animals and humans. We tested if secreted B. malayi miRNAs were involved in the damage to lymphatic cells, which could lead to lymphedema. We used miRanda, an algorithm to predict miRNA-mRNA pairs, to find potential human mRNA targets of B. malayi miRNAs that were previously found to be secreted by worms. First, we prioritized the human targets that encode proteins involved in cell-to-cell connection and the extracellular matrix: fibronectin, integrins, as well as proteins of tight junctions (claudins) and adherens junctions (VE-cadherin). We identified 2 Brugia miRNAs—bma-mir-86 and bma-mir-5864—that have potential target sites in these genes. To validate the interactions predicted and determine their effects on target genes, we treated LECs with miRNA-mimics, which mimic selected parasite miRNAs, and analyzed the expression of the human proteins to determine if there was suppression. We showed that the 2 parasite miRNAs tested significantly decreased the expression of human fibronectin and VE-cadherin. We also observed a reorganization of integrins in treated cells. As these parasite miRNAs are secreted by the worms in the lymphatics, they could participate in the

pathology by reducing cell-to-cell connection and adhesion of the cells, as well as increase the permeability of the endothelial monolayer. Defining the role filarial miRNAs play in the pathogenesis could help establish a mechanism that could be targeted therapeutically.

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A HUMAN PLURIPOTENT STEM CELL DERIVED MODEL OF THE BLOOD-BRAIN BARRIER IN CEREBRAL MALARIA

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Blood-brain barrier (BBB) disruption is a central feature of cerebral malaria (CM), a severe neurologic complication of Plasmodium falciparum (Pf) infections that presents clinically as an unarousable coma and is a significant driver of childhood mortality. The pathogenesis of CM involves sequestration of Pf-infected red blood cells (Pf-iRBCs) to the brain microvasculature. In-vitro BBB model-based studies have provided insight into CM-mediated brain injury, but limitations of these models include endothelial monolayers in the absence of cells like astrocytes and neurons and reliance on immortalized or primary brain microvascular endothelial cell (BMECs) that lack physiologically relevant barrier properties and show batch-to-batch variability. We have developed a multicellular BBB model comprised of human-induced pluripotent stem cell (iPSC) derived BMECs, neurons, and astrocytes representing a physiologically relevant BBB as determined by elevated trans-endothelial electrical resistance (TEER). Using the HB3var03 parasite strain that expresses proteins bind to endothelial cells, we conducted co-culture experiments with multiple timepoints over 9 hours. By the 6-and 9-hour timepoint, in iPSC-derived BMECs co-cultured with Pf-iRBC but not uninfected RBC controls, we observed disruptions in barrier integrity measured by TEER and confirmed by immunofluorescence imaging to visualize changes in the localization of tight junction (TJ) proteins occludin and zona-occludin-1. Western blots of BMEC lysates to determine Pf-iRBC co-culture mediated changes in TJ protein expression on BMECs, and immunoassays with co-culture supernatants to detect changes in expression of angiogenesis, and endothelial activation markers are ongoing. Furthermore, we will validate the effects of Pf-iRBC in a co-culture model of the BBB comprising of BMECs, astrocytes, and neurons to investigate neuronal injury. Upon completion, this work aims to establish the iPSC-derived multicellular BBB model as a new in vitro standard for investigating pathways underlying neuronal injury in clinical CM.

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THE BRCT DOMAIN FROM LEISHMANIA MAJOR LMJPES PROMOTES MALIGNANCY AND DRUG RESISTANCE IN MAMMALIAN CELLS

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According to IARC, 15% of cancer cases are attributable to pathogens including parasites. Epidemiological studies suggest an association between cancer and leishmaniasis. Recently, the homologue of the human oncogene PES1 was identified in Leishmania major and named LmjPES encoding a conserved protein containing a BRCT domain. This domain is a key factor in DNA damage-response checkpoints. Interestingly, previous results have demonstrated that LmjPES is involved in parasite infectivity. In addition, BRCT domain was used as a therapeutic target and new antileishmanial drug candidates were identified. Our work aimed to elucidate the hypothetical oncogenic implication of BRCT domain from LmjPES in host cells. We generated a lentivirus carrying this BRCT domain sequence (lentiBRCT) and a lentivirus expressing the luciferase protein (lentiLuc), as control, and used them to infect mammalian cells. We observed that the expression of BRCT domain from LmjPES conferred to HEK293T and NIH/3T3 mammal cells a greater replication rate and higher survival in vitro. Moreover, such lentiBRCT infected cells were less sensitive to genotoxic drugs 5-FU and etoposide. In addition, lentivirus infected cells were used to induce tumorigenesis process. The in vivo experiments showed faster tumor growth in mice inoculated with lentiBRCT respect to lentiLuc HEK293T infected cells. To shed some light on the molecular mechanisms involved in the cellular alterations described after the expression of the studied domain in mammalian cells, we performed a high-throughput RNA sequencing of LentiBRCT- and Lentiluc-infected HEK293T cells. The gene expression profiling analysis revealed that BRCT domain from LmjPES altered the expression of proliferation- (DTX3L, CPA4, BHLHE41, BMP2, DHRS2, S100A1 and PARP9), survival- (BMP2 and CARD9) and chemoresistance-related genes (DPYD, Dok3, DTX3L, PARP9 and DHRS2). Altogether, our results reinforced the idea that in eukaryotes, horizontal gene transfer might also be achieved by parasitism like Leishmania infection driving therefore to some crucial biological changes such as proliferation and drug resistance.

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SUPER RESOLUTION IMAGING REVEALS CYTOSKELETON REGULATION IN PLASMODIUM SEXUAL STAGE DEVELOPMENT

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The transmission of Plasmodium falciparum parasites from human to mosquito relies on the formation of a specialised sexual form known as the gametocyte. The gametocyte develops through five distinct morphological stages over a period of 10 days, adopting a unique crescent shape upon reaching sexual maturity. Formation of these mature stage V gametocyte is essential for transmission. The distinct morphology of the gametocyte is driven by the assembly of a dense microtubule (MT) network that assembles under an additional cisternal compartment called the inner membrane complex (IMC). In addition, the parasite also has an actin cytoskeleton which accumulates at the apical tips of the parasite and co-locates with the MT network across gametocyte development. Despite the importance of these structures to maintaining parasite morphology, we know very little about how these networks are regulated and how they work together to control gametocyte shape and transmission. In our work we investigate IMC proteins (GAPM 1-3), the actin nucleating protein formin 2 and important proteins of mitosis (centrin 1-3 and NDC80). To investigate the function of these proteins we have employed a conditional knockout approach and combined this with ultra-expansion microscopy, super-resolution imaging and electron microscopy. We show that early gametocyte have novel non-mitotic microtubules within their nuclei that bind and redistribute chromatin inside the nucleus of gametocytes. In addition, these novel MTs function in positioning the nascent IMC and subpellicular microtubules, initiating gametocyte elongation. We show that deletion of GAPM proteins ablates IMC expansion leading to an inability of the MT network to align and elongate the gametocytes. Lastly, we demonstrate that Formin 2 locates at the apical tips of the gametocyte interleaving between the actin and MT networks, stabilising the crescent shape. Deletion of Formin 2 results in a collapse of gametocyte shape. In this work we reveal a holistic picture of the function and interplay between key proteins controlling IMC, MT and actin cytoskeletons dynamics across gametocyte development.

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DEVELOPMENT OF AN IN VIVO MOUSE MODEL FOR TRANSMISSION BLOCKING STUDIES WITH HUMAN MALARIA PARASITE PLASMODIUM FALCIPARUM

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Malaria elimination/eradication will need a coordinated effort involving multiple strategies including those that interrupt transmission of malaria parasites from humans to mosquitoes. Transmission blocking drugs, vaccines and genetically modified mosquitoes represent an appealing approach. Standard membrane feeding assay (SMFA), which involves feeding mosquitoes with cultured Plasmodium falciparum gametocytes using glass membrane feeders is used as primary screen for different transmission blocking interventions (TBI). However, further development of TBI is hindered by the lack of a reliable P. falciparum small animal model to test TBI before proceeding to the controlled human malaria infection studies or field trials. To develop the mouse model for assessment of TBI we have utilized extremely immunodeficient NSG (NOD-scid IL2Rgammanull) mouse. The immunodeficiency allows the mice to be humanized by the engraftment of human red blood cells. P. falciparum asexual blood stages, when inoculated in RBC humanized NSG mice, are promptly cleared from circulation, either by macrophages or through splenic clearance. However, when we inoculated mature stage V gametocytes, they remained in circulation for at-least a week, which allows us to use these mice to feed Anopheles stephensi mosquitoes. Mosquitoes fed on NSG mice inoculated with P. falciparum mature gametocytes developed midgut oocyst and passive transfer of transmission blocking monoclonal antibody to Pfs25 (4B7) significantly reduced the transmission. To further standardize the assay, we are currently testing known transmission blocking drugs and antibodies.

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GLOBAL RELEASE OF TRANSLATIONAL REPRESSION ACROSS PLASMODIUM'S HOST-TO-VECTOR TRANSMISSION EVENT

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Malaria parasites must be able to respond quickly to their environment, including during their transmission between mammalian hosts and mosquito vectors. Therefore, before transmission, female gametocytes proactively produce and translationally repress mRNAs that encode essential proteins that the zygote requires to establish a new infection. This essential regulatory control requires the orthologues of DDX6 (DOZI) and LSM14 (CITH), which along with ALBA proteins, form a translationally repressive complex in female gametocytes that associates with many of the affected mRNAs. However, while the release of translational repression of individual mRNAs has been documented, the details of the global release of translational repression have not. Moreover, the changes in spatial arrangement and composition of the DOZI/CITH/ALBA complex that contribute to translational control are also not known. Therefore, we have conducted the first comparative transcriptomics and proteomics of Plasmodium parasites across the host-to-vector transmission event to document the global release of translational repression. Using female gametocytes and zygotes of P. yoelii, we find that over 150 transcripts are released for translation soon after fertilization, including those with essential functions for the zygote. However, we also observed that some transcripts remain repressed beyond this point. In addition, we have used TurboID-based proximity proteomics to interrogate the spatial and compositional changes in the DOZI/CITH/ALBA complex across this transmission event. Consistent with recent models of translational control, proteins that associate with either the 5' or 3' end of mRNAs are in close proximity to one another during translational repression in female gametocytes and then dissociate upon release of repression in zygotes. These interactions in female gametocytes were further validated through Structured Illumination Microscopy and Ultrastructure Expansion Microscopy. Together, these data provide a model for the essential translational control mechanisms used by malaria parasites to promote their efficient transmission.

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DYNAMICS OF ASYMPTOMATIC PLASMODIUM FALCIPARUM AND P. VIVAX INFECTIONS AND INFECTIOUSNESS TO MOSQUITO IN LOW TRANSMISSION SETTING OF ETHIOPIA: A LONGITUDINAL OBSERVATIONAL STUDY

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The natural history of Plasmodium falciparum and P. vivax asymptomatic infections and the magnitude of their contribution to onward transmission in co-endemic low transmission settings is incompletely studied. We conducted a 15-month longitudinal study in asymptomatic PCR-detected asymptomatic parasite carriage with mosquito membrane feedings every 14 days for 2.5 months and subsequent monthly parasitology assessments in Adama, Ethiopia. Transmission results were compared with passively recruited clinical malaria cases from the same setting. From 596 feeding experiments in 162 asymptomatic individuals, 0.3% (69/24,966) of mosquitoes were infected by 4 individuals. Two microscopy detectable asymptomatic P. falciparum carriers infected 18.8% (15/80) of mosquitoes and one sub-microscopic P. falciparum carrier infected 30% (14/46) of mosquitoes. No sub-microscopic P. vivax mono-infection was infectious. Among clinical cases, P. falciparum clinical patients were less infectious (2.7% infected mosquitoes, 38/1389) compared to P. vivax patients (42.4% infected mosquitoes; 1068/2519). When analyzing infection duration at a continuous scale, the median duration of infection was 33 days (IQR:15-56) for individuals who were P. falciparum microscopy positive at enrolment and 30 days (IQR:15-48) for individuals who were P. falciparum PCR positive (but microscopy negative) at enrolment. The longest infection duration we observed was 363 days. For P. vivax parasite carriers who were PCR positive at enrolment, the median duration was 33 days (IQR:15-60). We conclude that a minority of asymptomatic infections are of long duration and infectious to mosquitoes. Clinical cases are a relevant source of transmission for P. vivax.

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EFFECT OF CHLOROQUINE ON PLASMODIUM VIVAX PARASITE TRANSMISSION TO MOSQUITOES IN THE EARLY POST-TREATMENT HOURS, ARBA MINCH, ETHIOPIA

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Ethiopian malaria guidelines prescribe chloroquine (CQ) for Plasmodium vivax. Data on human-mosquito malarial parasite transmission in the initial days following CQ therapy is scarce. This study examines CQ's early transmission-blocking impact. Thirty microscopically confirmed P. vivax patients in Arba Minch, Ethiopia, participated in an open-label

experimental follow-up investigation. Participants were treated with CQ for three days and observed for 42 days. Clinical, microscopic blood film and quantitative polymerase chain reaction (qPCR) tests were performed. Anopheles arabiensis colony mosquitoes were tested using artificial membrane feeding. While nested polymerase chain reaction (nPCR) was used to measure the clearance of asexual parasites, qPCR was used to measure the clearance of mature gametocytes. 67% (20/30) were positive for P. vivax alone, 7% (2/30) for both P. vivax and P. falciparum, and 10% (3/30) were positive for P. falciparum by nPCR. Plasmodium vivax mono-infection cases confirmed by nPCR were included in the analysis. 85% (17/20) of confirmed cases were infectious to mosquitoes before treatment and 59% (10/17) after 8 and 24 hours of treatment. The median oocyst infection rate dropped from 51% (245/480 mosquitoes) (ranges: 14-83%) at baseline to 36% (209/522 mosquitoes) after 8 hours and 17% (81/440 mosquitoes) at 24 hours post-treatment. The circumsporozoite protein rate of An. arabiensis was 3% (95% CI: 1-7) before treatment, 3% (CI: 1-5) at 8 hours post-treatment, and 0.7% (CI: 0.1-2.5) at 24 hours post-treatment. Eight hours post-treatment, all patients had gametocytes and sexual parasites. After 24 hours of treatment, positive cases dropped to 50%, but mosquitoes continued to transmit parasites. On day three post-treatment, 19 of 20 patients obtained gametocyte clearance and all patients showed complete asexual parasite clearance. This finding implies that the P. vivax-positive cases continue supporting parasite transmission for at least 24 hours after treatment; therefore, protective intervention and anti-malarial medications that immediately kill mature gametocytes could be recommended.

6503

CLINICAL INVESTIGATION STUDY TO EVALUATE THE CONSISTENCY AND REPRODUCIBILITY OF TWO CONSECUTIVE MOSQUITO FEEDING ASSAYS IN ADULTS WITH VARYING PLASMODIUM FALCIPARUM GAMETOCYTE DENSITIES

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New malaria control tools are needed to prevent the transmission of parasites from host to the mosquito vector and vice versa. Infectiousness of Plasmodium falciparum gametocytes obtained from individuals to lab reared mosquitoes should be estimated and quantified in order to apply assays that are easily applicable for evaluating transmission-blocking interventions. The aim of this of this study was to establish relationship between parasite transmission from humans to mosquitoes both within a person and across persons by assessing the variation in the proportion of infected mosquitoes with at least one oocyst (oocyst prevalence) in direct membrane feeding assay (DMFA) and direct skin landing feeding assay (DSFA) performed at two consecutive time points in the same human subject with P. falciparum gametocytemia. A total of 400 adults residing in Western Kenya without symptoms of malaria were enrolled. A blood sample was tested for the presence of P. falciparum gametocytes. Subjects that tested positive for gametocytes had both direct membrane feeding assays (DMFA) and direct skin landing feeding assay (DSFA) on day 1 and day 2 to compare infection rates between the two feeds. Blood samples from 42/400 individuals testing positive for gametocytes underwent mosquito infection assays. Survival rates of mosquitoes at initial day 1 and subsequent feeding day 2 were 12.1 and 11.4 days for DSFA, and 13.2 and 11.6 days for DMFA. The mean oocyst prevalence by DSFA on days 1 and 2 was 5.2% and 2.3% on days 1 and 2; and 6.3% and 2.2% for DMFA, respectively, suggesting comparable readouts for initial versus subsequent feeding timepoints. The correlation between day 1 and day 2 and between assays was low. Exploratory analysis suggests a lower probability of infection the second day, with lower oocyst density. We will discuss the implications for future study designs in testing transmission-blocking interventions based on these results.

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HYPER-DIVERSE ANTIGENIC VARIATION AND RESILIENCE TO TRANSMISSION-REDUCING INTERVENTION IN FALCIPARUM MALARIA

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In falciparum malaria under high transmission, high asymptomatic prevalence co-occurs with incomplete immunity given vast antigenic variation of the parasite. The var multigene family encodes for the major surface antigen of the blood stage of infection. A field longitudinal study in northern Ghana relied on deep sampling of var sequences from individual isolates to monitor response to transient IRS (Indoor Residual Spraying) intervention. Resulting estimates of parasite population size and structure showed persistent features of high transmission regions despite considerable decrease in prevalence, consistent with a rapid rebound post-IRS. To ask whether the transmission system had been brought closer to losing its persistence, we investigate with a stochastic agent-based model (ABM) the existence of a sharp transition with intervention intensity. We also seek molecular indicators capable of revealing proximity to such a transition in the model, and apply those to the field molecular data on var genes across multiple surveys and the IRS intervention. The ABM explicitly incorporates the evolution of var genes and the acquisition of specific immunity by individual hosts. A sharp transition occurs in the model across a narrow region of intervention intensity in the capacity of the transmission system to rapidly rebound to high prevalence. Molecular indicators are identified, informative about the approach to this transition. Their application to the field data indicates that the system was brought close to transition by IRS, so that sustaining and intensifying intervention could have pushed it to a slow-rebound regime with a high probability of extinction. Our results establish a link between population dynamics of the disease and observations of parasite population genomics from the perspective of hyper-variable antigen-encoding genes. They indicate that the structure of diversity revealed via molecular surveillance can inform intervention against malaria in high-transmission endemic settings. These findings should be relevant to other pathogens with similar immune evasion strategies based on high antigenic diversity.

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DENGUE SEVERITY BY SEROTYPE IN 17 YEARS OF A PEDIATRIC HOSPITAL STUDY IN NICARAGUA

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The four dengue virus serotypes (DENV1-4) cause a range of clinical manifestations, from mild to severe and potentially fatal disease. Understanding dengue severity by serotype is critical, particularly in the context of the introduction of new vaccines that have differential efficacy by serotype. We studied the clinical spectrum of all 4 DENV serotypes over 17 years in the Nicaraguan National Pediatric Reference Hospital. Study participants 6 months to 14 years of age were followed during their hospital stay or as ambulatory patients. Cases were confirmed by molecular, serological and virological methods. A clinical report form with >150 variables with detailed clinical information was completed daily. Cases were classified according to the World Health Organization 1997 (Dengue Fever/Dengue Hemorrhagic Fever/Dengue Shock Syndrome; DF/DHF/DSS) and 2009 (Dengue without Warning Signs/Dengue with Warning Signs/ Severe Dengue) guidelines. A total of 2,811 participants were enrolled, with 1,570 (56%) laboratory-confirmed as DENV-positive. Of 1,355 cases with serotype result by RT-PCR, 281 corresponded to DENV1, 572 to DENV2, 466 to DENV3 and 36 to DENV4. With DENV2 and DENV4, secondary (2°) cases were more prevalent, with 478 (88.7%) and 30 (93.8%), respectively, while with DENV1 and DENV3, 136 (51.1%) and 237 (53.1%) were primary cases, respectively. Plasma leakage was associated with DENV2 (OR: 1.46; 95% CI: 1.16-1.85) and DENV3 (OR: 1.3; 1.02-1.66), with 190/572 (33.2%) DENV2 and 105/466 (22.5%) DENV3 cases resulting in DHF/DSS, respectively. Of the DHF/DSS cases, 167/178 (93.8%) of DENV2 cases were 2°, compared to 63/103 (61.2%) of DENV3 cases and 22/36 (61.1%) of DENV1 cases. Comparing serotypes, DENV2 was associated with DHF/ DSS (OR: 2.06; 1.67-2.75), while DENV3 was associated with Severe Dengue (OR: 2.08; 1.60- 2.70). Overall, we found that clinical manifestations of dengue differ by serotype and immune response, with DENV2 and DENV3 being most associated with severity. Our findings indicate that the clinical spectrum of all serotypes should be considered in the development of a safe and effective DENV vaccine.

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COMPARATIVE EVALUATION OF FIVE RAPID DIAGNOSTIC TESTS FOR DENGUE DIAGNOSIS

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Every year, dengue outbreaks cause substantial humanitarian and economic hardship worldwide. Dengue causes a wide spectrum of symptoms. Primary dengue can range from subclinical disease to flu-like symptoms. Although less common secondary dengue is associated with increased morbidity and mortality. Accurate, efficient and rapid diagnosis of dengue in acute stage is essential as delay in diagnosis increases the risk of severe dengue and can lead to poor disease outcome. In dengue-endemic areas, laboratories and clinics have to date relied on simple and cost-effective serological rapid diagnostic tests (RDTs) to diagnose dengue. This study evaluated the performance of five commercially available RDTs which can detect NS1 antigen and IgM/IgG antibodies: SD Bioline Dengue Duo, Atron Dengue virus IgG/IgM and Ag cassette, Standard Q Dengue Duo, Humasis Dengue combo kit and ALL Test Dengue Combo Rapid Test. Well characterized archived dengue and non-dengue serum samples at Aga Khan University, Pakistan were screened. Each RDT was evaluated separately and in combination to determine diagnostic parameters [non-structural (NS1) antigen and/or immunoglobulin M (IgM) positive]. 430 serum samples were evaluated (255 NS1 ELISA positive and 175 negative NS1 ELISA). Compared to the reference NS1 enzyme-linked immunosorbent assay (ELISA) samples, sensitivity of RDTs ranged from 69.8% to 94.12% with best overall sensitivity shown by Atron Dengue virus IgG/IgM and Ag cassette (94.12%) All RDTs showed a specificity of >99%. Atron Dengue virus IgG/IgM and Ag cassette (96.78%) had the highest diagnostic accuracy. In conclusion, Atron Dengue virus IgG/IgM and Ag cassette showed the highest sensitivity and diagnostic accuracy, while Standard Q Dengue Duo and ALL Test Dengue Combo Rapid Test showed the highest specificity. Moreover, these results confirm that combining antigen- and antibody-based RDTs can have huge value for dengue diagnosis and that very good commercial tests exist and should be used.

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POTENTIAL UTILITY OF CONTINUOUS PPG MONITORING IN THE MANAGEMENT OF SEVERE DENGUE

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Dengue infection can progress to shock, driven by increased intravascular permeability and plasma leakage. Management of patients with dengue shock is challenging as the risk of repeated episodes of shock (reshock) due to insufficient fluid replacement and ongoing plasma leakage must be weighed against the risk of volume overload when too much fluid is given. Therefore, a dynamic measure of intravascular volume to guide fluid management has the potential to improve clinical outcomes. We investigated the use of continuous photoplethysmogram (PPG) monitoring using a wearable device for the management of dengue in a prospective study involving 250 patients who were admitted to the Hospital for Tropical Diseases in Ho Chi Minh City, Vietnam in 2020 to 2022. Detailed clinical data were collected and PPG monitoring was performed for 24 hours after enrollment. We hypothesized that the PPG waveform can provide actionable information about a patient's volume status. The 2-hour time window preceding a reshock event, was predefined as an "empty" intravascular state, while the 2-hour time window between 1 to 3 hours following a fluid bolus, was predefined as "full". We then sampled PPG segments (1 minute duration) from these time windows and, accordingly, labelled each as "empty" or "full". Labelled segments were transformed into spectrograms and used to train and test a convolutional neural network model. There were 96 patients with sufficient data for the analysis. Data from 67 patients (70%) were used to train the model and the remaining data were reserved for testing. We repeated the analysis 3 times using 3 different patient splits. The overall performance of our model included accuracy of 0.76 (range 0.73-0.80), F1 score of 0.84 (range 0.84-0.85) and ROC-AUC of 0.77 (range 0.73-0.82). In summary, preliminary analyses suggest that information regarding intravascular volume during severe dengue can be extracted from real-life PPG recordings. Since PPG signals are measured continuously, there is the potential for dynamic guidance. We are continuing to refine our model and will present our updated analysis.

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METFORMIN AS ADJUNCTIVE THERAPY IN OVERWEIGHT AND OBESE PATIENTS WITH DENGUE: AN OPEN-LABEL SAFETY AND TOLERABILITY TRIAL (MEDO)

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Dengue is a major public health burden for Vietnam and globally. Patients with certain risk factors, including obesity, are at higher risk of developing severe disease. There is no antiviral for dengue and novel host-directed therapeutics are urgently needed, particularly in high-risk patients. We conducted an open-label trial using Metformin as an adjunctive therapy for dengue patients with obesity. Our hypothesis was metformin would attenuate obesity-induced lipid-inflammatory mediators, improve clinical parameters and reduce viral replication through AMPK activation and immunomodulation mechanisms. This trial recruited 120 overweight/obese patients with dengue who were admitted to the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam between 2020 and 2022. Patients were eligible for enrolment if they were 10- 40 years old, had a BMI > 25kg/m2 or BMI-for-age > 1SD, were within 72 hours of fever, and had a positive NS1 test. Sixty patients were treated with metformin (treatment group) and compared with 60 patients receiving standard of care (untreated group). Following a pilot of 10 patients given a low dose of metformin, the dosing for the remaining 50 patients was weight-based, with patients receiving either 1g or 1.5g per day in divided doses for 5 days. The primary outcome was number of adverse events (AEs) and secondary outcomes included comparisons of clinical, laboratory parameters, plasma viraemia, NS1 antigenaemia and biomarker kinetics. Majority of patients enrolled were male (68% in treatment group versus 73% in untreated) with a mean age of 18.4 ± 7.9 years in both groups. Preliminary analysis shows most of the patients developed more than 1 warning sign during their hospitalization (85% versus 88%) and 10% developed dengue shock syndrome (in both groups). Twenty-five patients (42%) had to discontinue metformin due to predefined AEs, including hypoglycemia (7%), severe diarrhea (22%), increased lactate > 3mmol/L (13%). The full trial results will be presented at the conference. ClinicalTrials.gov identifier: NCT04377451

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AFTERSHOCK: PERSISTENT INFLAMMATION AND ENDOTHELIAL ACTIVATION IN ADULT SURVIVORS OF DENGUE SHOCK

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Dengue shock (DS) is the most severe complication of dengue virus infection; the syndrome results from plasma leak through an activated, disrupted endothelial barrier and may be complicated by hyperinflammation. It is assumed that inflammation and endothelial disruption subside with clinical recovery, but no studies have followed up survivors to confirm this. We conducted a prospective observational study of adults (age≥16 years) with DS in Vietnam between 2018-2022. Patients completed the following assessments at hospital discharge, 1-, 3- & 6-months follow-up: health related quality of life (HRQOL) (EQ-5D-5L), cognitive function (Montreal Cognitive Assessment, MoCA), plasma inflammatory (IL-6, ferritin) and endothelial (Ang1, Ang2, VCAM1) biomarkers & endothelial function testing (EndoPAT). Healthy controls (HC) and survivors of septic shock (SS) participated as comparators. Survivors of DS (n=125) experienced rapid functional recovery, with median EQ-5D-5L visual analogue score >90/100 at all timepoints. MoCA scores were lower than normal (≥26) at hospital discharge (med:23/30, IQR:20-26), but scores had largely normalized by 3 months (med:27/30, IQR:25-29). However, compared to HC (n=25), DS patients had persistent subclinical inflammation (elevated IL-6 & ferritin vs HC, p<0.01 at all timepoints), endothelial activation (lower Ang1 and elevated VCAM1 vs HC, p<0.01 at all timepoints) and impaired endothelial function (median Reactive Hyperaemia Index below normal threshold of 1.67 at 1-,3-&6-months). Survivors of SS (n=26) also had persistent inflammation, with worse functional and cognitive outcomes than DS survivors. This is the first report that survivors of DS have persistent inflammation, endothelial activation, and impaired endothelial function for at least 6 months after discharge. Further study is needed to determine the duration of this phenomenon, and whether individual or repeat infections have an impact on long term cardiovascular health; if so, these findings could have important public health implications for dengue endemic regions.

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NEURODEVELOPMENTAL OUTCOMES IN TWO YEAR OLD CHILDREN BORN DURING THE ZIKA EPIDEMIC IN BRAZIL: A PROSPECTIVE COHORT STUDY

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Key questions remain on the impact of Zika virus (ZIKV) exposure on long-term developmental outcomes, especially among infants who were exposed in utero during the pandemic in the Americas but did not develop congenital Zika syndrome (CZS) at birth. Therefore, we prospectively evaluated the clinical and developmental outcomes of a cohort of children with two years of age who were born during the Zika epidemic in Salvador, Brazil. We enrolled mothers and their newborn infants at a maternity hospital between Oct 01, 2015 and Jan 31, 2016. Performed anthropometric, auditory, ophthalmologic evaluations, Hammersmith Infant Neurological Examination and Bayley Scales of Infant and Toddler Development-3 assessment. We ascertained ZIKV exposure in utero by assaying for neutralizing antibodies in sera from mothers during childbirth and evaluated the association with clinical and developmental outcomes. Among 469 children enrolled at birth, 364 (78%) completed follow-up evaluations at a mean age of 26.9 (±4.0) months. Of these, 214 (58.8%) were born to mothers with serologic evidence of ZIKV exposure. Of these, 22 (10.2%) were identified to have neurodevelopmental impairment (31.8% cognitive, 45.5% language and 22.7% motor domains). After adjusting for maternal age, ZIKV exposure was not associated with specific domain impairments but was associated with a higher risk (OR=2.36; 95% CI 1.05-5.80) for global neurodevelopmental impairment. The attributable fraction of neurodevelopmental impairment associated with ZIKV exposure was 36.0%

(95% CI 3.4 to 68.6%). Significant associations were not observed between exposure and anthropometric, auditory or ophthalmologic deficits. Our study found that ZIKV exposure in utero imparts mild neurodevelopmental deficits, primarily associated with language acquisition, in a significant proportion of children without CZS by two years of life. Given the large numbers of infants that had unapparent ZIKV exposures during the pandemic, routine screening and intervention will be needed in affected regions of the Americas to mitigate these impacts on development, especially as these children enter schools.

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PERSISTENT RHEUMATOLOGICAL DISEASE AFTER SEVEN YEARS OF CHIKUNGUNYA VIRUS INFECTION: RESULTS FROM A COHORT STUDY IN PIEDECUESTA, COLOMBIA

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Chikungunya virus (CHIKV) has circulated and caused outbreaks in the Americas region since 2014. There is a need to better characterize post-CHIKV chronic rheumatism and its impact on quality of life (QoL). The objective was to estimate the prevalence of post-CHIK chronic rheumatism in adult patients 7 years after the CHIKV outbreak (2014-2015) in Piedecuesta, Colombia.We evaluated 106 patients, 94 (88.7%) of which had symptomatic infection. The exposure was determined by RT-qPCR, IgG/IgM ELISA, or the ArboMIA multiplex immunoassay. In 2022, approximately 7 years post-infection, all patients completed a set of surveys (screening for rheumatic disorders [GALS], stiffness [MSQ], functional capacity [HAQ]), provided a blood sample, and were examined by physicians who were trained by a rheumatologist. A subgroup completed the surveys fatigue [FSS], and QoL [SF-36]. A second evaluation was performed by a rheumatologist to those patients (n=46; 43.3%) who screened positive to GALS but whose clinical findings were not associated with trauma.The prevalence of post-CHIK chronic inflammatory rheumatism (pCHIK-CIR) was 10.8% (IC95%: 5.5, 18.5) whereas 35.3% (95%CI: 26.0, 45.4) had a diagnosis of Non-inflammatory pain likely degenerative. Among patients with pCHIK-CIR, 4 (36.4%) had oligoarthritis/polyarthritis, 4 (36.4%) post-viral arthralgia, 2 (18.1%) fibromyalgia, and 1 (9.1%) fasciitis; moreover, 63.4% (n=7) of pCHIK-CIR cases had arthralgia (pain scale median=7), and the joints most affected were hands (57.1%), knees (57.1%) and feet (42.9%). A small proportion had stiffness (n=2; 18.2%; stiffness scale median=9). In addition, overall, 33.7% of participants screened positive for fatigue, whereas those with pCHIK-CIR scored lower than the recovered cases in the QoL questionnaire (medians: 37.4% vs. 49.4%, p=0.001; and 46.1% vs 55.8%, p=0.000; for mental and physical domains, respectively). This study implemented a comprehensive clinical assessment to objectively estimate and characterize the prevalence of chronic rheumatological disease attributed to CHIKV infection. These results correspond to a preliminary analysis.

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MAPUTO SANITATION TRIAL 60-MONTH FOLLOW-UP ANTHROPOMETRIC MEASUREMENTS AND CHILD HEALTH

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Safe water, sanitation, and hygiene (WASH) can interrupt enteric pathogen transmission and may improve growth outcomes in children. Growth deficits manifest as children age, with early childhood the critical window for interventions. We conducted a cross-sectional assessment of long-term growth outcomes in a cohort of children exposed to differential sanitation infrastructure from birth in Maputo, Mozambique. We enrolled 1014 children aged 1 - 60 months living in household clusters in two arms: those having received improved shared sanitation (n = 473) intervention and those from matched clusters with unimproved sanitation (n = 541) but meeting eligibility criteria for the intervention. We used standard length, height, and weight measurement methods with appropriate quality control checks to reduce measurement bias. We calculated height/length-for-age (HAZ) and weight-for-age (WAZ) and weight-for-height (WHZ) z-scores and compared them with the 2010 WHO Child Growth Standards reference dataset, utilizing the R package z-scorer. We estimated the prevalence of stunting, wasting, and underweight children in both arms. Approximately 26% (95% CI: 23%, 30%), 4.6% (95% CI: 3.1%, 6.7%), and 6.1% (95% CI: 4.4%, 8.4%) of control children were stunted, wasted and underweight, respectively, compared with 16% (95%CI: 13%, 20%), 4.6% (95% CI: 3.1%, 6.9%), and 4.6% (95% CI: 3.1%, 6.9%) of children in the intervention arm, suggesting visible reductions in stunting among children born into better sanitation conditions. Mean differences in HAZ/LAZ, WAZ and WHZ z-scores between treatment arms are shown HAZ 0.32 (95% CI: 0.129, 0.51), WAZ: 0.20 (95% CI: 0.06, 0.33), and WHZ: -0.028 (95% CI: -0.20, 0.14). We estimate that children in the safe sanitation group experienced 41% reduced odds of stunting (OR 0.59, 95% CI: 0.43 - 0.82), after controlling for age, sex, household wealth indicators, and caregiver education. Because interventions were not randomly assigned, we cannot rule out unmeasured confounding. Ongoing analyses will account for associations with enteric pathogen gut carriage to interrogate sanitation-related drivers of undernutrition.

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EFFECT OF A WATER, SANITATION AND HYGIENE PROGRAM ON HANDWASHING WITH SOAP AMONG DIARRHEA PATIENTS AND ATTENDANTS IN HEALTHCARE FACILITIES IN THE DEMOCRATIC REPUBLIC OF THE CONGO: A RANDOMIZED PILOT OF THE PICHA7 PROGRAM

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Healthcare-acquired infections are a major problem in healthcare facility settings globally. The Democratic Republic of the Congo (DRC) has over 2 million diarrhea patients admitted to health facilities annually. Health facilities can be a high-risk environment for transmission of diarrheal diseases. The objective of the Preventative Intervention for Cholera for 7 Days (PICHA7) program is to develop evidence-based water, sanitation, and hygiene (WASH) interventions to reduce cholera and other severe diarrheal diseases in DRC. This study evaluated the effectiveness of PICHA7 program delivery in increasing handwashing with soap at stool, vomit, and food related events in a healthcare facility setting among diarrhea patients and their attendants. A randomized pilot of the PICHA7 program was conducted among 284 participants from 27 health facilities from March 2020 to November 2021 in urban Bukavu in South Kivu Province of DRC. The 'Standard Message' Arm received the standard message given in DRC to diarrhea patients on the use of oral rehydration solution. The PICHA7 arm received the PICHA7 WASH pictorial communication module bedside to the diarrhea patient, and a soapy water bottle in the healthcare facility during the time of treatment. Within 24 hours of intervention delivery, three-hour

structured observation of handwashing practices at stool, vomit, and food related events (key events) was conducted in healthcare facilities of diarrhea patients and their attendants. Compared to the Standard Message Arm, there was significantly higher handwashing with soap at key events in the PICHA7 Arm (39% vs. 12 %) (Odds Ratio: 5.32; (95% Confidence Interval (CI): 2.00, 14.10). These findings demonstrate that delivery of the PICHA7 WASH pictorial communication module and provision of a soapy water bottle to diarrhea patients and their attendants presents a promising approach to increase handwashing with soap among this high-risk population in healthcare facilities in eastern DRC.

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THE LONG-TERM EFFECTS OF IMPROVED WATER, SANITATION, AND HYGIENE (WASH) AND IMPROVED COMPLEMENTARY FEEDING ON SCHOOL-AGE GROWTH AND DEVELOPMENT IN RURAL ZIMBABWE: FOLLOW-UP OF THE SHINE CLUSTER-RANDOMIZED TRIAL

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The SHINE cluster-randomised trial tested the effects of a household WASH intervention and/or infant and young child feeding (IYCF) on child stunting and anemia at age 18 months in rural Zimbabwe. SHINE showed that IYCF increased linear growth and reduced stunting by age 18 months, while WASH had no effects. Here, we present long-term follow-up data from 1000 HIV-unexposed children (250 in each intervention arm) who were re-enrolled at age 7 years to evaluate growth, body composition, cognitive and physical function. We measured cognition using the Kaufman Assessment Battery for Children (KABC-II) as a primary outcome, and executive function, literacy, numeracy, fine motor skills and socioemotional function as secondary outcomes. Physical function was assessed by handgrip strength, broad jump and shuttle-run test. Growth was assessed by anthropometry, body composition (using bioimpedance analysis) and skinfold thicknesses. Contemporary household socioeconomic status, demographics, nurturing, food and water insecurity were measured by a caregiver questionnaire. Data were analyzed using generalized estimating equations with an exchangeable working correlation structure to account for clustering. Of 1000 children assessed, 10 were excluded from analysis for severe disability. Children (51% female) were median 7.2 years old (IQR 7.1, 7.4). IYCF and WASH each had no effect on the primary outcome (KABC-II score) or secondary cognitive outcomes, except a small difference in socioemotional function in the WASH arms (-1.2 marks, 95%CI -2.0, -0.5, p=0.002) which remained in adjusted analyses. Children in IYCF arms had a greater handgrip strength (+0.3 Kg, 95% CI 0.0, 0.5, p=0.03), which remained in adjusted analyses. There were no significant effects of IYCF or WASH on growth or body composition measures at 7 years. Overall, long-term follow-up of a subgroup of children enrolled to SHINE showed minimal long-term effects of early-life IYCF and WASH on school-age function, despite improved linear growth following IYCF in the original trial.

6515

SURPRISE SOAP: EFFECT OF A NOVEL HYGIENE INTERVENTION ON OLDER CHILDREN'S HANDWASHING IN COMPLEX HUMANITARIAN SETTINGS: RESULTS OF TWO CLUSTER-RANDOMIZED CONTROLLED EQUIVALENCE TRIALS

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Children in emergencies are particularly vulnerable to infectious diseases such as diarrhoea and respiratory infections. Improving handwashing with soap (HWWS) can greatly reduce transmission, however, there is limited evidence on which approaches to child targeted HWWS promotion are effective. One recent innovation - the "Surprise Soap" intervention - was successful in a small-scale efficacy trial in an IDP camp in Iraq. This novel intervention includes transparent soap with embedded toys delivered in a short household session comprising a glitter game, instruction of how to wash hands, and HWWS practice. Whilst promising, this approach has not been evaluated at programmatic scale in a complex emergency setting. To address this gap, we conducted two cluster-randomised controlled equivalence trials, one across IDP camps in Somalia, and one in a refugee settlement in Sudan. In each trial, 200 households were randomly allocated (1:1) to receive the Surprise Soap intervention or an active comparator intervention including plain soap delivered in a short household session involving standard health-based messaging and instruction of how to wash hands. The primary outcome was the proportion of pre-specified occasions when HWWS was practiced by children aged 5-12, measured at baseline, 4-weeks, 12 weeks, and 16 weeks post intervention delivery. In both trials, we observed a large and sustained increase in HWWS in both arms (Somalia: 48 and 51 pp increase in the intervention and comparator arm, respectively; Sudan: 27 and 23 pp increase, respectively). However, there was no difference in HWWS between the two arms. In these two settings, where soap availability and past exposure to HWWS promotion was low, it appears that interventions that directly target children at the household-level and provide soap can increase their HWWS and potentially reduce disease risk. Here the Surprise Soap intervention offers no marginal benefit over providing plain soap within a household-level "standard" intervention that would justify the additional costs. Applying contextual knowledge to decisions on Surprise Soap implementation is recommended.

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EFFECTIVENESS OF SEWAGE INTERVENTION ON LEPTOSPIRA TRANSMISSION AMONG RESIDENTS OF URBAN INFORMAL SETTLEMENTS

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Leptospirosis is an environmentally-transmitted zoonotic disease that affects impoverished urban and rural populations worldwide. In informal settlements, leptospirosis is associated with precarious sanitary infrastructure. Yet, the role of sewerage in reducing Leptospira transmission has not yet been rigorously evaluated. We conducted a cluster-controlled

natural experiment in a slum community in the city of Salvador, Brazil to prospectively evaluate the effectiveness of a government sewerage intervention. We selected two intervention clusters which comprised of a regions where open sewers were closed without implanting rainwater drainage in 2018 and 2021 and one control cluster for each period, which did not receive the intervention. As part of an on-going cohort study, we performed biannual serosurveys of the study community during the study period from 2015 to 2022. Leptospira infection was ascertained by detecting seroconversion or a four-fold rise in titer during microscopic agglutination testing and used in time series analysis to estimate effectiveness of the intervention using generalized estimating equations models. Age, sex, and elevation level were used to adjust estimates. Among 1,058 residents who were enrolled and followed during the study period, the Leptospira infection rates varied between 13 and 48 per 1000 follow-up events. A significant difference was not observed in the odds of Leptospira infection between control and intervention clusters in the post-intervention period (OR: 0.78; 95% CI 0.35-1.13). After the closure of sewage, residents in intervention clusters reported frequently exposed to flooding, mud, and soil. Our findings suggest that isolated closure of human fecal sewage without implanting enclosed rainwater drainage systems was not effective in reducing Leptospira transmission. Effective interventions in high-risk slum communities must therefore incorporate multiple sanitation dimensions and ensure sustainability.

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IMPACT OF THE WASH IN SCHOOLS FOR EVERYONE (WISE) PROGRAMME ON CHILD HEALTH AND SCHOOL ATTENDANCE IN ADDIS ABABA, ETHIOPIA: A CLUSTER-RANDOMISED CONTROLLED TRIAL

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Water, sanitation and hygiene (WASH) interventions in schools (WinS) have been proposed to reduce morbidity in schoolchildren, including gastrointestinal and respiratory infection, and improve school attendance, particularly among post-menarcheal girls. However, evidence of the impact of WinS interventions on pupil health and educational outcomes has been mixed. We evaluated the WASH in Schools for Everyone (WISE) programme implemented by US-based NGO Splash in partnership with the Government of Ethiopia, which aims to achieve universal WASH coverage in schools in Addis Ababa, Ethiopia over a five-year period. We conducted a cluster-randomised trial among 60 randomly selected primary schools and randomly assigned them 1:1 to receive the intervention during the 2021/22 academic year or the following year (waitlist control). The intervention comprised WASH infrastructure improvements, including water storage and filtration, drinking water / handwashing stations and upgraded sanitation facilities, and behaviour change promotion. Within each participating school, we enrolled between 2 and 4 randomly selected classes in to reach a total school enrolment of approximately 100 pupils. Individual pupils (ages 7 - 16) were enrolled in November 2021. At four follow-up visits between March and July 2022, enumerators recorded roll-call absence, pupil-reported illness (diarrhoea, respiratory infection) and pupil-reported absence in past week among pupils present. Secondary outcomes including wellbeing and menstrual hygiene self-efficacy were recorded at the final follow-up. We found a 17% reduction in odds of pupil-reported respiratory infection in the past week during the follow-up period among pupils in intervention vs. control schools (OR: 0.83, 95% CI: 0.70, 0.99), notable in the context of the COVID-19 pandemic. No impacts on diarrhoea or absence were observed. There was evidence of greater intervention effects among boys vs. girls. The Splash intervention was delivered with high fidelity. Further analyses will explore the heterogeneity in effects and the link between compliance and observed outcomes.

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PROCESS EVALUATION OF THE PREVENTATIVE INTERVENTION FOR CHOLERA FOR SEVEN DAYS (PICHA7) WATER, SANITATION AND HYGIENE MOBILE HEALTH PROGRAM

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In the Democratic Republic of the Congo (DRC) there are estimated to be 85 million diarrhea episodes annually. Effective and scalable water, sanitation, and hygiene (WASH) interventions are urgently needed to reduce diarrheal diseases globally. Phone-based reminders of public health information have been shown to reduce disease morbidity and increase health-protective behaviors. The objective of the Preventative Intervention for Cholera for 7 Days (PICHA7) program is to develop evidence-based WASH interventions to reduce cholera and other severe diarrheal diseases in DRC. The PICHA7 mobile health (mHealth) program delivers weekly voice, text, and interactive voice response (IVR) messages to diarrhea patient households promoting handwashing with soap and water treatment and safe water storage. The randomized pilot of the PICHA7 program demonstrated this intervention was effective in increasing handwashing with soap and water treatment behaviors during the three-month program period compared to the standard message given in DRC on the use of oral rehydration solution for rehydration. The objective of this study was to assess the implementation of the PICHA7 mHealth program during this randomized pilot to determine the feasibility of delivering this program in urban Eastern DRC. This study was conducted in Bukavu in South Kivu province in eastern DRC. Three hundred fifty-six participants were in households that received weekly text, voice and IVR messages from the PICHA7 mHealth program over the 3-month program pilot. Outcome indicators included unique text, voice, and IVR messages received (fidelity) and % of unique messages fully listened to (dose). Eighty three percent of text messages were received by program households. Eighty seven percent of voice and 88% of IVR messages sent were answered by at least one household member. Ninety percent of voice messages were fully listened to, and 62% of IVR messages. These findings have shown high fidelity and dose of mobile messages delivered for the PICHA7 mHealth program, demonstrating the feasibility of delivering the PICHA7 mHealth program in our study setting in Eastern DRC.

6519

BACTERIAL ZOONOSES DETECTED BY 16S RRNA METAGENOMICS AMONG FEBRILE ADMISSIONS IN KILIMANJARO, TANZANIA, 2007-2009

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Bacterial zoonoses are prominent causes of severe febrile illness in East Africa. While most of these diseases are highly treatable, many require specific therapies beyond standard empiric antimicrobials. Diagnosis remains a challenge, as these fastidious or non-culturable organisms thwart conventional culture and serologic diagnosis requires convalescent sample collection. Within a well-characterized fever etiology cohort, we applied a high-throughput 16S rRNA metagenomics assay validated for targeted detection of bacterial zoonotic pathogens. A prospective cohort study enrolled pediatric and adult medical patients admitted with fever

to 2 referral hospitals in Moshi, Tanzania, September 2007- April 2009. Red cell pellets were archived at -70ºC after plasma fractionation of EDTA whole blood obtained from participants within 24 hours of admission. DNA extracts from the cell pellets were subjected to PCR targeting the V1-V2 of 16S rRNA, followed by metagenomics deep-sequencing of V1-V2 amplicons.Taxonomic identifications were analyzed after subtraction of background taxonomic identifications of ubiquitous DNA contamination from the environment. Among 788 participants enrolled the median (interquartile range) age was 20 (2-38) years, 239 (32.1%) were HIV-infected, 384 (50.4%) were male, and 314 (47.3%) lived in an urban setting. A bacterial zoonotic pathogen was detected in 10 (1.3%): 3 Rickettsia typhi, 1 Rickettsia conorii, 2 Bartonella quintana, 1 Leptospira borgpetersenii, 1 Leptospira species, 1 Coxiella burnetii, 1 sample with reads for an apparently novel organism in the Anaplasmataceae family. This targeted 16S metagenomics approach made important identifications: a potentially novel agent of anaplasmosis; and to our knowledge the first molecular evidence of R. conorii in East Africa, improving our understanding of the species responsible for spotted fever group rickettsioses in the region.

6520

DETERMINING FLEA VECTOR SUSCEPTIBILITY TO INSECTICIDES AS PART OF PLAGUE RISK MONITORING IN MADAGASCAR

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Fleas have medical importance in Madagascar in relation to human plague. Through infected bites, they transmit Yersinia pestis from rodents to humans. Two species, Xenopsylla cheopis and Synopsyllus fonquerniei, are known vectors. Insecticides are the primary response tool to control fleas; therefore, susceptibility monitoring is essential to ensure this intervention is effective. We aimed to determine susceptibility of plague flea vectors to insecticides. Between 2019 and 2022, fleas were collected alive then reared in insectary. Following WHO protocols, eighteen, twelve and ten assays were performed using fenitrothion, permethrin and deltamethrin respectively. Per assay, 40 fleas were exposed to paper impregnated with the following concentration/duration combinations: fenitrothion 1% for 5h (organophosphate), permethrin 0.75% or deltamethrin 0.05% for 8h each (pyrethroids). After 24 hours, mortality rates (MR) were recorded. Fleas were either resistant (MR < 80%), tolerant (80% ≤ MR < 98%) or susceptible (98% ≤ MR ≤ 100%). Sixteen populations (sites) from eight districts were tested. Eighteen, twelve and ten assays were performed using fenitrothion, permethrin and deltamethrin respectively. Susceptibility to fenitrothion was heterogenous but 50.0% of populations remained susceptible, two were tolerant (11.1%) and seven were resistant (38.9%). All S. fonquerniei were fenitrothion susceptible whereas X. cheopis showed heterogenous responses. Two S. fonquerniei populations were permethrin tolerant (16.7%) and ten were resistant (83.3%). Almost all districts showed permethrin resistant X. cheopis. Nine X. cheopis populations were deltamethrin resistant and one was tolerant. These findings showed heterogeneity responses to insecticides considering sites and species. All populations were non-susceptible to pyrethroids. Susceptibility to fenitrothion persisted although trends indicate resistance emergence which may be related to plague control or other usage. Monitoring flea susceptibility to insecticides should be continued to guide data driven decision making for plague control.

6521

RISK FACTORS ASSOCIATED WITH RURAL HOUSEHOLD FLEA INFESTATIONS IN THE PLAGUE ENDEMIC AREA OF MADAGASCAR

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Human and domestic animals may experience skin reactions and discomfort due to heavy flea bites. Some species are vectors of pathogens such as Yersinia pestis, the agent of bubonic plague. In this study, we are interested in the species composition, prevalence, abundance, seasonality, and risk factors for the host-seeking fleas infesting households in plague endemic areas of Madagascar. We used a structured questionnaire and observational checklist to collect data from households in 4 villages. Fleas were sampled during the dry and the rainy season using a candle trap for 3 consecutive nights. We used a generalized linear mixed model to identify the factors that are associated with flea abundance in households. We found that more than 98% of the households were infested by fleas, dominated by the species Pulex irritans (98.18%, n=9,352). No seasonal pattern was found in flea abundance, but the number of fleas detected per household was highly variable with an average of 37.16 fleas per household during the dry season and 45.66 during the wet season. Our model showed that flea infestation was associated with having a male head of the household (aOR=1.75), reported rodent activity (aOR=1.31), mat floor (aOR=1.98), and thatched roof (aOR=1.22). The risk increased with the number of chickens (aOR=1.03), pigs (aOR=1.07), and household size (aOR = 1.09). Head of the household education level above primary school (aOR=0.58), sleeping two stories away from the ground floor (aOR=0.81) where livestock was kept at night, and the proximity of a separated livestock housing (aOR=0.91) were found to be protective against flea infestation. High flea burden in the household motivated the use of insecticide, which may induce resistance among the vectors. Interventions targeting an increased quality of life, access to education, and security may alleviate the flea burden in rural villages experiencing high flea infestation. The human flea, P. irritans is one of the probable vectors in Madagascar and the present description of its infestation ecology is a first step toward understanding its potential role in plague transmission.

6522

SURVEILLANCE FOR METASTRIATE TICKS AND SPOTTED FEVER GROUP RICKETTSIOSES IN SOUTHERN ILLINOIS

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Reported human cases of Spotted Fever Group Rickettsioses (e.g., Rocky Mountain Spotted Fever) have been increasing in Illinois over the past few decades. The majority of SFGR cases have been reported from the southern region of the state. However, until beginning the Illinois statewide active tick surveillance program in 2019, relatively little information was available regarding population densities and SFGR pathogen prevalence in Illinois ticks, and there was a need to address gaps in understanding of human exposure risk to different tick-borne Rickettsia sp. pathogens. Based on the hypothesis that some of the reported human SFGR cases in southern Illinois could be due to Rickettsia sp. other than R. rickettsii, and possibly due to R. parkeri, we designed a sampling strategy to identify environments most likely to harbor the Gulf Coast tick (Amblyomma maculatum), the vector of R. parkeri. During targeted collection events, we also retained any other tick species encountered. Sampling yielded collections of A. americanum, A. maculatum, and D. variabilis. We collected

782 adult Gulf Coast ticks in 8 southern Illinois counties in summer 2020, a 30-fold increase over the sum total of all prior historical reports in Illinois. We tested all three metastriate tick species for Rickettsia amblyommatis, R. parkeri, and R. rickettsii. Tick infection prevalences and densities of adult and nymphal ticks were compared to the incidence of reported human SFGRs. Gulf coast ticks were strongly overdispersed, as they were found to be highly abundant in specific focal locations. Overall, 17.4% of Gulf Coast ticks were positive for R. parkeri, 48.5% of lone star ticks were positive for A. amblyommatis, and we detected no R. rickettsii in the 3,324 ticks tested. The standardized incidence ratio of SFGRs at the county level was most strongly associated with the density of R. amblyommatis-infected A. americanum nymphs and adults. Understanding the distribution of tick species and Spotted Fever Group Rickettsiae diversity in southern Illinois is essential for accurate and timely diagnosis of tick-borne disease and design of effective tick-bite prevention messaging.

6523

SEROLOGIC TESTING FOR THE DIAGNOSIS OF BARTONELLA INFECTIONS IN PATIENTS IN MARYLAND

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Bartonella species are gram negative, vector-borne bacteria which cause a range of human disease. Bartonella species are an underrecognized pathogen and infections are often missed by routine microbiological testing. Bartonella infections in the United States are initially diagnosed by serologic testing for antibodies to B. quintana, the causative agent of trench fever, and Bartonella henselae, the causative agent of cat scratch disease, however the number of Bartonella species that are known to cause human disease is growing each year. To better understand the prevalence and diagnosis of Bartonella infections in Maryland a retrospective analysis of all serologic testing for Bartonella species through the University of Maryland Medical System from 2020-2022 was conducted. 271 serologic tests were ordered between 2020-2022. Clinical indications for testing included homelessness, contact with cats, fever, lymphadenopathy, animal bites, and endocarditis. However, in many cases there were no clinical indications for testing. Overall, twenty were positive for IgM and/or IgG to B. quintana and/or B. henselae. Eight were positive for IgM and IgG and twelve were positive for IgG alone. While molecular testing following serologic diagnosis indicated that B. henselae and quintana along with B. rochalimae were causes of positive serologic results, several cases were complicated by false positive serology for Chlamydia, Coxiella and/or Brucella, confusing those who are unfamiliar with serologic testing causing delayed treatment. Additionally, false positive/borderline positive serologic results and/or results due to previous infection delayed treatment in cases where clinical syndromes were mistakenly ascribed to acute Bartonella infections. Results from serologic testing show that Bartonella is an important yet poorly understood human pathogen with the potential to cause significant morbidity. Lack of appropriate laboratory tests and education result in treatment delays and increased morbidity in patients with suspected Bartonella infections. Increased awareness of Bartonella as a human pathogen is imperative.

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MOLECULAR SURVEY OF ANAPLASMATACEAE AGENTS AND BARTONELLA SPP IN COATIS NASUA NASUA FROM URBAN FORESTED AREAS IN BRAZIL

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The Anaplasmataceae and Bartonellaceae families encompasses vector-borne obligate and facultative, respectively, intracellular αproteobacteria of human and veterinary medicine importance. While Ehrlichia and Anaplasma are tick-borne agents, Neorickettsia can be transmitted through the ingestion of intermediate hosts harboring trematodes infected with Neorickettsia. Depending on the species, Bartonella can be transmitted by fleas, lice, bites and scratches. This study investigated the molecular occurrence of Ehrlichia, Anaplasma, Neorickettsia, and Bartonella in coati's blood samples in Midwestern Brazil. Twenty-five out of 165 samples, 15.1%, were positive in the screening PCR based on the dsb gene of Ehrlichia spp. and were characterized using 16S rRNA, sodB, groEL, and gltA genes and the 23S-5S intergenic space region ITS. Phylogenetic analyses based on all six molecular markers positioned the sequences into a new clade, with a common origin of Ehrlichia ruminantium. Genotype analyses of 16S RNA sequences revealed the presence of two distinct Ehrlichia genotypes. Six samples, 3.6%, were positive in the screening nPCR for the 16S rRNA gene of Anaplasma spp. and were submitted to an additional PCR targeting the ITS for molecular characterization. Phylogenetic analyses based on both 16S rRNA gene and ITS positioned the Anaplasma sp. detected in the present study in a large clade with other Anaplasma sp. previously detected in ticks and wild animals and in a clade with Candidatus Anaplasma brasiliensis, respectively. Neorickettsia sp. 16S rDNA, showing high identity to Neorickettsia risticii, was detected in 6 coati blood samples. None of the coati blood samples was positive for Bartonella spp. in a combined approach using BAPGM (Bartonella AlphaProteobacteria Growth Medium) and isolation onto chocolate agar followed by a qPCR based on the nuoG gene. The present work described a putative novel Anaplasmataceae agent, namely Candidatus Ehrlichia dumleri, Anaplasma sp. closely related to the previously described Candidatus Anaplasma brasiliensis, and Neorickettsia sp. in coatis from urban forested areas in Brazil.

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DOGS AS RICKETTSIA SPP. SENTINELS IN A PERUVIAN AMAZON NATURAL RESERVE BUFFER ZONE

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Countries neighboring Peru, such as Brazil and Colombia, have reported human cases of high and mildly pathogenic Spotted Fever Group rickettsiae (SFGR), including R. rickettsii and R. parkeri strain Atlantic rainforest, respectively; however, these species have not been reported in the Peruvian Amazon basin. Dogs play essential roles in the transmission cycles of these spp, since they serve as amplifying hosts. We conducted a cross-sectional study in a rural community of Madre de Dios (MdD) to characterize the species of ticks in dogs and to determine the presence of ticks and dogs positive to Rickettsia spp. We collect whole blood and ticks (n=23) from 23 dogs living around Kawsay Biological Station, located in the Tambopata National Reserve buffer zone. We collected 23 ticks from 23 dogs, including Amblyomma ovale (n= 22) and Rhipicephalus sanguineus (n=1). We tested blood samples and ticks by real time-PCR targeting the rickettsial conserved gene gltA. We found 2 (8.2%) Rickettsia-positive dogs and 12 (54.2%) ticks. Of the 12 positive ticks, 11 were identified as A. ovale (50% of all 22 A. ovale) and one as R. sanguineus. Our results indicate that dogs living in rural areas of MdD are infected with Rickettsia spp. Moreover, we have found that, as has been reported in Brazil, A. ovale, which normally infests rodents and wild carnivores, is infesting pet dogs in MdD, bringing ticks into the households and surrounding environments. Since, A. ovale and R. sanguineus are well known vectors of two of the most important rickettsial agents, R. parkeri strain Atlantic rainforest and R. rickettsii, our results suggest these pathogens may be circulating in rural communities of MdD. This study is still ongoing, and we will sequence the positive samples to determine the circulating Rickettsia species in rural areas and also we will explore the role of pet dogs as sentinels of rickettsia infections in rural areas of MdD. The role of dogs as rickettsia sentinels has been proven in

developed countries; however, in developing countries this may be different due to different dog ecology and human-dog interactions, especially in rural areas where dogs are allowed to roam free

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BIOMETRICS DATA COLLECTION FOR TRACHOMATOUS TRICHIASIS SURGERY PROGRAM IN OROMIA, SNNP AND SIDAMA REGIONS, ETHIOPIA: LESSONS LEARNT

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Trichiasis patient identification, documenting Trachomatous Trichiasis (TT) cases known to the health system is a challenge using paper based records. Paper based data systems are vulnerable for loss, wear and tear as well as mis location, which leads to loss of medical history, making post operative follow up overtime challenging. To register all TT cases with biometrics and provide biometrically verified TT management, get real-time data for program monitoring and decision making. The paper form trichiasis patient register has been changed into digitized form using SurveyCTO (SCTO) to capture trichiasis patient records that works with or without internet connectivity. SCTO has been linked to a data system that captures unique fingerprint using scanning technology. Enrolment and identification are the two steps in the system. The system allows health service providers to identify patients any time when they seek care. 283 IECWs were trained from three regional states. A total of 6,970 patients have been enrolled into the system so far. Of which, 5,303 (76%) were enrolled through biometrics. Electronic data collection was considered as empowering by health service providers; Biometrically verifiable digital trichiasis recording system is found more convenient, reliable, accurate and timely recording and reporting system; Due the implementation of the system, no data duplication, no misuse of standard formats, no missing records, no delay of reports; Got real-time information dashboard that auto update as soon as data is submitted and is capable of transitioning into the mainstream health information system run by the Ministry of Health. The dashboard is accessible to the health systems staff, implementing partners and program leaders, which facilitated timely evidence based action and decision making. Train IECWs in Amhara region, refresh and closely support the already trained IECWs and work to simplify SCTO dataset and dashboard.

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SPATIAL VARIATION IN HOUSING CONSTRUCTION MATERIAL IN LOW- AND MIDDLE-INCOME COUNTRIES: A BAYESIAN PREDICTION MODEL OF A KEY INFECTIOUS DISEASES RISK FACTOR AND SOCIAL DETERMINANT OF HEALTH

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Housing quality is a well-recognized social determinant of health. Many infectious diseases of global concern are transmitted within and between households and features of the built peridomestic environment and infrastructure can promote or impede the spread of pathogens and their insect vectors. In tropical and rural regions where vector borne and neglected tropical diseases circulate, dwellings are often constructed using locally available, naturally occurring materials and traditional techniques. Disease-causing insects and microbes are well-adapted to exploit the ecological niches that such buildings provide. This study modeled spatial variation in housing material types using covariates with global coverage to map predicted coverage across LMICs. Data on materials used in construction of dwelling floors, walls and rooves were compiled from 334 nationally representative, population-based household surveys, and classified into natural, rudimentary, and finished types. A novel georeferencing methodology was developed and implemented here for the first time. A suite of time-static environmental and demographic spatial covariates in raster format were compiled based on their hypothesized associations with the outcome variables. Variable values were extracted at the georeferenced cluster locations and a Bayesian Multi-level based logistic regression approach was used to model associations and generate predictions for all LMICs at a 6km resolution. A Markov Random Field (MRF) smooth algorithm was employed to improve spatial correlation and continuity of the prediction maps. Models for wall and roof material performed better than for floors giving a precision of 0.82 for the finished category and a weighted average precision of 0.7 and 0.73 respectively. Cropland areas, urbanization, and distance to water source were important variables in all models. Resulting prediction maps enable the identification of areas of low coverage of improved housing material across large areas of Sub-Saharan Africa, South Asia, and Amazonian South America among others, and can be used to prioritize populations for housing improvements.

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USE OF MATHEMATICAL MODELING TO INFORM INSECTICIDE-TREATED BEDNET DISTRIBUTION CAMPAIGNS: A HAITIAN CASE STUDY

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Despite numerous natural- and human caused disasters, Haiti has made significant progress towards malaria elimination. In 2021, the number of presumed and confirmed malaria were 10642, down from over 84153 in 2010. As cases have fallen, they have become increasingly concentrated; thus, interventions such as insecticide treated bednets should be strategically targeted to reach maximal epidemiological impact. In order to identify the optimal set of communes in which bednet distribution would result in the most cases averted through the once-every-three years distribution campaign, we use a metapopulation model that was fitted on historical reported cases between 2014 and 2021 and on spatial data estimates from the Malaria Atlas Project. The model includes past bednet distributions, case management indicators and human inter-commune mobility as informed by mobile phone data. Several versions of the model are compared to evaluate the sensitivity to the input data. The fitted model was used to identify the communes in which the intervention would have the most impact at the national scale. The model ranked 125 communes, of which we selected the top 25 given the diminishing benefit of each additional commune and the defined number of bednets the country would receive. The selected communes accounted for 82% of observed cases in 2021. As this model combines the effects of connectivity, past interventions and local trends in transmission intensity, it provides a useful additional piece of information in prioritized communes for interventions such as LLIN distributions and communication campaign aiming at increasing bednet usage. The results provided insights about the impact of the targeted communes at the national scale and identified communes to be targeted with communication campaign. Finally, this calibrated model provides an additional tool to support routine campaign planning including the 2023-2026 Global Fund application.

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NET WORTH: A MODELING EXPLORATION OF COST AND COST-EFFECTIVENESS IN INSECTICIDE-TREATED NET INTERVENTIONS

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As the malaria funding envelope plateaus while burden grows and the number of people in need of protection continues to rise, it becomes ever

more crucial to ensure that every dollar spent on malaria interventions is utilized as efficiently and effectively as possible. Insecticide-treated nets (ITNs) are one of the largest line items in global malaria expenditures, making this intervention a major target for improving cost-effectiveness. This is especially true in the rapidly diversifying landscape of ITNs, with multiple novel products on the market and a growing understanding of this intervention's multifaceted nature and heterogeneous historical effectiveness. We utilized the mechanistic modeling software EMOD to explore three common operational questions across a range of transmission intensities, climates and vector mixes: First, is it more cost-effective to attain a specified coverage level by distributing more nets, or by improving the efficiency of net campaigns such that nets are more appropriately allocated? Second, at what level of insecticide resistance does it become cost-effective to move from pyrethroid-only ITNs to pyrethroid + piperonyl-butoxide (PBO) ITNs? And finally, in a situation in which one could either increase pyrethroid-only ITN coverage or maintain current coverage levels with PBO nets, which is more cost-effective? Results show that increasing campaign efficiency is more cost-effective than distributing additional nets, and that a switch to PBO nets is generally cost-effective in areas with high insecticide resistance, though the specific magnitude varies meaningfully depending on the local context. This analysis only scratches the surface of possible operational tradeoffs to explore, but demonstrates the power of modeling for optimal intervention planning and provides insight into best practices for future ITN campaigns.

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MULTIFACETED INTERVENTIONS FOR UNINTERRUPTED MALARIA COMMODITIES: LESSONS FROM MALAWI

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There has been significant progress in malaria control in Malawi. The malaria incidence rate reduced by almost 50%, from 407/1,000 population in 2016 to 208/1,000 population in 2022. Malaria mortality declined from 23/100,000 population in 2016 to 8/100,000 population in 2022. In fighting malaria, the Ministry of Health (MOH) implemented malaria case management and vector control programs. To support the National Malaria Control Program, in 2017, the USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) project made some changes to the parallel supply chain program, which was instituted in 2012 to ensure uninterrupted availability of malaria commodities. GHSC-PSM engaged third-party logistics (3PL) firms to run its in-country warehousing and distribution of malaria commodities to all the 716 service delivery points in the country. The 3PLs use all modes of transportation including boats, motorbikes, and trucks, to ensure that the products reach their destination. Further, GHSC-PSM provided a comprehensive support to the malaria program supply chain with periodic forecast reviews; developing coordinated procurement plans with other funders; procurement and delivery of malaria commodities, including pipeline monitoring, and capacity strengthening of MOH staff to manage their supplies. This multifaceted support helped the NMCP track commodities from 716 SDPs with a 92% average reporting rate in 2022 resulting in a sustained supply of malaria commodities in health facilities and communities through the parallel supply chain program. From 2017 and 2022, there has been less than 1% stockout rate of first-line malaria treatment at service delivery points and this is likely contributing to the significant decrease in the malaria burden in the country.

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MULTI-OBJECTIVE CALIBRATION OF THE AGENT-BASED MALARIA TRANSMISSION MODEL, EMOD, TO SYMPTOM, PARASITE, GAMETOCYTE, AND MOSQUITO INFECTION DATA FROM A TRIAL OF ASYMPTOMATIC SCREENING IN SAPONE, BURKINA FASO

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Mathematical models of malaria transmission have been used to predict the impact of various screening and treatment interventions where clinical trials may not be feasible. To make accurate predictions, models must reproduce key quantitative relationships between parasites, symptoms, gametocytes, and infectiousness within modeled human and mosquito hosts, all of which can vary between malaria-endemic settings. With many variable inputs and desired outputs, manual calibration of mathematical models is complex and tedious, making automated calibration algorithms an attractive alternative. We adopted a Bayesian optimization framework employing Gaussian process emulators to simultaneously calibrate 15 core parameters of the complex agent-based malaria transmission simulator, EMOD. These parameters describe aspects of modeled vector life cycles, parasite dynamics, human host immunity and symptom development, and vector-human interactions that are assumed to be constant across modeled settings. We evaluate each possible core parameter set against 8 fitting objectives describing key epidemiological and within-host relationships observed from field data. Compared to previous calibration approaches, ours leveraged data from the INDIE-1a trial in Sapone, Burkina Faso, which included detailed P. falciparum parasite and gametocyte data from human blood samples, and mosquito infection data from direct membrane feeding assays. We first calibrated core model parameters to data from the INDIE control arm, and then validated the effect size of simulated screening interventions in the recalibrated model against primary endpoints from the trial. This approach resulted in a better fit compared with the previous parameterization more quickly than sequential calibration approaches. The reparametrized model will be used in future modeling studies to predict the impact of proposed interventions on population-level malaria transmission.

6532

IMPLEMENTING A LARGE-SCALE COMMUNITY DIGITAL HEALTH PLATFORM IN MOZAMBIQUE: LESSONS LEARNT FROM UPSCALE

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From 2009 to 2016, MC tested interventions to improve the quality of care provided by community health workers in Mozambique, locally known as (APEs), including a smartphone application introduced in Inhambane province through the inSCALE project. Building from this success and in order to link APEs with the national HIS, MC worked in collaboration with the MOH and UNICEF to develop the upSCALE platform - a digital strategy to strengthen health systems and community health delivery. The upSCALE APE and supervisor apps are built using CommCare, an open source, multi-media rich software running on Android that can work offline. Dashboards on DHIS2 can then display the aggregate data for all APE monthly indicators, as outlined in the MoH's Monitoring and Evaluation plan for the APE programme.Automated performance reports on how APEs and supervisors are using the applications are emailed on a weekly and monthly basis to district, provincial and national levels.Implemented in 7 out of 11 provinces, with over 2,778 APEs and 777 supervisors using the app. MoH is planning to roll out the platform to all 8,800 APEs and 1,300 supervisors nationally by the end of 2024. Lessons learned from upSCALE implementation in large scale, we used desk review interviews from March

to May 2021 with 12 key stakeholders who had significant involvement with upSCALE. We led discussions with all of whom gave their consent for verbatim notes. We analysed notes in four categories: advocacy, engagement and acceptability; data collection and uptake; technology and usability; and ownership and sustainability. Finds shows established relationships at the beginning, accompanied by close engagement on planning promoted successful implementation; data quality and timeliness are key considerations for decision-making; linking data, uptake and use at various levels of the health system presents a challenge; the integration of data into the national health information system is key for sustainability and fostering a data-to-action the provision of equipment, is a valuable investment, training, is essential to promote accurate use of technology and knowledge retention.

6533

PREDICTIVE MODEL FOR REAL WORLD PERFORMANCE OF RAPID ANTIGEN TESTS BASED ON LABORATORY EVALUATION

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Controlling spread of disease due to infectious agents require a quick response from the public health sector. In the ongoing COVID-19 pandemic, the use of antigen tests (ATs) has shown to be an excellent tool to inform users and help mitigate the spread of the disease. In this communication we demonstrated how performance of an antigen test -- as a diagnostic in vitro device -- can be properly validated using a combination of quantitative laboratory experimentation and self-testing data from a clinical study. Furthermore, the work demonstrates that the clinical performance of an antigen test can be predicted using mathematical modeling based on laboratory validations. The proposed appraisal methodology of antigen test performance under real-world conditions could be a useful tool to inform the decision making of regulatory officials. This approach standardizes, simplifies and quickens the process of validation, analysis, and comparison of antigen rapid tests. If accepted as a standard, it will help democratize the process of compliance to show test performance to the public (and regulatory agencies) and ultimately will help with the execution of effective public health responses.

6534

EVALUATING A DHIS2 BASED PLATFORM FOR REAL TIME MONITORING OF MASS DRUG ADMINISTRATION OF NEGLECTED TROPICAL DISEASES MEDICINES: LEARNINGS FROM NIGERIA

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Mass drug administration (MDA) of Neglected Tropical Diseases (NTDs) medicines has proven to be the most effective NTD prevention strategy globally. MDA is implemented annually in endemic areas in Nigeria, where campaigns are tracked using a combination of paper and spreadsheet-based methods. This tracking system is inefficient, slow, and prone to errors. In collaboration with Nigeria's Federal Ministry of Health (FMoH), Sightsavers developed a DHIS2-based tool for real-time capture, analysis, and reporting of MDA data. We assessed the tool's accessibility, data quality, and utility for MDA planning, monitoring, and reporting, as well as its scalability regardless of funding source or location. Data was collected at the local government level (LGA), state, and federal levels during the pilot and scale-up phases using a combination of qualitative and quantitative methods. We investigated the potential for use at scale by evaluating in three Nigerian states (Jigawa, Enugu, and Kwara) with different support models and partners. The ability of DHIS2 to detect and address a variety of MDA-related technical and programmatic issues was generally highlighted as beneficial by participants. The tool reportedly improved timeliness in tracking incoming data, detecting data inconsistency and flagging data quality issues, as well as identifying areas of low coverage, informing supervisory visit decisions, and tracking drug inventory. Our findings showed that scaling-up to different settings was feasible; however, plans would need to address several challenges including insufficient funding, poor internet infrastructure, particularly in rural areas, increased workload, and high staff attrition rate from the NTD program. Furthermore, because of differences in operating models, cultural contexts, technology capacity, and levels of willingness to change, successful scale-up into new locations will not be a one-size-fits-all approach. The Nigerian FMoH has taken these findings and recommendations into account as they scale up the system across the country.

6535

A PROBABILISTIC FRAMEWORK OF MALARIA EPIDEMIOLOGY USING AGE OF INFECTION

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The epidemiology of Plasmodium falciparum malaria can be understood jointly through observed prevalence, parasite densities, measures of cumulative exposure, and outcomes of infection. Malaria epidemiology has proven difficult to capture using simple models because of complex, heterogeneous infection dynamics and a biased, noisy observational process. Parasite densities, which are highly variable over long infections and controlled by immunity, act as strong predictors of infectiousness, detection rates, and disease. Exposure stimulates immunity, but infections are also modified by treatment and chemoprotection, superinfection, and various sources of population heterogeneity. Immunity is presumed to develop with cumulative exposure, decreasing the 'typical' parasite density below the baseline naïve infection. To deal with all these features in compartmental models, the number of state variables would increase combinatorically and become unwieldy. Stochastic models that include all these sources of heterogeneity are complex and implemented as agent-based models to be simulated. These models are effectively black boxes and are difficult to analyze or fit to data without a heavy computational burden. Here, departing from traditional compartmental or agent-based models, we present a new, probabilistic approach using a semi-Markov framework for modeling both infection age and multiplicity of infection, which jointly can predict statistical properties of individual infections in a cohort of humans as it ages. Using the distributions of parasitemia fitted to a model of the time since first patency in malaria-naïve human subjects from the malaria therapy dataset, we can use our infection age distribution to produce a dynamic predictor of parasitemia with the effects of immunity. Ultimately, using a state-space modeling approach, we can derive equations that model the distributions of both observable (e.g., observed prevalence, fever) and unobservable (e.g., true prevalence, immunity) quantities, allowing for both qualitative analysis of the expected behavior and quantitative measures of uncertainty.

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DENGUE--AN EMERGING THREAT WORLDWIDE: A MATHEMATICAL MODEL EXPLORING GLOBAL RELATIVE RISK USING CLIMATIC, GEOLOCALIZED ECONOMIC, AND VECTOR DISTRIBUTION DATA

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Dengue is a vector-borne viral disease affecting humans that is endemic in tropical and subtropical areas worldwide. A complicated web of factors that determine disease transmission dynamics, including the human

host's infection status the age of the mosquito vector and the ingested viral dose during bloodmeal acquisition, specific viral characteristics, and environmental conditions, such as temperature and humidity. The aim is to evaluate the impact of temperature and precipitation on the global risk of dengue outbreaks at a 5x5 km2 resolution.A spatiotemporal model using an extended version of the Ross-Macdonald theory calculated a Relative Global Dengue Basic Reproductive Model (R0). It included temperature, rainfall, Aedes aegypti vector distribution, and geolocalized economic factors to evaluate disease transmission dynamics. The geolocalized economic data integrated the association between mosquito and human interaction and economic prosperity, which is heavily dependent on the availability of running water, access to air conditioning, and screens on the windows.Overall, the R0 model's projections align with the observed distribution of the Dengue virus. The Brière and Quadratic Functional forms of precipitation demonstrate widespread dengue risk throughout the year in equatorial regions and a coordinating increase in R0 values at higher latitudes in the northern hemispheres during the summer months and lower latitudes in the southern hemisphere during the summer months. The model predicts a global relative Dengue outbreak risk profile and demonstrates its spatiotemporal heterogeneity by identifying areas at risk of high virus transmission throughout the various months of the year. It shows an increase in the geographic risk during summer temperatures, demonstrating an optimal temperature and precipitation range for the genesis and proliferation of an outbreak. For simplicity, our model considers the impact of precipitation and temperature on Ae. Aegypti life cycle as independent variables. Future work should investigate their potential synergistic impact on mosquito population dynamics and outbreak risks.

6537

THE SINGLE PATCH PLASMODIUM FALCIPARUM APPLICATION - A TOOL FOR MALARIA MODELLING IN LMIC

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With a global push towards malaria elimination, modellers are increasingly supporting national and regional policy design in LMIC, and have the ability to contribute directly towards achieving malaria elimination in these countries. Innovations in modelling and scientific communication become necessary as timelines for decision-making vary. One such innovation is to develop user-friendly computer applications designed to allow policy-makers to run simple mathematical models and navigate the output of millions of simulations of more complex models with the aid of interactive graphs. The primary novelty is the focus on implementation and translation of the modelling results allowing policy-makers to design an elimination/control strategy incrementally by combining candidate interventions to predict the desired impact and cost. The Single Patch Plasmodium falciparum (SPPf) tool is disease modelling software that simulates Plasmodium falciparum malaria transmission for a population of interest. The software allows the user to simulate malaria policies and intervention strategies, alone and in combination, to determine the impact on malaria incidence and the cost thereof. The tool has been developed in the open-source RShiny Application framework and can be made available to the user in both an online and offline format. Beyond allowing the user to upload local data into the tool, the SPPf tool simulates key interventions such as scaling up or down of vector control activities including long lasting insecticide treated bednets and indoor residual spraying, health systems strengthening through improved access to and receipt of care, chemoprevention during pregnancy and seasonally, and the impact of the RTS,S vaccine. Both the epidemiological and cost results are available for download for further analysis. The SPPf tool has already been used to design malaria policy in South Africa, Ghana and several other settings. The principal benefit of the SPPf tool is to allow the modeller to co-design malaria policy with the decision-maker to enable true participatory modelling.

6538

RESPONSIBLE ACCESS TO DATA FOR ANALYSIS AND RESEARCH (HEALTH: RADAR) – A PROJECT FOR BETTER CLIMATE SENSITIVE INFECTIOUS DISEASE MODELS IN THE GLOBAL SOUTH AFRICA

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A recent literature review by the Wellcome Trust found that the majority of digital tools related to Climate Sensitive Disease Modelling (CSID) have been developed by institutions in the global North, while the major burden of disease remains in the global South. Disease models accounting for local context, diversity and culture in model development can lead to recommendations that are more implementable and acceptable to the populations on whom these models are based. This is maximised when the models and analysis are generated by modellers from the geographies under study. One of the greatest obstacles to CSID modelling in LMIC is accessibility to operationalisable datasets in a format that is digestible and acceptable to modellers and analysts. Health: Responsible Access to Data for Analysis and Research (Health: RADAR) is a project funded by the Wellcome Trust which seeks to contribute to the development of useful CSID models within an African context. The project partners include the Modelling and Simulation Hub Africa (MASHA), the Climate Systems Analysis Group (SAG), the Clinton Health Access Initiative (CHAI) and the South African Medical Research Council (SAMRC). A key project output is an open-source online resource where users can access contextually enriched data sources for climate sensitive infectious disease models. For this project, the pilot application is on Malaria in the Southern African region though the nature of the project allows for more general scope at a later stage. Another key output is the establishment of a community of users who contribute to the online resource through procedures developed over the coming years. Data included in the resource should follow certain criteria - it should be readily accessible and befitting of the context focused on by the tool and citeable. The data should be incorporated in a way which adds contextual relevance as to how it could be incorporated into a CSID model, with example code on how one might work with the data.

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A PREDICTIVE MODEL FOR NON-INVASIVE ANEMIA DIAGNOSIS

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Anemia, a disease characterized by impaired tissue oxygen supply, is a condition that affects about a fifth of the world's population and is the second leading cause of disability. Individuals in western and central sub-Saharan Africa and South Asia are disproportionately affected by anemia, with young children and pregnant individuals experiencing the highest prevalence with life-threatening consequences. The objective of this study is to develop a predictive model which accurately estimates hemoglobin concentrations from nail bed images. Predictive models, including logistic regression and random forest, are trained on a data set that maps hemoglobin concentrations to patient nail bed images. Preliminary results are promising, suggesting that these predictive models have the potential to develop a cheaper and more accessible diagnostic tool for anemia diagnosis. Future work will focus on implementing additional predictive models such as a binary classification model or deep learning to improve

predictive performance. Ultimately,these results will be used to improve point-of-care anemia diagnostics by developing a better hematology tool that is non-invasive, accurate, and affordable for low-resource settings.

6540

IMPACT OF GOVERNMENT-REGULATED LOCKDOWNS DURING THE COVID-19 PANDEMIC ON ACCESS TO MENTAL HEALTH SERVICES THROUGH A TERTIARY PSYCHIATRIC CARE FACILITY AND THE NATIONAL MENTAL HEALTH CALL HELPLINE IN SRI LANKA

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During the COVID-19 pandemic, many countries imposed restrictions on human mobility, limiting access to healthcare. We examined how these measures affected access to psychiatric services in Sri Lanka. We analyzed 15,122 outpatient presentations (OPs) to tertiary care psychiatric service at the National Hospital of Sri Lanka, and 56,363 calls to the national mental health helpline of the National Institute of Mental Health between 2019 and 2021. Selected presentations for pre-pandemic (01.01.2019-20.03.2020) and pandemic (21.03.2020-31.12.2021) periods were compared using Chi-Square test at a significance level of 0.05. Using the Google residential mobility index as a proxy for the intensity of community response to nationwide lockdown, we evaluated its delayed association with OPs and helpline calls using distributed lag non-linear models. Statistically significant increases in OPs were observed for females (10%), somatic (28%) and mood (10%) symptoms, and behavioral changes (18%) during the pandemic while OPs for self-harm and substance use decreased significantly by 22% and 25%, respectively. Treatment termination rate by provider was significantly higher among patients during the pandemic. Compared to pre-pandemic period, we observed a significant increase in calls for mental health concerns and a significant reduction in calls for domestic violence and alcohol use during pandemic period. Similarly, relative to the pre-pandemic period, increases in residential mobility index were associated with statistically significant increases in risk of OPs due to mood, somatic and behavioral symptoms, and self-harm with a lag of 21 days. The risk of helpline access due to mental health concerns, relationship issues, and suicidal ideation increased significantly with a lag of 3-5 days. Our findings indicate that OPs and psychiatric service provision patterns changed significantly during the pandemic. The shorter lags for helpline calls, when compared to OPs, indicate the importance of providing continued access to mental health services through telephone helplines during times of mobility restrictions and lockdowns.

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CREATING A DATA LIBRARY USING PUBLICLY AVAILABLE RESEARCH DATA ON NEGLECTED AND EMERGING INFECTIOUS DISEASES

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Neglected and emerging infectious diseases are vastly understudied due to being uncommon in high income countries and the lack of resources in low-income countries have led to underfunding for research. The goal is to search for publicly available data on neglected diseases so that researchers can utilize them to answer research questions they may have on neglected diseases. A search was conducted for data on each neglected disease through data repositories including Harvard Dataverse, Cliniclatrials.gov, zenodo.org, All of Us Cohort Study, and Data dryad.org. The research studies with data were collected and a data library was developed including each neglected disease, the name of the study, a brief description of the research, the origin of the research data, and links to the research data. The results from the search revealed that data is publicly available on each neglected disease with some diseases having more research results compared to others. A search for Schistomiasis on Harvard Dataverse yielded only 6 studies while Chagas disease generated 4694 results on research with data on zenodo.org. More than 50 studies with data on neglected diseases within the last 5 years were obtained from the online data repositories which makes the limited data available and can facilitate research.

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FEASIBILITY AND ACCEPTABILITY OF MOBILE TECHNOLOGY TO IMPROVE ONE HEALTH OUTBREAK REPORTING IN BWINDI, UGANDA

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The Bwindi Impenetrable National Park (BINP) in Southwest Uganda is an extremely dense and biodiverse forest. A highly dense human population living in proximity to forest animals results in numerous opportunities for zoonotic spillover. This work was part of NIAID CREID Network's Epicenter for Emerging Infectious Disease Intelligence (EEIDI) that investigates regional emerging infectious diseases (EIDs). A One Health, transdisciplinary strategy is used for surveillance and response for EIDs of pandemic potential.This exploratory study was undertaken as a needs assessment and acceptability study to inform a large technology-development project intended to improve data reporting and outbreak responses in areas at high risk for zoonotic spillover. Methods employed primarily focus group discussions (FGDs) in both hard-to-reach rural communities around BINP, and the urban setting of Kabale city. Though smartphone app-based technology is replacing SMS-based technology, local communities rely solely on simple button phones to communicate. This study had the goals of 1) determining the primary methods of mobile communication and 2) estimating community acceptance of a mobile reporting system to report and record location.Ten rural FGDs were conducted around BINP in 3 districts (Kanungu, Rubanda, and Kisoro), and 5 FGDs were conducted in the urban setting in Kabale district. Each FGD had 6-8 participants, totaling 102 people. With written informed consent from each participant, we recorded the discussions, translated them from the local language into English, and transcribed them. Line by line coding of major categories and themes was performed using NVivo software. This analysis revealed that all 15 FGDs reported simple button (SMS based) phones as the predominantly available cell phone type. All 15 FGDs also reported willingness to participate in a mobile outbreak reporting system and willingness to have their geolocation data reported. Communities in Bwindi have access to, and prefer, Simple button (SMS) phones. Community acceptance was very high. These results combined reveal high potential for a new mobile reporting system.

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INVESTMENT CRITERIA FOR THE DEVELOPMENT OF NEW DIAGNOSTICS

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When making decisions to invest in the development of new diagnostics, most manufacturers from high-income countries (HIC) require extraordinarily high prerequisite levels of projected annual sales, market growth and rates of return. Because of these investment criteria, medical technologies are rarely designed for use in low- and middle-income countries (LMICs). Transferring healthcare solutions and technologies from HIC to LMICs is slow, expensive and challenging if not impossible. Appropriate diagnostic products designed specifically for implementation in LMICs are best developed with local knowledge and understanding of needs, context, and available resources. For local innovation of health technologies to become a new standard, capabilities in health technology are required for needs assessment, market analysis, product design, prototyping, validation testing, manufacturing and management. The NIH-funded Center for Innovation in Point-of-Care Technologies for HIV/AIDS and Emerging Infectious Diseases at Northwestern (C-THAN) is one of the Point-of-Care Technology Research Network (POCTRN) centers of the NIH that supports biomedical engineering capacity in LMIC-centered diagnostics. C-THAN includes 9 academic centers across Africa that catalyzes innovation in diagnostic technologies through a model that enhances complementary strengths to build multidisciplinary partnerships across technology platforms, clinical, regulatory and commercialization domains with a specific focus on HIV/AIDS and emerging infectious diseases. During C-THAN's first five years, 43 projects were successfully supported, 26 involved technology development, 9 clinical validation, and 9 technology dissemination. 34% of projects have African Principal Investigators and most involve collaborations between HIC and LMIC investigators. In the next 5 years, C-THAN will emphasize specific technologic domains by establishing working groups in molecular, lateral flow, synthetic biology, and product engineering in HIV and emerging infectious diseases related diagnostics.

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CLOSE ENCOUNTERS OF THE ENVENOMATING KIND: MISSIONARIES, INSECTS, AND SNAKES DURING THE SCRAMBLE FOR AFRICA, 1885 - 1914

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Encounters with envenomating insects and reptiles of all kinds were, and remain, common in sub-Saharan regions throughout Africa. As Europeans, whether secular, military, or religious, pushed more deeply into these areas, these meetings grew increasingly likely. Missionaries who worked for the Church Missionary Society (CMS), an evangelical Anglican organisation founded in 1804, provide an excellent case in point. They provide vivid, humorous, and sometimes tragic, encounters with arthropods and reptiles. Naïve newcomers, blissfully ignorant of hazards that might await them in the bush, faced particular risk. Relying on published and archival contemporary accounts by CMS missionaries during the late 19th century Scramble for Africa, this presentation will highlight encounters, both comical and tragic, with envenomating insects in sub-Saharan Africa.

6545

IMPACT OF AN ANCILLARY CARE POLICY DURING AN EBOLA VACCINE TRIAL IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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Between 2019 and 2022, the Universities of Antwerp (Belgium) and Kinshasa (DRC) conducted an Ebola vaccine trial (clinicaltrials.gov: NCT04186000) in the remote area of Boende in DRC, characterized by insufficient access to essential health care and a previous Ebola outbreak. After the trial started, a policy with decision algorithm was developed to support participants' concomitant medical events. To evaluate its impact on the management of related and unrelated (Serious) Adverse Events ((S) AE), we assessed for each event reported if and which type of support was provided. Potential outcomes were administering medication, direct payment or reimbursement of medical costs, or no support possible. Data was summarized using descriptive statistics. In total, 629 AE and 62 SAE were reported; the majority (613 and 58 respectively) were unrelated to the investigational product or to trial participation. Medication from the study pharmacy was administered to 555 AE and 18 SAE. Additionally, for 155 cases the medical costs were directly covered by the study budget. Reimbursements were provided for 20 AE and 24 SAE, but for 17 AE and 24 SAE this was impossible. With AE, treatment consisted of medication (from multiple sources) in 611 cases, 32 were hospital consultations. The remaining 12 were managed otherwise, e.g. via blood checks, observation, or surgical interventions. With SAE, 52 participants were hospitalized, 50 were treated with medication and 13 received surgery. The policy's largest impact lays with the provision of medication, offered directly or reimbursed when coming from other sources. Study pharmacies can thus contribute majorly to participant care. Financial support, although not the largest support outcome, had a considerable impact on reducing participants' out of pocket payments for health care. Unsupported medical costs were mostly due to (unrelated) events occurring prior to policy implementation, or to the absence of documentation. This underlines the importance of planning an ancillary care policy upfront, and of informing participants at recruitment in order to adequately address their health needs during research.

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THE SOUTH AND SOUTHEAST ASIAN COMMUNITY BASED TRIALS NETWORK (SEACTN)

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The South and Southeast Asian Community-based Trials Network (SEACTN) was launched in October 2019 to establish the foundational infrastructure for monitoring the incidence, causes and outcomes of febrile illnesses in rural communities in these regions, and later the trialling of interventions delivered by village health workers and rural clinics to improve their diagnosis and treatment. SEACTN activities span approximately 750 villages across five South and Southeast Asian countries (Bangladesh, Myanmar, Laos, Cambodia, and Thailand). It is a uniquely multi-national network with governmental, non-governmental, and academic partners focused on rural and remote healthcare provision in areas often neglected by the health system, and with data being collected electronically and collated in real time. As of March 2023, over 60,000 patients with a febrile illness have been recruited in these remote and underserved communities, as well as over 2100 patients admitted in higher level facilities. Multiplex serological and molecular assays have been developed to establish the causes of illness in these patients. In parallel, over a thousand deaths have been investigated with verbal autopsies, and household health surveys are being conducted in hundreds of villages. This is providing an unprecedented account of the incidence, morbidity and mortality associated with acute febrile illness as well as other causes of morbidity and mortality in rural South and Southeast Asia. This will support evidence-based decisions as to which interventions are likely to have the largest positive impact on population health in these remote, underserved, and understudied communities and these interventions will later be trialled in the same network. This session will provide an overview of SEACTN and interim findings on presenting syndromes and outcomes in the community and hospital-based cohorts.

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FEEDBACK FROM THE FAMILY FOLLOW-UP SESSIONS WITH DECEASED FAMILIES TO SHARE THE CAUSE OF DEATH REPORT: LESSON LEARNT FROM THE CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) PROGRAM IN BANGLADESH

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In Bangladesh, determination of cause of death (CoD) is often imprecise due to under-resourced diagnostic facilities and culturally low acceptance of full autopsy. The Child Health and Mortality Prevention Surveillance (CHAMPS) offers minimally invasive tissue sampling (MITS) at Baliakandi sub-district and Faridpur district to identify the cause of stillbirth and of <5 deaths. The team promised families to return the CoD report determined by an expert panel within 120 days of the death, but if delayed team informed them the cause of delay. The CoD reports were prepared in a descriptive format and a trained, gender balanced team including a physician and community engagement staff shared the report to families in their home through an interactive session. To make it more effective, we observed 110 sessions between 2018 to 2020 and documented participants' acceptance, queries, opinions and our team's responses. The parents, key decision makers, relatives and some neighbors attended the sessions with duration of 35 minutes. Families generally appreciated that our team returned to them with CoD report. In the initial sessions, families requested to share the case specific preventions. Subsequently, the panel prepared cause specific and general prevention messages that the team shared with families. Although families accepted the report; some perceived that the child death was expected as some maternal factors mentioned as CoD i.e. high blood pressure, diabetes and domestic violence. After explaining how such conditions were treatable, families stated that now they realized the death occurred due to their negligence, not sending mother for antenatal care and some families argued, the death occurred due to physicians' negligence. Families common queries were how to prevent future deaths and how CHAMPS can support mother during subsequent pregnancies i.e. for treatment and team explained the need for ANC and CHAMPS could support mother to receive it in CHAMPS facilities. Our findings suggest that such interactive session could sensitized families about CoD and need for ANC or required treatment during pregnancy to prevent unwanted child death.

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HOW DO SUBSTANDARD AND FALSIFIED ANTIMICROBIALS AFFECT THE EMERGENCE AND SPREAD OF ANTIMICROBIAL RESISTANCE?

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Approximately 10% of antimicrobials used by humans in low- and middle-income countries are estimated to be substandard or falsified (SF). In addition to their negative impact on morbidity and mortality, they may also be important yet neglected drivers of antimicrobial resistance. Despite concern over their potential role in the emergence and spread of antimicrobial resistance, and the consequences this would have on public health, our current understanding of this relationship is rudimentary. In this study, we used mathematical models to examine the relationship between SF medicines and antimicrobial resistance. Combining observed distributions of active pharmaceutical ingredients in randomly sampled antibiotics with different assumptions about the relationship between dosing level and resistance emergence, we quantified the expected rate of population level resistance emergence. Results suggested that when ~10% of medicines are SF, the effect on resistance may be relatively small. However, in pockets where SF medicines are more common, representing ~50% or more of antimicrobials, SF medicines may have a substantial effect on resistance emergence. Second, we combined these outputs with epidemiological models to understand the role that both transmission of resistant microbes and heterogeneity in the frequency of SF medicines play in driving the spread of resistance. This suggested that those pockets with higher frequencies of SF medicines have the potential to drive resistance in other areas too. Together, our results add to our understanding of this important and neglected global health problem, and provide a framework for future work assessing the importance of different intervention points to reduce the impact of SF medicines on resistance.

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THE DEVILS INVADE THE HOUSE THROUGH THE HOLES IN THE BAMBOO BOOTH: A NARRATIVE OF LOKU AND TAKAYA FEVER ILLNESS AMONG CHILDREN IN EASTERN INDONESIA

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Fever is the most prevalent presenting ailment during childhood. On the eastern Indonesian island of Alor, the Abui people recognize two fatal fever-

related folk illnesses called Loku and Takaya. From June 2021 to July 2022, an ethnographic study was done using in-depth interviews, participant observation, and informal interactions. Following the ethnographic work, census, and behavioral surveys were carried out to measure the impact of distance to a health facility and degree of illness on treatment seeking behavior for fever. The study explored how people perceive and seek treatment for childhood fever. Five individuals were purposively chosen from 50 key informants. The narratives of two eminent healers and three mothers of feverish children illustrate the cultural understandings of febrile illness. The mothers consulted traditional healers and home remedies or holy water were offered. When illness progressed to severe, mothers acknowledged that the child may need to be admitted to a health facility. However, cost and poor service quality were cited as impediments to that treatment-seeking. Consequently, mothers often opted to care for their children at home, even understanding the danger that imposed. The healers believed both Loku and Takaya would be diagnosed as malaria at the health facility. Yet, they believed that antimalarials are unable to cure due to its supranatural causes. In summary, traditional understanding and management of febrile illness and treatment seeking behavior within this impoverished rural community continues and leads to potentially dangerous delays in treatment of feverish children. Health promotion and community engagement by public health workers who understand local perceptions of fever are more likely to devise more effective health interventions and mitigate preventable infectious harm to Abui children.

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PREVALENCE OF ANTIBIOTIC USE AMONG THREE SELECTED TERTIARY LEVEL HOSPITALIZED PATIENTS, A POINT PREVALENCE SURVEY FINDING IN BANGLADESH

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Irrational use of antimicrobials in both humans, animals, and the food chain led to the emergence of antimicrobial resistance (AMR). Due to antibiotic resistance, patients are more likely to remain infectious for a longer time, increasing the risk of spreading resistant microorganisms to others. For supporting antibiotic stewardship interventions, the World Health Organization (WHO) categorized antibiotics according to AWaRe (Access, Watch, Reserve) classification. We aimed to describe the prevalence of antibiotic use (ABU) as stated by AWaRe classification in tertiary level acute care hospitals in Bangladesh. A point prevalence survey (PPS) was conducted adopting WHO PPS design among inpatients of three tertiary level public hospitals in Bangladesh from June to September 2022. Among the enrolled 1634 inpatients, 52% (860) were female and 66% (1093) were from the 15-64 years age group. Nearly, 75% (1241) of patients received at least one antibiotic during the survey period. Proportioning for different departments, 90% of the patients from burn ward, 87% of pediatric, 75% of gynae and obstetric, 72% of surgery, and 69% of medicine wards received at least one antibiotic. Third-generation cephalosporins (43%), imidazoles (15%), penicillins (13%), aminoglycosides (8.5%), and second-generation cephalosporin (8%) were documented as top 5 antibiotics. Different group of antibiotic usage at the same time was a common phenomenon. In the course of a single admission patients received ranging from single to seven antibiotics. Overall, 63% of Watch, 36% of Access, and 1% of Reserve group antibiotics were used for treatment. The use of watch group antibiotics is quite high in public hospitals. Our PPS findings underscores the need for urgent nationwide antibiotic stewardship progam for physicians along with development of disease specific and department-wise standard treatment guidelines and in-service training on ABU for the containment of AMR.

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IMPROVING MALARIA COMMODITY ACCOUNTABILITY: - THE CASE OF MALAWI

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In Malawi, before 2016, reports showed limited availability of malaria medicines with 10% facilities reporting stock out of first line malaria treatment. The discrepancy ratio between the number of commodities issued and the number of cases treated was also high (1.53 compared with 1.15 target); the base line documented that 10,178,5929 treatments were issued to treat 6,647,163 cases. The potential factors contributing for this discrepancy were identified as poor recording and pilferage at treatment site level. The USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM), project devised a Commodity Accountability and Performance Tracking (CAPeT) initiative. This initiative targets 30-60 health facilities with high discrepancies based on data analysis on malaria cases and first-line treatments reported through District Health Information Software 2 (DHIS2) and Open Logistics Management Information System (OpenLMIS) quarterly. It identifies the factors (such as missing records and data aggregation errors) responsible for the discrepancies and offers solutions at various levels of implementation to address these factors. GHSC-PSM engages facility staff to verify reports and review performance, identifying discrepancies as a measure of accountability and developing action plans shared with the district and central-level health offices for further follow-up. Results from the activity show a general decrease in the discrepancy ratio of 1.38 (2019), 1.26 (2020), 1.20 (2021), and 1.23 (2022). The proportion of facilities with a discrepancy ratio of less than or equal to 1.15 increased from 10% (3/30) in the initial visit to 50% (15/30) in the revisit. Similarly, the average national discrepancy ratio reduced from 1.53 before 2016 to 1.23 in 2022. Results showed that ensuring the accountability of health commodities in the supply chain plays a critical role in improving the availability of life-saving drugs at service delivery points, as evidenced by consistently low stock-out stock rate (<1% for ACT) and decreased discrepancy ratio.

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ANTIMICROBIAL STEWARDSHIP IN SOUTH ASIA: A SYSTEMATIC REVIEW OF QUALITATIVE LITERATURE

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Antibiotic resistance is a global public health crisis. Effective antibiotic stewardship requires an understanding of the factors and context that contribute to inappropriate use of antibiotics. The goal of this qualitative systematic review was to synthesize themes across levels of the social ecological framework that impede antimicrobial stewardship in South Asia. In July 2022, a systematic search was conducted using the electronic databases Medline and Embase. Search terms were identified a priori, based on eligibility criteria of methods (qualitative), location (eight countries of South Asia), topic (antimicrobial and antibiotic stewardship; drug resistance), and English language. 130 articles were identified; after removing duplicates (n=11) and excluding articles that did not meet eligibility criteria (n=96), 34 articles were included in the review, with publications ranging from 2010 to 2022. Methodological quality was assessed using the qualitative Critical Appraisal Skills Program checklist. The studies represented six countries in South Asia, and included data from patient populations, health care providers, community members, and policy members. For each paper, a summary memo was written to extract the factors that impede antimicrobial stewardship. NVivo software was then used to code the memos; codes were organized by levels of the social

ecological framework. Themes emerged at the level of the individual patient (access to medical care, patient expectations, rationing of antibiotics, and perceived value of antibiotics), the formal provider (antibiotics as the first line of therapy, gaps in knowledge and skills, and financial or reputational incentives), the clinical setting (lack of resources, and poor regulation of the facility), the community (informal drug vendors, and social norms), and policy (lack of legislation, and poor implementation of existing policies). The findings highlight the importance of working across multiple sectors to build commitment for antibiotic stewardship in South Asia.

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A PHYSICIAN-LED PRIMARY PREVENTION CARE ON RISK OF CARDIOVASCULAR DISEASE: A RANDOMIZED CONTROLLED TRIAL (PRIMCARD STUDY)

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Cardiovascular diseases account for more than 36% of deaths among adults younger than 60 years in Nigeria. The WHO advocated primary prevention care as the cheapest and most cost-effective approach to managing cardiovascular risk. Even with standard guidelines, caregivers, especially physicians are yet to accept primary prevention in practice. Major barriers include its time-consuming nature and low yield of immediate effects. This study compared the effects of physician-led primary prevention care versus usual care on cardiovascular risk reduction among at-risk institutional workers.A parallel randomized control trial was conducted. A total of 223 respondents with moderate and high risk were enrolled and randomized into physician-led intervention (n = 118) and usual care (n = 105) and followed up for six months. Respondents in the intervention arm were offered a physician-led total cardiovascular risk management approach, while the control arm continued with their usual care. The primary outcome measure was cardiovascular risk score while secondary outcome measures were: blood pressure, fasting blood sugar and body mass index and waist-to-hip ratio. Data were analyzed using descriptive statistics, paired t-test and independent t-test at α0.05.Respondents were similar in both arms for baseline sociodemographic, behavioral and cardiometabolic characteristics. Between groups, the intervention arm achieved greater reduction in blood sugar and BMI, with a mean difference of -13mg/dl and -0.6kg/m2 respectively; there was a marginal mean difference in CV risk score of -0.1% with the number needed-to-treat being ten. Within the groups, the intervention arm demonstrated significant effects on systolic blood pressure(5.0mmHg), blood sugar(9.8mg/dl), and BMI (0.8kg/m2) at endline. The control arm only affected the systolic blood pressure(8.6mmHg).The physician-led primary prevention intervention was effective in reducing individual cardiovascular risk factors and may serve a beneficial prophylactic effect on the reduction of absolute cardiovascular risk at a population level.

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HYDROCEPHALUS - TWENTY YEAR TRENDS IN UGANDA

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Hydrocephalus is a life-threatening condition due to excessive accumulation of cerebral spinal fluid within the brain's fluid spaces (ventricles). Untreated progressive hydrocephalus in children below two years of age leads to further brain damage, resulting in the majority dying and survivors left with severe cognitive and physical disabilities. It is thus critical to access early proper neurosurgical treatment in order to prevent the long-term deleterious effects and complications. Hydrocephalus is an underrecognized global health problem, and a major cause of childhood disability worldwide; with more than 400,000 new cases occuring annually; 100,000 of them from sub-Saharan Africa alone. These are additionally faced with the challenges of poverty, limited access to care, and low advocacy. Uganda is a low-income sub-Saharan country with high rates of both congenital and acquired hydrocephalus.CURE Uganda is a center of excellence for peadiatric neurosurgery treatment, training and research. Located in the Eastern part of the country, it is the main referral center for patients all over the country with hydrocephalus and spina bifida, including neighboring ones like Kenya, Tanzania, DRC, Rwanda, and South Sudan.It's estimated that 3,600 - 5,400 children in Uganda are born with or acquire hydrocephalus each year or 2 to 3 / 1,000 births (based on 1,800,000 new births per year). CURE Uganda is currently providing surgery for only approximately 20-30% of the estimated annual country need. Over the past two decades (2001-2020), CURE Uganda has provided care for 10,919 children with hydrocephalus (74%) and spina bifida (26%). The majority of the causes of Ugandan infant hydrocephalus are neonatal infections (67%) and spina bifida; both of which are preventable. The early neonatal infections have been attributed to the bi-annual rainfalls; and have a spatiotemporal distribution although the exact pathogenesis is not very clear. The recent novel discovery of the pathogens presents the perfect opportunity for preventative strategies in tropical medicine that will have huge impacts in addressing these growing disparities in global health.

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MALAWI INTEGRATED TYPHOID CONJUGATE VACCINE CAMPAIGN AND ROUTINE INTRODUCTION

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It is estimated that in Malawi in 2017, for all ages, there were 32,747 typhoid cases (191 cases per 100,000), 435 deaths, and 32,787 disability-adjusted life years lost to typhoid. Sixty-one percent of all cases and 65% of all deaths were in children under 15 years. The Ministry of Health in collaboration with its partners, will conduct an integrated Typhoid Conjugate Vaccine (TCV) and Measles Rubella (MR) vaccination campaign and later introduce TCV into routine immunization. The main objective for TCV introduction is 1) To provide typhoid vaccine to all the children aged 9 months to 14 years through the campaign by reaching ≥ 95 % of the target population 2) To introduce TCV into routine immunization at age of 9 months by targeting at least 80% of eligible children aged 9 to 23 months at their 9 month immunization visit. The integrated TCV MR supplemental immunization activity (SIA) will be conducted for five days in April 2023.In addition, bivalent Oral Polio Vaccine (bOPV) and Vitamin A will be administered to children aged 0 - 59 months and 6 to 59 months respectively. There will be static, outreach clinics and mobile sites that will be opened for five days. Static sites are located at permanent government and private health facilities which will also serve as storage and distribution points of vaccines and other supplies to outreach sites. The rationale for the for the integrated SIA is; 1) To efficiently use of scarce human, financial resources and easier logistics 2) a high demand for one intervention can boost coverage of others given at same time 3) to reach the marginalized with more services 4) to respond to the public's demands for broader services during campaigns 5) for easier management of logistics and management. The campaign is currently planned whilst Malawi is battling cholera and polio outbreaks which could contribute to staff fatigue and poor quality of services. There could be challenges establishing causality when serious adverse events following immunization occur due to similar administration routes. Flooding caused by climate change will decrease access to vaccines whilst increasing transmission of waterborne diseases such as typhoid.

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THE NUTRITIONAL IMPACT OF THE COVID-19 PANDEMIC ON YOUNG CHILDREN IN PERI-URBAN PERU: A MIXED METHODS STUDY

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Peru has experienced immense suffering due to the Covid-19 pandemic, with the highest per capita Covid-related mortality in the world. In peri-urban areas, strict control measures and loss of work in the informal sector affected already vulnerable communities' ability to seek healthcare and provide nutritionally adequate food to their families. The goal of this study is to assess the pandemic's impact on child nutrition in peri-urban Lima by (1) examining the prevalence of household food insecurity and stunting, as compared to pre-pandemic levels; and (2) qualitatively exploring caregivers' experiences feeding their children since March 2020. The study employed three data collection methods. First, field workers administered a structured questionnaire to 300 caregivers of children 6-23 months of age to assess socio-economic status, food insecurity, and infant and young child feeding practices. Second, anthropometric measurements (weight and length) were taken for each. Third, in-depth interviews were conducted with a subset of 30 caregivers. Data are being analyzed for key trends and themes using Stata 16 and Dedoose. Preliminary statistical analyses indicate that 79.0% of participating households are moderately or severely food insecure according to USAID's Household Food Insecurity Access Scale, and that 10.3% of children 6-23 months of age are stunted. Future analyses will compare these data to data collected during a 2016-2019 cohort study in the same setting to estimate the pandemic's effects on food insecurity and child growth. Qualitative data analysis will shed light on how economic factors, food access, the healthcare system, and interruptions in social assistance programs affected child feeding during the early stages of the pandemic, as well as the coping strategies that caregivers have developed. In conclusion, study findings will contribute to our understanding of how low-resource, peri-urban households have been affected by the pandemic and its aftershocks, and how officials may better safeguard child health and nutrition in their responses to future public health emergencies.

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CONTRIBUTION OF VERBAL AUTOPSY INFORMATION TO CAUSE OF DEATH ATTRIBUTION AMONG CASES UNDERGOING MINIMALLY INVASIVE TISSUE SAMPLING: FINDINGS FROM CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) BANGLADESH

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Postmortem examination is a gold standard procedure for determining the cause of death (CoD). CHAMPS uses minimally invasive tissue sampling (MITS) with other information to assign specific CoD to stillbirths and under-five children. A panel of clinical and laboratory experts reviews each case's histology, laboratory, medical records, including maternal clinical records, if available, and a verbal autopsy (VA). The panel assigns underlying, immediate, morbid, and maternal conditions attributed to the death, including prevention recommendations. In this study, we examined how and to what extent VA data contributed to understanding CoD. From December 2022 to February 2023, the panel reviewed all existing data except the VA for 25 cases (7 were stillbirths and 18 neonatal deaths) and assigned CoD, maternal condition, and preventive actions. Then the panel re-evaluated the case, including the VA, and identified changes to CoD with this additional data point. After reviewing VA data for stillbirths, the underlying cause remained the same. However, a maternal condition was identified for one where maternal clinical record was missing, and the panel revised their prevention recommendations in 29% (2/7) cases. VA data changed the causal chain in 28% (5/18) of neonatal cases. In two cases, the lung histology was unremarkable, and the panel assigned underlying CoD as intrauterine hypoxia based on medical records. After reviewing the VA, CoD was changed from intrauterine hypoxia to sepsis and respiratory distress syndrome. A morbid condition was added in 11% (2/18) cases and excluded in one case. In 33% (6/18) cases, a maternal condition was detected. For one case, the condition was revised from oligohydramnios (identified through ultrasound record) to premature rupture of membrane. Overall, the VA data were a helpful adjunct to understanding CoD for stillbirths and early neonatal deaths, especially for deaths with no or poor clinical or laboratory records. In the context of poor medical records, VA advances the accuracy and completeness of MITS procedures for CoD determination in stillbirths and neonatal deaths.

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ASSESSING THE ESSENTIAL DATA SOURCES FOR PRECISE CAUSE OF DEATH DETERMINATION USING MINIMALLY INVASIVE TISSUE SAMPLING: FINDINGS FROM CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE (CHAMPS) BANGLADESH

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CHAMPS is a multi-country project aimed at determining the precise causes of stillbirths and under-five child deaths. CHAMPS utilizes various data sources including maternal and child data abstracted from medical records, histopathology, microbial culture, and molecular detection using multiple specimens, postmortem examination, and verbal autopsy (VA) for the determination of the cause of death (CoD). The aim of this study is to assess the contribution of each data source to increase the competence of the CoD determination process which is essential to develop actionable prevention strategies. From March 2018 to February 2023, an expert panel of pediatrician, neonatologist, obstetrician, pathologist, epidemiologist, and microbiologist reviewed 535 deaths and assigned CoD to 529 (99%) cases in Bangladesh. Of these, 51% (275/535) were stillbirths, 43% (228/535) were early neonatal deaths (0 to 6 days), and 6% (32/535) were child deaths (7 days to under 60 months). Maternal clinical abstracted data was used to detect maternal conditions directly attributed to causing death in 69% (191/275) of stillbirths and 51% (117/228) of early neonates. Child clinical abstracted data contributed to understanding the causes of early neonatal and older child deaths in 59% of cases and 75% (24/32) of cases, respectively. Histopathology reports contributed to CoD determination in 52% of stillbirths and 59% of early neonates. Infection was the cause of stillbirths and under-five child deaths in 12% of cases where postmortem culture (64/535) and molecular detection (66/535) assisted to identify pathogens. In 74% of stillbirths and 58% of early neonatal deaths, VA data aided in detecting maternal conditions. Also, VA data contributed to ascertaining the causes of child deaths in 68% (22/32) of cases. Due to the inconclusiveness of data, CoD could not be assigned for only 1% (6/535). The study highlights the contribution of each data source to determining a definitive CoD. However, it is contingent upon the extent to which the data is available, reliable, and comprehensive.

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DETERMINANTS OF NEONATAL MORTALITY IN RIVERCESS: SECONDARY DATA ANALYSIS OF NEONATAL DEATH IN HEALTH FACILITIES IN RIVERCESS, 2016-2020

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Globally more than 6.3 million young adolescents and children died regularly from neonatal death causes. About 2.6 million newborn die in their first 28 days of life annually. Most newborn deaths, about 99% happen in countries that had limited income. Increased access to skilled birth attendants is another strategy that had been implemented in the reduction of newborn rate in Liberia. Liberia had made substantial improvement towards the decrease of neonatal death since 1970 till today's date. The research seeks to estimates live births and deaths of neonates in health facilities in Rivercess from 2016-2020. The research was conducted using a quantitative approach. Data was collected through reviewing the health facilities Health Management Information System (HMIS) report and neonatal deaths audit forms that were used by the twenty health facilities in Rivercess. The study population encompass all live born neonates and neonatal deaths records. The results revealed that the overall neonatal mortality rates (NMR) in Rivercess was 94 deaths per 11313 births or 8.3 per 1000 live birth of children occurred within the 5 year period preceding the study. The total number of neonatal deaths over this period was 94. The research revealed that neonatal deaths were most common among neonates born asphyxiated and with difficulty breathing. However, neonates who died at an early age were asphyxiated than neonates who died at late age. Another factor which was significantly associated with neonatal death at later ages was neonatal infection. The need to implement facility based newborn care interventions particularly educating midwives, nurses and traditional birth attendants about safe delivery practices is limited and therefore need improvement. Additionally, MoH should put in place a timely referral system and retain healthcare providers especially midwives to manage delivery complications and need to implement effective interventions to reduce risk of neonatal death in Rivercess.

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PROGRESS VS PERSISTENT CHALLENGES- WHAT WE HAVE HEARD: CHALLENGES AND OPPORTUNITIES

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The rate of maternal mortality in Liberia has been and still is one of the highest in the world. In contrast, the rate of neonatal mortality in Liberia—which had been one of the highest globally—has steadily reduced over the last decade. This study aims to synthesize existing evidence on the current state of maternal and neonatal health in Liberia, including approaches to intervention. In-depth interviews were conducted with a range of key stakeholders in Maternal and Neonatal Health in Liberia. These included policymakers in Monrovia, service providers in government facilities/NGO programs, community health workers and community leaders. Additionally, a series of Focus Group Discussions (FGDs) in communities across three of the most affected counties were conducted to explore perspectives regarding maternal and neonatal health in Liberia. Thematic content analysis was to determine emerging themes and Nvivo 12 software was used to structure the analysis. Key themes emerged around challenges to receipt and delivery of high-quality maternal and neonatal health in Liberia, as well as advances that have led to improvements in care. These included 1) Financial constraints exist due to disparate yet insufficient funding across multiple sources: the government, development partners and out of pocket expenses (OOP). 2) Management, accountability, and leadership in healthcare are clearly defined as priorities but not monitored. Policy documents provide clear descriptions of the authority, responsibilities, and competencies for leadership roles at all levels of the health system in Liberia. However, there seems to be a disconnect between what the policies state and the actualities due to a lack of leadership, political will, management skills, coordination and monitoring and evaluation 3) Health facilities, infrastructure and accessibility are generally poorly maintained. 4) Human resource capacity and training is limited due to relatively low numbers of trained health workers compromise adequate coverage in remote areas

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ASSOCIATED FACTORS WITH THE POOR PERFORMANCE OF THE MATERNAL DEATH SURVEILLANCE SYSTEM IN CAMEROON, 2020-2022

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In 2014, Cameroon decided to reduce preventable maternal mortality. Surveillance data reviews shows under-reporting. We aimed to identify factors associated with poor performance of Maternal Death (MD) surveillance in Cameroon. An analytical cross-sectional study was conducted in all 10 regions from January 2020 to June 2022. A multi-stage stratified sampling helped to include randomly 13 urban and 13 rural Health Districts (HD). Health facilities (HF) were divided into six categories: all category 1-3 and 2 in category 4-6 per HD were included. Two quarters/villages were randomly chosen in Health Area (HA) hosting the mean HF. All consenting Traditional, religious and administrative leaders, Community Health Workers (CHW), traditional birth attendants and tradipratician were interviewed. Health care workers (HCW) were randomly included depending on the units. The 2001 CDC guidelines of Robert German group work was used to evaluate attributes of MD surveillance system. A KAP survey of community actors was done throw a pre tested questioner. Kobo collect software helped for data collection and Excel software for analyses. OR (CI: 95%, P<0,005) used to identify associations. A total of 2425 people were interviewed, with 1356(56%) female (F/H sex ratio of 1:1). The median age was 34(15-85) years and 1285(53%) aged 25-40 years. HCW were 1106(46%) and CHWs 1041(43%) of the interviewed. DHIS2 recorded 3046 MDs but only 1964(64.5%) were founded in HF's registers. MD causes were mostly unknown, with 80(21%). Littoral region had highest maternal mortality rate either 380 MD for 100000 live births. The surveillance system was moderately simple, unacceptable and sensitive. The promptness and completeness were acceptable. Only 6681(55,8%) MD were reviewed with 29(28%) review's recommendations fully implemented. The MD surveillance system sensitivity is significantly associated with the area (urban or rural) of implementation (OR=1.534; CI: [1,18-1,99]; P<0.001). The MD surveillance system shows globally shortcomings. We recommend training all level actors, surveillance tools elaboration, and resources allocation for activities.

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ASSESSMENT OF KNOWLEDGE, ATTITUDES, AND PRACTICES (KAP) TOWARD COVID-19 IN KINSHASA, DRC

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The Democratic Republic of the Congo (DRC) has reported fewer COVID-19 cases and deaths compared to other countries. Determining the community-level prevalence of infection, knowledge, and behaviors that may mediate transmission is essential for improving COVID-19 control measures. The Seroepidemiological Insight into COVID-19 transmission in Africa study (SICA) aims to measure host and ecological factors influencing incidence in Kinshasa Province, DRC. This sub-study assessed the knowledge, attitudes, and practices (KAP) surrounding COVID-19. SICA study participants >15 years were administered a KAP survey. The World Health Organization Social and Behavioral Insights on COVID-19 Data Collection Tool (SBI Tool) was adapted, and included six sections: knowledge of transmission and symptoms, perceived risk and impact, prevention practices, prior illness and testing, trusted information sources, and vaccination. The frequency and proportions of the KAP indicators were calculated. From August to September 2022, 420 participants were interviewed. The median respondent age was 42 years, and 254 (61%) were female. Only 12% rated their knowledge of COVID above average, but the knowledge of one or more specific symptoms of COVID was high (86%). The two most common symptoms mentioned were cough (71%) and fever (59%). Almost three-quarters of participants (72%) considered COVID-19 a problem for their community. Most respondents (72%) reported currently practicing preventative measures, the most common of which were wearing a mask (58%), hand washing (40%), avoiding shaking hands (25%), and physical distancing (23%). Twenty-three percent of respondents reported receiving the COVID vaccine. Of those not yet vaccinated, 40% reported that they would not be vaccinated against COVID-19 in the future, due to a lack of confidence in all vaccines (43%) and unsure of its efficacy (38%). Despite self-reporting a low knowledge of COVID-19, this study population had a good level of knowledge about COVID-19. However, improvements in attitudes and practices toward preventative behaviors could further reduce transmission during seasonal peaks.

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PROFILING THE QUALITY OF LIFE OF SLUM RESIDENTS DURING THE COVID-19 PANDEMIC, AND THE EFFECTS OF SOME SOCIO-DEMOGRAPHIC AND ECONOMIC MEASURES

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Brazil has recorded over 36 million cases and 650,000 deaths due to COVID-19 and remained the most affected country in Latin America. Efforts targeted at stemming transmission through non-pharmaceutical interventions (NPIs) have impacted on the socio-economic status of slum populations, however, little is known on their impact on the quality of life (Qol). We describe the Qol of residents in one of the largest slum communities in the city of Salvador, Brazil, and explored the effects of socio-demographic and economic predictors on QoL during the pandemic. We performed a cross-sectional study between November 2021 and July 2022, and administered questionnaires to obtain information on demography, employment, income, access to COVID-emergency and family support fund, food insecurity, physical health and mental health. We explored the effects of socio-demographic and economic data on physical and mental health scores using generalized linear mixed models. Among the 907 eligible participants, 633 (69.8%) with age greater than 18 years were recruited (61% females; 39% males). Unemployment rate increased from 49.9% before the pandemic to 87.8% during the pandemic. Only 53.6% received COVID-emergency funds, and 67.3% reported lack of food. Regression models found that physical health was significantly associated with age, education and losing a job during the pandemic. Scores for physical health were significantly low among participants aged 41-60 (-4.10, 95CI: -6.21, -1.98, p<0.01), those who had no formal education (-16.34, 95CI: -25.77, -6.91, p<0.01), and those who lost their job (-2.21; 95CI: -4.15, -0.26, p<0.01). In contrast, mental health was significantly associated with age and gender, with lower scores among females (-5.09; 95CI: -3.02, -3.12, p<0.01) and participants above age 60 (-0.20; 95CI: 3.69, 4.43, p<0.01). The lower quality of life observed in our study, especially for adults, females and those who have lower school attainment, supports the importance to sustain and increase the coverage of financial aids in these slums, in addition to interventions targeted at improving school enrollment and food insecurity.

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AN IN -SILICO APPROACH ON THE EFFECT OF LOPHENOL AND ITS DERIVATIVES ON PANCREATIC LIPASE, ALDOSE REDUCTASE AND DIPEPTIDYL PEPTIDASE-IV AS POTENTIAL TARGET FOR DIABETES MELLITUS(TYPEII)

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Diabetes mellitus is a metabolic disorder that is characterized by persistent hyperglycaemia. Aloe vera has been reported to have anti-hyperglycaemic effect on diabetic patients which is reported to be due to the presence of phytosterols. The protein receptors: pancreatic lipase, aldose reductase and dipeptidyl peptidase-IV were retrieved from the PDB. Their energy was minimized using Gromacs. The targeted phytosterols of aloe vera was retrieved from PubChem and virtually docked against the targeted protein receptors using AutoDock Vina. The drug likeness and the pharmacological profiling of lophenol, methylene lophenol, methylene cycloartanol, ethylidene lophenol and ethyllophenol were evaluated using Lipinski rule of 5 and ADMET properties. Results of the pancreatic lipase, aldose reductase and dipeptidyl peptidase-IV after the molecular dynamics showed the energy of the three protein receptors were reduced and was found to be stable. All the ligands that were docked was found to have binding affinities between -6.8 and -9kcal/mol and docked firmly to the protein. All the ligands were found to be drug-like except for methylene cycloartanol that violated two rules of Lipinski rule of 5.

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EVERY CASE CONFIRMED: EXPANDING UGANDA'S INTEGRATED COMMUNITY CASE MANAGEMENT THROUGH INNOVATIVE PARTNERSHIP

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Uganda is aiming for 100% success in parasitological confirmation of all suspected malaria cases before prompt and accurate treatment of positive cases with ACTs, at all levels of care. For community based health care, the Ministry of Health has adopted a strategy for integrated community case management (iCCM) to facilitate access to and reduce the treatment gap for malaria, pneumonia and diarrhea, a strategy proven to reduce severe illness and death. The iCCM program uses ACTs to treat malaria after confirmation with malaria RDTs, amoxicillin for prompt treatment of pneumonia and oral rehydration solution and zinc for the management of diarrhea at the community level. Every district in Uganda is expected to employ iCCM per the national strategic plan, but many gaps remain, even in high burden districts-- particularly after unexpected early withdrawal of bilateral funding for iCCM in 27 districts in 2021. Uganda's funding for

iCCM through the Global Fund 2020-2023 provided only for ongoing supervision and supply, and not for start-up training and equipping. In 2022, the National Malaria Control Division (NMCD) partnered with The Rotary Foundation, the Muyenga Rotary Club, the Oklahoma Rotary Club, Malaria Partners International, The Aids Support Organization (TASO), World Vision, Pilgrim Africa and the Bill & Melinda Gates Foundation to start up iCCM in Katakwi District, a high transmission district in NW Uganda, by training and equipping 1100 community health workers. This unusual partnership, in which iCCM scale-up was funded by three partners new to malaria implementation funding in Uganda, required coordination with, and adjustment of, the country's current Global Fund grant (2020-2023) and the cooperation of all its sub-recipients for its success. NMCD program staff were able to arrange this, and in early 2023, after successful scale up in 2022, iCCM in Katakwi was sustainably transitioned to ongoing support through Uganda's Global Fund grant, proving a model for successful large-scale engagement of Rotary in creatively aiding in the achievement of national malaria reduction strategic goals.

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FEASIBILITY OF A SOUTH SOUTH NORTH COLLABORATION ON IMPLEMENTING A STUDY TO COMPARE VACCINATION COVERAGE SURVEY METHODS: CASE OF DEMOCRATIC REPUBLIC OF CONGO AND CENTRAL AFRICAN REPUBLIC

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In 2018, the World Health Organization (WHO) established a revised method for assessing vaccination coverage using either a one-stage or two-stage cluster sampling design. This WHO method is considered as a gold standard to assess vaccine coverage. However, the method requires a large number of small clusters which makes the technique prohibitive when sub-national estimates are wanted in low- and middle-income countries (LMIC) such as the Democratic Republic of Congo (DRC) and Central African Republic (CAR), highlighting the need to evaluate alternative coverage survey methods. We describe the feasibility of a South-South-North (S-S-N) collaboration in implementing a study to compare the WHO method with alternatives methods, including Lot Quality Assurance Sampling (LQAS) method, the WHO method modified by the Kinshasa School of Public Health (KSPH), and a grid-based Geographic Information System (GIS) method, in terms of efficiency, cost and time. We used a participatory approach whereby the team from KSPH in DRC and the team appointed by the Ministry of Health in CAR, with technical support from the training program of the University of California Los Angeles in DRC (UCLA-DRC) set a collaborative network through both online and in-person meetings. The team developed the study protocol and had it approved by both local ethic committees. Joining expertise from all collaborators, the teams produced mapping for application of the GIS method in DRC and CAR. As of March 20, 2023, two meetings - one in each country had been held, protocols had been approved and the DRC team was preparing for field deployment. Deployment in CAR will follow - with all collaborators involved. The teams will thereafter jointly proceed to data management, analysis, and dissemination The S-S-N collaboration was feasible with involvement of local stakeholders and was an important way for both LMIC countries to share their experience in implementing coverage survey.

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DISTRIBUTED MANUFACTURING STRATEGIES TO CIRCUMVENT SUPPLY CHAIN COMPLEXITIES, LOWER COST, AND INCREASE ACCESS TO COMPOSTABLE MENSTRUAL HYGIENE PRODUCTS

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Agaves are robust, drought-tolerant plants that have been cultivated for their high-strength fibers for centuries and they hold great promise as a crop in the face of increasing water scarcity associated with a warming planet. Meanwhile, millions of women lack access to sanitary products to safely manage their menstruation particularly in LMIC countries characterized by a dry climate. To address this issue, we show a processing route (involving mild delignification and mechanical fluffing) that transforms the leaves of succulent Agave sisalana into a highly absorbent and retentive material. We find that this process leads to a material with an absorption capacity exceeding those found in commercially available menstrual pads. We show that the carbon footprint associated with this process is comparable with common alternatives with the added benefit that it can be carried out at small scales while remaining environmentally sustainable. This work paves the way for developing partnerships between technologists, agriculturists, and entrepreneurs to enable sustainable manufacturing of compostable menstrual pads rooted in the communities.

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SOCIAL DETERMINANTS OF COVID-19 VACCINE ACCEPTANCE AND UPTAKE IN A BRAZILIAN SLUM COMMUNITY: A LONGITUDINAL TIME-TO-EVENT STUDY

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Slum residents are at high risk for involuntary COVID-19 exposure and are the least likely to access medical care, thus making vaccine-driven prevention critical in this at-risk population. Despite robust vaccination campaigns in Brazil, uptake and timing continue to be influenced by social factors and contribute to health disparities. To address this, we conducted a sequential survey in a cohort of 952 residents of an urban favela in Salvador, Brazil where participants were interviewed in 2020, before vaccines were rolled out, and in 2022. We collected data on demographics, social characteristics, and COVID-19 vaccination status and intent. Primary series uptake was high (87% for 1st dose and 85 % for 2nd dose among those eligible); however, booster uptake was lower (63% of eligible population) at the time of the second interview, suggesting a decreasing interest in vaccination. To account for both vaccine refusal and delays, we conducted a Cox time-to-event analysis of dose uptake using sequential independent outcomes. Exposure times were determined by dose eligibility date to account for age and comorbidities. Intent to vaccinate in 2020 was associated with higher vaccination rates for the 1st (0.257, CI: [0.063, 0.452]) and 2nd (0.301, CI: [0.068, 0.534]) doses. We also found that uptake was associated with a better physical health score (0.147, CI: [0.014, 0.280]) for the 3rd dose. Men were less likely to receive the 1st dose (-0.244, CI: [-0.413, -0.075]), and 2nd dose uptake was lower for employed participants (-0.250, CI: [-0.443, -0.057]). The results show that vaccination beliefs in 2020 are still associated with uptake, suggesting a level of crystallization of COVID-19 beliefs that was not addressed by subsequent campaigns. The fact that healthier and unemployed individuals are more likely to receive certain doses may suggest that those factors ease navigating the vaccination system or are associated with receptivity to

health messaging. Gender also plays an important role. The data, together with qualitative evidence from the community, offers policy lessons to build a long-term COVID-19 vaccination strategy beyond availability.

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MEASLES OUTBREAKS IN REGIONS NEIGHBORING ARMED CONFLICT ZONES; EXPERIENCES FROM THE WEST REGION OF CAMEROON, 2018 TO 2022

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In 2019, a nationwide measles/rubella vaccination campaign was organized in Cameroon. However, in 2022, 67 districts reported measles outbreaks. The West region (WR) reported outbreaks in seven districts among which four border the Northwest region (NWR). Since 2016, an armed conflict in the NWR and Southwest region has caused massive influx of people into the WR. Population displacement negatively affects routine immunization and favors outbreaks. We therefore aimed to determine factors associated with measles outbreaks in the WR of Cameroon. A retrospective study of the West regional surveillance data was carried out from 2018-2022. Data on the classification, demographics and vaccination status of measles cases were retrieved. Data was analysed and trends, seasonality by moving means method and Odds Ratios (OR) were determined and; logistic regression used within 95% confidence limits. A total of 878 cases were reported from 2018-2022. The number of cases/years progressively increased from 106 in 2018 to 309 in 2022. The median age was 34 months (2 months – 57 years), 55% were male and a majority (74%) lived in rural areas. Seventeen percent (n=149) of cases were laboratory confirmed while 30% (n=271) were epi linked; 2.4% (n=21) were Rubella cases. About half (n=441) had received at least one dose of measles containing vaccine. Through the years 60% of symptom onset occurred during epi weeks 1 and 13 with a peak at week 11. Trends showed seasonality. Risk factors identified were living in a health district neighboring the NWR, OR 5.7 (95%CI, 3.7- 8,7) and being unvaccinated OR 5.8 (95%CI, 4.1- 8.4). In conclusion, population displacement due to the armed conflict in the NWR has created pockets of susceptible children in the WR. Periodic intensification of routine immunization should be organized in the affected districts while emphasizing on vaccination in hard-to-reach populations.

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HEAT EXPOSURE AND IMPACTS ON HEALTH AND PRODUCTIVITY OF READY-MADE GARMENT WORKERS BANGLADESH: A QUALITATIVE STUDY

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The ready-made garment (RMG) sector is key to growing Bangladesh's economy, providing export opportunities and employment for its majority female workers. To ensure sustained productivity and a thriving workforce, workplace hazards like heat, must be acknowledged, assessed and managed. The existing heat experienced in the sector is set to worsen as temperatures in the country increase due to global warming. For example, under a high emissions scenario (i.e. RCP 8.5) the estimated average annual temperatures will increase by 3.9 degreeC by the end of this century. This study highlights the impact of heat on health and productivity and explores heat management through the eyes of workers, managers and other sector stakeholders. Qualitative data were collected from workers of two RMG factories in Dhaka in 2022 to identify perceived heat related health and productivity impacts and explore barriers to workers accessing cooling options and heat-related medical care. Key-informant-interviews were conducted with factory officials, onsite health professionals, government officials, the RMG peak body, and NGOs. Workers and health professionals attribute symptoms like headaches, dizziness, fatigue and nausea to heat during summer months. Factory health professionals also observed high blood pressure in workers during summer and other informants identified higher absenteeism in summer. Heat was identified as an important influence on productivity by workers themselves and others working in or with the sector. Workers felt a high degree of pressure to meet daily quotas and the impacts of heat on worker performance and subsequent productivity were identified by workers, managers and health professionals. This production quota pressure also impacted on workers taking rests or hydrating sufficiently – both of which are important heat mitigation strategies. Factories provide some medical services including dedicated infrastructure, though during the hottest periods, they were reported to be insufficiently cooled. The key-informants ranked improved ventilation and space cooling solutions as the most feasible heat mitigation strategies.

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TOO HOT FOR BED NETS IN A CHANGING CLIMATE: SPATIAL ANALYSIS AND RISK MODELLING OF MALARIA INDICATOR SURVEY DATA IN SUB-SAHARAN AFRICA 2018-2022

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Bed nets are a cornerstone of malaria control. However, with increasing global temperatures driven by climate change, survey participants in the Malaria Indicator Survey (MIS) now select "too hot" as a key reason for not using a bed net. This study aimed to examine the factors associated with selecting this reason at a community and household level in Sub-Saharan Africa. MIS data from 2018-2022 were reviewed for survey questions related to temperature factors and bed net usage. All countries in Sub-Saharan Africa with georeferenced MIS data since 2018 were included. The "too hot" for a bed net response proportions were summarised. The spatial distribution of this response was analysed, and the Getis-Ord Gi* statistic used to detect significant clustering of high values (hot spots). Regression analysis was conducted at two spatial levels with various environmental covariates. First, temperature, rainfall, humidity, and elevation data were used to determine the ecological factors associated at a community level. Second, data on building materials (e.g. mud, tin), access to electricity, and ownership of electric fans were used to determine the characteristics at the household level. MIS data from seven (44%) of the 16 countries surveyed had responses including "too hot" for a bed net, with a marked difference in the proportion of this response: Ghana (25%), Nigeria (16%), Senegal (4.8%) and Mali (1%). In Nigeria, for example, there was significant spatial clustering (Z-score = 3.69, P-value <0.001). Survey participants in the south, particularly the Akwa Ibom region, were four times more likely to have a "too hot" response than further north. This region had the highest average temperature and precipitation ranges and a statistically significant negative correlation with electric fan ownership. Further spatial and regression analyses are underway in all countries and will be presented in full. The possibility that global warming plays a role in the non-use of bed nets is alarming, and more information is needed to better understand the problem's scale. This may help national malaria programmes to develop strategies to overcome this challenge.

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CLIMATE CHANGE ADAPTATION MEASURES INFLUENCE HOUSEHOLD FOOD INSECURITY IN SOUTHERN ETHIOPIA

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As part of the project "Co-producing Gender-responsive Climate Services for Enhanced Food and Nutrition Security and Health (COGENT)" project in Ethiopia and Tanzania, we evaluated how the variation in rainfall and potential climate change adaptation measures influence household food insecurity. We did a quarterly survey involving 910 households from nine randomly selected rural kebeles (lowest political administration unit) in the Boricha district between June 2021 and March 2022. The data were collected using pretested, structured questionnaires, and potential causal

links between weather variability, such as rainfall, and food insecurity were measured after controlling for possible confounding variables. The household food insecurity rate (HFI) was highest in June (89.3 %) and lowest in December (67.7 %) after the harvesting season. Months with high rainfall were followed by improved food security, coinciding with increased household wealth. Furthermore, the average Body Mass Index (BMI) in September was the lowest, followed by an increment of 0.35 in December 2021. Households whose heads had not attended formal education [Adjusted Odds Ratio (AOR) 6.02, 95 % confidence interval (CI) 4.70, 7.71], had low-income (AOR 1.30, 95 % CI 1.07, 1.57), households with poor dietary diversity score (AOR 1.43, 95% CI 1.21, 1.63), who were not beneficiaries of the Food safety net programme (AOR 1.77, 95 % CI 1.51, 2.01), and who were not members of the community-based health insurance (AOR 3.49, 95 % CI 2.83, 4.30) had higher risks of food insecurity. Our study shows that better education, higher economic status, participation in the Food safety net programme and community-based health insurance membership reduce the population's vulnerability to food insecurity.

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Reducing medical waste is a critical mitigation strategy to reduce health care's contribution to greenhouse gas emissions. In order to understand our lab's waste generation, we conducted a waste audit in our laboratory at the Stanford School of Medicine in the Division of Pediatric Infectious Disease. For two weeks (16-27 January 2023) waste was collected and sorted into three categories (recyclable, compostable and landfill). All waste was then weighed using Fisher Science Education precision balance and Tanta BVB-800 scale equipment with a resolution of 0.1 lb. Two authors were present and led all waste sorting and weighing. All study personnel wore isolation PPE throughout the waste audit and upon completion of the waste audit; all waste was disposed of in compliance with Stanford Environmental Health & Safety policy. Over the two weeks of the study period, we generated a total of 716 gr (24%) of compostable waste and 1316 gr (43%) of recyclable and 995gr (33%) landfill waste. Cardboard boxes, pipette tips, tubes (PCR, conical), gloves, gallon-size liquid containers, and pipet tip boxes were the largest categories comprising 597gr, 546 gr, 406.9 gr 359 gr, 200 gr and 200 gr, respectively. Cardboard boxes comprised 75% of our compostable waste, followed by paper towels (10%). Bio-hazardous solid waste made up 100% of our landfill category. Hazardous waste disposal costs 10–20 times more than non-hazardous waste disposal and our study revealed that one third of our waste was considered hazardous. Other studies have documented 20 - 34% of healthcare waste (HCW) is infectious and hazardous, similar to our results of 33%. Although this audit was performed during a period when fewer individuals were actively working in the lab, we are using this data to first educate ourselves on our waste generation and management, and to highlight opportunities to encourage reuse and decrease waste streams significantly.

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ASSESSING DISTRIBUTIONAL CHANGES OF BULINUS TRUNCATUS, INTERMEDIATE SNAIL HOST OF SCHISTOSOMA HAEMATOBIUM, UNDER CLIMATE CHANGE USING AN INTEGRATED APPROACH

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Climate change influences species' distributions, including those of disease vectors and their associated diseases. However, accurate range shift predictions remain scarce due to a lack of ecological data on most of these species. Bulinus truncatus is an intermediate snail host of Schistosoma haematobium and Schistosoma bovis, causing human and animal schistosomiasis, respectively. It's broad distribution represents the maximum geographic spread of schistosomiasis in Africa, Europe and the Middle East. There is, however, a general lack of data on the ecology of B. truncatus, precluding reliable forecasts of this species' distribution and the associated schistosomiasis risk under climate change. Here, we performed experimental tests with 2500 second generation snails from different field-collected origins (France, Senegal and Zimbabwe), subjecting them to chronic temperature treatments ranging from 4°C to 36°C. Life-history and physiological data were collected on the performance of the snails at each temperature. The data shows that cold origin snails have faster growth rates overall, and that warm origin snails have higher mortality rates at warm temperatures that might be offset by their increased fecundity. The warm origin snails had a higher available energy budget, lower respiration rates and lower hemoglobin levels than cold origin snails, indicating a more efficient energy use at high temperatures. They also showed a stronger immune response, which could translate in a stronger defense response to parasite infections. Furthermore, population genetic analyses based on 4913 single nucleotide polymorphisms show a high genetic differentiation between snail origins that can be linked to adaptation to local climatic conditions. All collected data is used to assess the species' distribution at present and in the future using mechanistic niche models that are compared to more established correlative niche models. The mechanistic niche models consider the differences in life history traits between different origins and the implications on B. truncatus distribution and the associated schistosomiasis risk.

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THE PLANETARY CHILD HEALTH AND ENTERICS OBSERVATORY (PLAN-EO): AN INTERDISCIPLINARY RESEARCH INITIATIVE AND WEB-BASED DASHBOARD FOR MAPPING ENTERIC INFECTIOUS DISEASES AND THEIR RISK FACTORS AND INTERVENTIONS IN LOW- AND MIDDLE-INCOME COUNTRIES

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Diarrhea remains a leading global cause of childhood illness and is caused by various species of climate-sensitive pathogens. The emerging Planetary Health movement emphasizes the interdependence of human health with natural systems, with much of its focus on infectious diseases and their interactions with environmental and human processes. Meanwhile, the era of big data has transformed the curation, aggregation and dissemination of health information engendering a public appetite for open access, web-based repositories of infectious disease data. However, enteric infectious diseases (EID) have largely been overlooked by these developments. The Planetary Child Health and Enterics Observatory (Plan-EO) is a new initiative that builds on existing partnerships between epidemiologists, climatologists, bioinformaticians, and hydrologists as well as investigators in numerous low- and middle-income countries (LMICs). Its objective is to provide the research and stakeholder community with an evidence base for the geographical targeting of EID-specific child health interventions. The initiative will produce, curate, and disseminate spatial data products relating to the distribution of enteric pathogens and their environmental and sociodemographic determinants, making them available to decisionmakers via an online dashboard. To date Plan-EO has compiled microdata from 23 studies with ~80,000 diagnostic results from 35,000 children aged 0 - 59 months at sites in 24 LMICs and georeferenced to over 9,000 unique locations and outreach to additional studies is ongoing. An initial published analysis of Shigella has yielded detailed prediction maps and insights into the mechanisms underlying transmission. These approaches will be extended to other pathogens and their findings used to assess their relative sensitivity to changes in climate compared to other determinants such as sanitation improvements. Plan-EO will eventually develop a scenario-

based framework to support decision-making, resource allocation and identification of priority populations for targeting EID-specific interventions such as novel vaccines.

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ADAPTING TO CLIMATE CHANGE IN SUB-SAHARAN AFRICA: ONE MALARIA INTERVENTION AT A TIME

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Climate change is making malaria-endemic countries especially vulnerable and causing operational challenges for National Malaria Programs (NMPs). Unprecedented fluctuations in rainfall and extreme weather events are changing the seasonality and distribution of Anopheles mosquitoes and transmission patterns of malaria - a disease that caused 593,000 deaths and 234 million cases in sub-Saharan Africa in 2021. We present here climate-related actions that have been integrated in malaria prevention and control programs in several countries, that were designed to adapt to the shift in climate so as to keep effective interventions. In Madagascar, mosquitoes are biting earlier and longer than before (~ 4-fold increase in biting rate). To adapt, the NMP targeted messaging to address population behavior to consistently use insecticide treated nets regardless of the temperature. Several districts in Senegal added another round of seasonal malaria chemoprevention (SMC) in order to account for the 1-month shift in the rainfall peak and/or longer rainy season where total rainfall at the end of the season in October were, on average, 13 mm above normal in the past 3 years. Proactive community case management operations were increased from 6 months to year round in 5 districts. The Zambia NMP prioritized IRS in flood prone communities before the onset of the rainy season and front loaded essential medicines to 140 out of 3,000 health facilities to increase resilience of communities that become inaccessible during the rainy season and avoid interruption of services. These operational challenges affect NMP budgets and personnel needs. Hence, highlighting the need for monitoring climatic indicators (ie. rainfall and temperature) alongside malaria incidence to identify correlations between climate related events and malaria incidence and implement early warning systems. These systems can better inform NMP decision-making to ensure effective interventions. Ultimately, NMPs need budget flexibility and better access to temperature and rainfall data to make evidence-informed decisions to improve prevention and control interventions.

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MALARIA MANAGEMENT IN AN ERA OF CLIMATE CHANGE

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Africa has experienced temperature increases 1.5 faster than the global temperature . For malaria elimination, strategies and opportunities in mitigating the impact for the most vulnerable populations requires an understanding of the climate change. A pragmatic approach has been used to inform the Climate changes and the relationship with malaria. How rapid diagnostics can influence malaria diagnosis? Implications of early diagnosis to address the spread of malaria. The UN has presented the argument, leading to the increase in the literature around climate events and the complex relation with malaria. The literature has noted substantive arguments that climate change as noted in the last 10 years may impact vector borne diseases especially Malaria. The World Bank has been capturing trends that have monitored temperature changes yearly and seasonally. The question arises: is this adequate in addressing an increase in Malaria and other vector borne diseases? Early diagnosis to address the spread of Malaria, especially, during climate events during seasonal - or approximately 4 months post heavy rainfalls and/or temperatures that cause high precipitation. This includes an increased budget allocations for widespread and real-time testing in affected geospatial areas. There is thus a conclusive argument that increasing RDT testing may be an opportunity for countries to address climate changes. Noting, the elements contributing to an increase in malaria prevalence, governments cannot be complacent around the issues of climate change and the health associations. There needs to be an intention to prepare budgets, programs, and implementation of malaria RDTs. Abbott Rapid Diagnostics has sought to understand this issue and aims to accelerate and cement the implemental intervention that moves the dial gauge towards malarial elimination. Furthermore, supporting the monitoring of malaria prevalence to strengthen programs. Malaria control programs will demand timely responses to mitigate negative impacts on populations and their health.

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FROM FOOD SECURITY TO PUBLIC HEALTH - HOW CLIMATE INFORMATION CAN BE USED IN EARLY WARNING SYSTEMS AND PREPAREDNESS FOR DISEASE THREATS

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Climate change has been called the biggest global health threat. Rising temperatures, increased incidence of severe weather, and shifting precipitation patterns can increase disease transmission, create the conditions for existing and emergent pathogens to thrive, and exacerbate disease burden on human populations. This is especially true in countries that suffer from myriad climate-sensitive health challenges and lack the information, resources, or capacity to fully address these challenges. In Somalia and Mozambique, the United States Agency for International Development (USAID) is implementing a set of pilot projects to expand the use of health data in the Famine Early Warning System Network (FEWS NET), a leading provider of early warning and analysis on acute food insecurity around the world. Each pilot spans eight months. Multisectoral data, including climate data, will support decision-makers and health practitioners to access information about how climate change impacts public health risks. The FEWS NET Health Threat Extension pilot activity results from a partnership between USAID, the National Oceanic and Atmospheric Administration (NOAA), and the United States Geological Survey (USGS). The following USAID Bureaus jointly manage the pilots and offer technical support: Development, Democracy, and Innovation; Global Health; Africa; and Humanitarian Assistance. Lessons learned from these pilots can be used to extend efforts and to include additional data to inform climate-sensitive health threats and regions. Pilot activities aim to emphasize the role and importance of a One Health approach to inform sustainable development efforts and can contribute to ongoing early warning systems for preparedness and response to disease threats.

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COVID-19 VACCINE BOOSTER DOSE UPTAKE AMONG A COHORT OF HEALTHCARE WORKERS IN BANGLADESH

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The WHO recommended COVID-19 vaccine booster dose for high-priority groups, including healthcare workers (HCWs). We explored COVID-19 vaccine booster dose uptake among front-line HCWs in Bangladesh. icddr,b in collaboration with the Communicable Disease Control of DGHS,

established a cohort of HCWs to record COVID-19 illness prospectively. The cohort enrolled HCWs from purposively selected 20 hospitals of four divisions across Bangladesh. At enrolment, we collected HCW's demographics, COVID-19 infections since the start of the epidemic, and vaccination records. The study physician followed the enrolled HCWs biweekly and recorded any change in vaccination status, including booster uptake. We summarised the data using frequency and percentages. Between July 2021-March 2023, the cohort included 3684 HCWs: nurses (1763), doctors (810), ward boy/Aya (439), health assistants (226), cleaners (155), community health care providers (125), medical technologist (108), lab attendant (30), receptionist (17), and ambulance driver (12). The median age of the HCWs was 35 years (IQR, 29-44), and 67% (2,465/3,684) were female. Overall, 90% (3,309/3,684) of the HCWs completed the primary series (first and second doses) of the COVID-19 vaccine. However, only 55% (2,020/3,684) of the HCWs received the first booster dose (third dose), and only 24 of them reported receiving the second booster dose (fourth dose). 55% (446/810) doctors and 54% (968/1,763) nurses received the first booster vaccination. The booster uptake was higher among lab attendants (93%) and medical technologists (76%) and lower among receptionists (29%) and cleaners (37%). HCWs in primary health facilities (68%) had a higher booster uptake compared to those in secondary (54%) and tertiary-level facilities (51%). The overall COVID-19 vaccine booster uptake among front-line HCWs in Bangladesh remains suboptimal. Identifying the reasons for low booster dose uptake and implementing a tailored vaccine program to address those factors can safeguard HCWs and maintain critical health services during future waves of SARS-CoV-2.

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ADAPTING SUB-NATIONAL PUBLIC HEALTH EMERGENCY MANAGEMENT: THE MBALE REGIONAL EMERGENCY OPERATIONS CENTER EXPERIENCE IN EASTERN UGANDA

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The COVID-19 pandemic has tested the capacity for emergency responses in low- and middle- income countries (LMICs), which has highlighted the importance of local public health interventions. Uganda has a robust national response coordination mechanism; however, limited capacities exist at the sub-national level. In 2020, the Uganda Ministry of Health established the Mbale regional emergency operations center (REOC) to coordinate responses to public health and natural disasters in eastern Uganda. The Mbale REOC multidisciplinary regional response team works closely with the Ministry of Health, regional referral hospitals, implementing partners, and academia. We aimed to describe the experience of the Mbale REOC over the 3 years from inception including during the COVID-19 pandemic. We conducted a qualitative study including a review of key documents and reports, and semi-structured interviews of participants involved in the establishment of the Mbale REOC and subject matter experts. We used a thematic approach and framework analysis using NVivo 12 software to analyze qualitative data. After the establishment of the Mbale REOC, complete daily regional surveillance reporting increased from 43% to 93%. Over 12 months, the REOC conducted on average 15 partner coordination meetings. The REOC supported 16 districts with logistics and inventory management including coordination of material supply transfer between districts. The REOC provided training in laboratory outbreak monitoring and evaluation to 21 regional trainers, 72 district mentors, and 256 facilities. The REOC established a mobile laboratory in the region that reduced COVID-19 PCR sample result turnaround time from ≥7 to ≤2 days and increased the number of tested samples from 200 to 500 per day. The Mbale REOC improved the sub-national response to infectious diseases outbreaks and disasters in eastern Uganda and was recognized by the Ministry of Health as a model for sub-national public health emergency management. A regional REOC strategy could be adopted by other LMICs to build local public health emergency response capacity.

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AN ASSESSMENT OF RESEARCH, SURVEILLANCE, LABORATORY, AND OUTBREAK RISK MANAGEMENT CAPACITIES FOR NIPAH AND AVIAN INFLUENZA VIRUSES IN BANGLADESH

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In 2021, as part of USAID STOP Spillover activities in Bangladesh, and based on priorities established by stakeholders, we assessed research, surveillance, laboratory, and outbreak risk management capacities for avian influenza virus (AIV) and Nipah viruses (NiV) to appraise the current capacity of different institutions within the country. Both in-person and virtual meetings were arranged for data collection using structured and semi-structured questionnaires. We conducted 49 interviews with stakeholders from government and research organizations, and academia. We collected data on six research projects and three surveillance systems focusing on NiV, 11 surveillance systems and 16 research projects for AIV. Gaps for AIV surveillance include a lack of community-based, farm-based, and wild bird surveillance and the unavailability of sustainable funding. Lack of community-based surveillance, limited integration of human and animal data, and donor-dependency for funding were the gaps in NiV surveillance. Transmission dynamics and spillover risks for both pathogens are understudied. The causes of Nipah's high case fatality rate are yet to be explored. Six laboratories were reported as capable of testing samples for AIV, while the NiV can be tested in only two laboratories. None of these laboratories has BSL-3 facilities. These laboratories reported inadequate sample storage facilities, a lack of skilled human resources, and funding challenges. One government organization conducts outbreak investigations of different zoonotic diseases with the support of other government and research institutions and development partners. Sampling wild birds and nearby poultry to compare strain similarity and estimate the frequency of spillover events is needed to understand AIV transmission dynamics. Community-based surveillance of NiV is necessary to detect missing cases and understand the spillover of these viruses from animals to humans. Increased laboratory capacity, including a BSL-3 laboratory in the country, is required for rapid diagnosis and control measures for infectious disease outbreaks.

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COVID-19 VACCINE ACCEPTABILITY AMONG HEALTH WORKERS IN THE DEMOCRATIC REPUBLIC OF CONGO

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COVID-19 vaccination coverage in sub-Saharan Africa countries has lagged behind the rest of the world, with the Democratic Republic of Congo (DRC) having one of the lowest rates. Health workers are a high-risk exposure group and key actors in vaccination response and risk communication. The objective of this study was to conduct a survey among health workers in

seven DRC provinces, and determine factors associated with COVID-19 vaccine acceptance. This survey was administered from January to October 2022 and included questions on demographics and health history, COVID-19 vaccine uptake, risk perception and exposure to COVID-19, confidence in the COVID-19 response, reasons for acceptance or rejection of the COVID-19 vaccine, exposure to information about COVID-19 and intention to self-vaccinate. Health facilities were selected through simple random sampling, and convenience sampling utilized to administer the questionnaire to personnel in health facilities. A total of 5,102 health worker responses were collected. Results showed while 75.9% of respondents perceived a moderate or high risk of contracting COVID-19, almost half reported receiving at least one dose of the COVID-19 vaccine. Differences in vaccine coverage varied across provinces with significant factors amongst vaccinated health workers in age, gender, occupation, rural settings, and having received other adult vaccines. Among vaccinated health workers, the most frequently reported reason for vaccine acceptance included protection of oneself and others, whereas the top reasons for refusal among non-vaccinated was insufficient safety data, concern about side effects, and vaccine effectiveness. As influential community members, health workers' reasons for acceptance and refusal of the COVID-19 vaccine can help inform strategies to improve vaccine uptake among the general population. Risk communication and engagement efforts among health workers in DRC should emphasize COVID-19 vaccine safety and efficacy as potential opportunities for improving uptake.

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NATIONAL AND SUB-NATIONAL AUTHORITIES' DECISION-MAKING PROCESSES DURING THE COVID-19 PANDEMIC: LESSONS FROM NIGERIA

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Public health decision-making during the COVID-19 pandemic was challenging for decision-makers due to the dynamic epidemiological situation combined with time constraints and immense public pressure. In this study, we analyzed the process of COVID-19 response decision-making in Nigeria. We undertook a desk review to gather information on the country's context and conducted a series of key informant and focus group discussions with a range of stakeholders including national and sub-national officials, civil society representatives, development partners, and academics in Nigeria. Several important themes and perspectives emerged through this analysis. First, Nigeria's previous experiences responding to disease outbreaks provided lessons for establishing health emergency decision-making structures and mechanisms. Second, the establishment of high-level decision-making taskforces at both the national and subnational levels facilitated coordination among different levels of government. However, there is a need for enhancing collaboration due to the emergence of conflicts between levels of government, hindering a cohesive and coordinated pandemic response. Additionally, while decision-makers relied on input from academic experts and civil society members as part of advisory bodies, stakeholders emphasized the need for additional efforts to engage partners and actors in decision-making processes, particularly during the early preparedness and response stages of a health emergency. Third, adapting decisions to account for emerging technical information and the social and economic context enabled the response to be context specific and evidence based. However, more efforts are needed to ensure that decision-making is inclusive, equitable and transparent, to help improve public trust in governance processes, thus increasing compliance with public health measures. By understanding the process of decision-making during health emergencies, we can identify opportunities to improve and strengthen pandemic preparedness efforts.

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GLOBAL ARBOVIRUS INITIATIVE: TACKLING MOSQUITO BORNE VIRUSES WITH EPIDEMIC AND PANDEMIC POTENTIAL

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The risk of emergence and re-emergence of arboviruses with epidemic and pandemic potential has increased as a global public health threat and will continue to do so in the years to come. The geographic range of arboviruses will also keep extending due to increased human movement, urbanization, climate change with environmental adaptation and uncontrolled expansion of mosquito vector populations. WHO has been working on strategic plans for multipathogen pandemic preparedness and response for health emergencies to strengthen capacities in vulnerable countries from local to national, regional, and global levels. In March 2022 WHO and partners launched the Global Arbovirus Initiative, comprised of six pillars: 1)Monitoring risk and anticipation; 2)Reducing epidemic risk; 3) Strengthening Vector Control; 4)Preventing and preparing for pandemics; 5)Enhancing innovation and new approaches; and 6)Building a coalition of partners. This initiative is convening partners across multiple sectors including health, agriculture, urban administration, and environment, as well as national, academic and private sector partners to forge a collaborative approach that builds on existing disease-specific programs to strengthen national integrated arbovirus disease programs. This will enable optimal use of limited resources to achieve the greatest impact. Epidemic response must be grounded in strengthening of ongoing national efforts to surveil for and respond to endemic transmission and localized outbreaks. Over the first year since the launch of the Initiative, WHO and collaborators have progressed in developing integrated risk maps for Aedes-borne arboviruses, appointed regional arbovirus consultants to drive implementation at regional level, and worked with WHO Regional Offices and Member States to adapt the approach to their specific priorities, frameworks, and needs. The successful implementation of the Initiative hinges on continued and political will, development of a sustainable funding model, and ever greater collaboration by partners to advance the objectives of pandemic preparedness and reduction of disease burden.

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DESIGN AND STANDARDIZATION OF MOLECULAR SYSTEMS BASED ON CRISPR-CAS TECHNOLOGY FOR THE IDENTIFICATION OF GENES ASSOCIATED WITH ANTIBIOTIC RESISTANCE

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Design and standardization of molecular systems based on CRISPR-Cas technology for the identification of genes associated with antibiotic resistanceEscherichia coli bacteria are commonly found in both community and hospital environments, where they can cause infections and develop antibiotic resistance. Recent studies have reported high prevalence of the resistance genes CTX-M-15 and floR, indicating the rapid dissemination of resistance genes that should be closely monitored. CRISPR-Cas12a technology has successfully detected carbapenem resistance genes and even viral sequences. In this study, we optimized the PCR-CRISPR-Cas12a system as a proof-of-concept for detecting the CTX-M-15 and floR resistance genes in E. coli. Locally produced Cas12a and Taq Polymerase proteins were used for this purpose, and E. coli isolates were obtained from 40 positive and negative samples that were confirmed by targeted sequencing. Taq Polymerase was used at 1 ng/ µl in 25 cycles for conventional PCR, while 2 crRNA were designed per resistance gene for the CRISPR-Cas system. The PCR-CRISPR-Cas12a system can detect up to 2 pg/µl of total DNA. The results compared with susceptibility tests

such as microdilution and disk diffusion and achieved a concordance index by Kappa ranging between 0.8 and 0.9, categorized as excellent. Unfortunately, in most low-resource laboratories only tests such as antibiograms are currently available. These laboratories may not have the financial resources to purchase and maintain high-tech equipment, such as next-generation sequencing platforms, which are commonly used for monitoring antimicrobial resistance. Therefore, technologies that use basic equipment such as PCR-CRISPR-Cas12a would help shorten the technical gap for early and timely detection of antimicrobial resistance. The implementation of this system can greatly support the One Health approach, which recognizes the interconnectedness of human, animal, and environmental health. Contributing to the surveillance of antibiotic resistance in both human and animal populations, as well as in environmental reservoirs in order to mitigate their spread.

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EFFECTS OF INTERPREGNANCY INTERVAL AND MATERNAL AGE ON GESTATIONAL DIABETES MELLITUS: FINDINGS FROM CHAMPS PREGNANCY SURVEILLANCE IN BANGLADESH

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Gestational diabetes mellitus (GDM) is a disorder of glucose intolerance that arises for the first time during pregnancy and is a significant health concern during pregnancy in Bangladesh. The relationship between maternal age, interpregnancy interval, and GDM remains unclear due to limited inference with small sample sizes, hospital-based cohort, and biased interval measurements (birth-to-birth intervals rather than birth-to-conception). Understanding the relationship would help healthcare providers to identify high-risk women and provide appropriate interventions. Child Health and Mortality Prevention Surveillance (CHAMPS) is conducting pregnancy surveillance in Baliakandi, a rural sub-district of Bangladesh, which tracks every pregnant woman to identify any health-related complications and outcomes. This analysis examined the association of interpregnancy interval and maternal age on GDM using multivariate logistic regression adjusted for other covariates such as socioeconomic status and education. We collected demographic and pregnancy data of all mothers who had two consecutive deliveries with at least 28 weeks of gestation in Baliakandi, Rajbari District, between February 2017 and February 2023. A total of 3168 women had ≥ 2 viable births, and among them, 2697 women were included after excluding previous diabetes and unknown GDM (15%) in the index pregnancy. Interpregnancy interval was measured in months difference between last delivery and next conception. Intervals were categorized as <6, 6-11, 12-17, 18-24 (reference), >24 months, and maternal age as <18, 18-24 (reference), >24 years. A total of 33 (1.3%) women had GDM in the subsequent pregnancy. A very short interval (< 6 months) is significantly associated with higher odds of GDM in the subsequent pregnancy (adjusted odds ratio [aOR]: 3.80; 95% CI: 1.14-12.65). Additionally, compared to women aged 18-24 years, women older than 24 years had higher odds of developing GDM (aOR: 3.48; 95% CI: 1.84-8.98). An integrated strategy combining intensive health education for longer intervals and early detection of GDM among older pregnant women should be strengthened.

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USE OF STOCHASTIC BRANCHING PROCESSES TO ESTIMATE THE EMERGENCE OF MPOX IN NORTH CAROLINA

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Emerging and re-emerging zoonotic infections are often self-limiting with the first transmission event ending prior to onward transmission. However, substantial heterogeneity may exist in secondary transmission chains allowing for subsequent epidemic growth and host adaptation to occur. Detection of emerging and re-emerging pathogens is subject to series of delays including the time between infection and symptom identification seeking testing, and ultimately the time between subsequent infections all of which obfuscate the index case. Understanding the likely time period of the initial emergence has important implications on subsequent public health interventions to limit an outbreak. In our analysis we estimate the most likely period of the initial emergence and we explore the role that different estimates for the basic reproduction number (R0) may have using the observed case rates, epidemiological parameters, and delay distributions from the 2022 Mpox outbreak in North Carolina. Using stochastic branching processes fit using a range of reported R0 values, we find that the first likely case of Mpox in North Carolina occurred between June 9, 2022, and June 23, 2022, compared to the first official reported case on June 23, 2022, indicating that it took 0-14 days before detection. Additionally, we observed that R0 values slightly above one were associated with longer estimated detection delays. These findings have implications for public health measures, as future outbreaks may be more likely to be seeded from these emergences. Estimates of the date of the first likely introduction of a pathogen can improve contact tracing, assist in targeting higher risk population for education and outreach, and inform other public strategies. Future evolutions of this approach could consider the role of mobility and contact patterns. These methods are applicable to other emergent pathogens with maximum benefit during the early transmission period among closed communities with high contact rates.

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A FRAMEWORK FOR PATHOGEN SELECTION USING TAQMAN ARRAY CARDS FOR SURVEILLANCE OF ACUTE FEBRILE ILLNESS IN NIGERIA

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Acute febrile illness (AFI) is a common reason for seeking medical care in many low- and middle-income countries. However, in malaria-endemic countries like Nigeria, AFI is commonly misdiagnosed as malaria, partly due to widespread limitations in laboratory diagnostics capacity. This hinders disease surveillance and delays outbreak detection, reporting, and response. Of particular concern are the endemic, reemerging and novel infectious diseases of public health importance, also presenting as AFI, that can go undetected. We began the Surveillance of AFI Aetiologies in Nigeria (SAFIAN) study using TaqMan-Array Card (TAC). TAC is a simple-to-use, customizable tool, which allows for accurate and simultaneous screening of 11 to 380 genetic targets, within a single assay. Although AFI is a common research focus, the literature is limited in methods for how to select which pathogens to include in these screening efforts. Due to the increased interest in AFI research/surveillance, and new commercially available multiplex tools, such as TAC, we developed a rapid model for pathogen selection for extensive screening efforts proposed by studies like SAFIAN. We used a 5-point stepwise process to identify 24-30 pathogens for inclusion in our customized TAC panel. First, we defined the study objectives and pathogen inclusion criteria: pathogens of high epidemiologic consequence, high morbidity/mortality, and priority diseases in other regional AFI studies. We aimed to provide a diverse representation

of pathogens (e.g., viral, protozoan, bacterial), with the potential for transmission in Nigeria. Next, we identified data sources for each criterion. Then we evaluated each pathogen's potential for transmission based on prevalence and routes of transmission in our study population. We designed scores based on data sources. Finally, we identified the final selection criteria to achieve the required number of targets. Based on this process, we evaluated 77 potential pathogens and customized a TAC panel with 26 targets. Our model for pathogen selection may be useful for others designing customizable tools for similar AFI screening efforts.

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ESTABLISHING THE SPATIAL DISTRIBUTION OF CIRCULATING ARBOVIRUSES IN URBAN AND RURAL LIBERIA

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Given the high number of arbovirus outbreaks in West African nations, as well as Central Africa, it is implied that mosquito- and tick-borne viruses account for a large proportion of non-malaria febrile illnesses in Liberia. Such etiologies are severely under-reported as they are frequently undiagnosed, misdiagnosed, or not recognized (if asymptomatic). Using a multiplex immunoassay based on high-quality, immunodominant antigens, our primary goal is to establish a spatiotemporal baseline of arbovirus exposure in Liberia. Approximately 600 human serum samples collected throughout the country, from communities with varying levels of urbanization, were analyzed for IgG reactive to nine common flaviviruses, alphaviruses, and bunyaviruses detected elsewhere in West Africa. Preliminary data indicate a higher seroprevalence of DENV-2 in urban counties and CHIKV in rural counties. Results generated through this study will help establish a baseline of infection which can be used to guide government policy in resource allocation and animal husbandry practices. Additionally, the success of this testing platform in generating accurate and reliable data validates the use of our thermotolerant, rapid, sample-sparing, and high-throughput bead-based multiplex immunoassay in outbreak situations, especially in the field as part of a mobile laboratory.

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EVALUATION OF ENVIRONMENTAL POLIO SURVEILLANCE SYSTEM IN GREATER ACCRA REGION, GHANA, 2021

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Since July 2019, thirty-one cases of circulating Vaccine Derived Polio Viruses (cVDPV) have been confirmed in nine out of 16 regions in Ghana, while two regions recorded environmental events. The Polio Environmental Surveillance (ES) system has been a remarkable tool for detecting poliovirus given its ability to highlight the spatial and temporal extent of viral circulation. Ghana started ES in 2018 to compliment Acute Flaccid Paralysis surveillance in the polio eradication efforts. We evaluated the ES system in Greater Accra Region to assess its attributes, usefulness and performance in meeting its objectives. The system's operation was evaluated from 2019 to 2020, using the Updated CDC Guidelines for Evaluating Public Health Surveillance Systems. Interviews, records review and observations were employed to assess the system's attributes and usefulness. We performed summary descriptive statistics on quantitative data and direct content analysis on qualitive data. Of the 140 samples collected within the period, 19 (13.6%) cVDPV-2, 8 (5.7%) orphan Vaccine Derived Polio Virus (oVDPV) and 59 (42.1%) Sabin-like viruses, were recorded with a positive predictive value of 22.1% (19/86). Timely processing and reporting from laboratory to next levels was done for all samples (144/144) with regular feedback from partner organizations. The system was well funded and well-staffed; however, site location was not adequately distributed in the region. Data completeness was 98% (141/144) and consistency was 100% (laboratory and surveillance data). Surveillance data informed initiation of reactive polio immunization campaigns nationwide. The ES system is achieving its objectives. It is useful, sensitive, stable and of good data quality. Representativeness needs improvement.

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ASSESSING REALIZED AND POTENTIAL NICHE OF PATHOGENS OF PUBLIC HEALTH IMPORTANCE TO DESIGN SURVEILLANCE TOOL FOR ACUTE FEBRILE ILLNESS IN NIGERIA

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The Surveillance of Acute Febrile Illness (AFI) Aetiologies in Nigeria (SAFIAN) study aims to support disease surveillance systems and global biological threat reduction efforts by detecting and monitoring pathogens among AFI presenting patients at two hospitals in Nigeria, both low resourced settings, with limited laboratory diagnostic tools. To maximize screening of potential pathogens among these populations, we are using the TaqMan-Array Card (TAC). This simple-to-use, customizable tool allows for accurate and simultaneous screening of 11-380 genetic targets, within a single assay, a target number which would otherwise be labor, time and cost prohibitive. There are innumerable pathogen target options for TAC and selection must be performed in accordance with study goals. To optimize the use of this tool, we sought to include only pathogens with transmission potential in the population. We conducted a literature review of 77 AFI-causing pathogens of public health importance and evaluated each for both the potential and the likelihood of pathogen detection in the study population. Binary (yes/no), tiered criteria in this assessment are 1. Capable of human-to-human transmission, 2. Previous detection (molecular, then serological) in humans, 3. Previous detection (molecular, then serological) in animals, 4. Presence of the host/reservoir, and 5. Ecological suitability for host/reservoir in Nigeria. Pathogens marked "no" for all criteria, we excluded from our AFI TAC-panel. Pathogens marked "yes" early in the tiered assessment, e.g. SARS-CoV-2 (1-human-to-human-transmission) or malaria (2-previous molecular detection in humans) were considered more likely to be detected. Pathogens marked "yes" lower in the assessment, e.g. O'nyong-nyong virus (4-vector present in Nigeria) or Bacillus anthracis (3- previous serological detection in cattle) were determined to have detection potential in our study, but that this detection would be novel or unexpected. This assessment helped us prioritize pathogen selection for inclusion in our AFI TAC panels based on their potential for detection in the study population.

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COMMUNITY-BASED SURVEILLANCE FOR INFECTIOUS DISEASES AMONG DISPLACED POPULATIONS IN IRAQ: EXPANDING BEYOND THE COVID-19 RESPONSE

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While common in sub-Saharan Africa and Asia, community-level disease surveillance does not occur in Iraq. During outbreaks, timely detection is imperative for slowing transmission - critically so in densely populated areas or displaced populations. Early warning through community-based surveillance (CBS) can help. CBS was first implemented in 4 IOM-supported IDP camps in Iraq in response to COVID-19. Building on that success,

CBS was expanded to include 8 additional diseases/conditions of concern: acute watery diarrhea (AWD), acute flaccid paralysis (AFP), Crimean-Congo hemorrhagic fever (CCHF), leishmaniasis, measles, rabies/animal bites, and scabies (based on recent outbreaks or impact on displaced populations), and suspicious community death. Six IDP camps were selected for expanded CBS activities (4 original+2 new locations). Qualified residents were hired as Community Health Promoters (CHPs). Field team size was specific to each camp (SPHERE standards=1 CHP/1000 people; n=30 CHPs [15 teams of 1 M/1 F]). Each team received a smart phone for reporting through KOBO. Working hours aligned with primary health care center (PHCC) hours. Active case finding, event-based surveillance, and misinformation tracking were conducted through interviews with consenting heads of households. Community alert definitions were used where available (e.g., AWD, measles, etc.) or developed for this context (e.g., CCHF). Community alert definitions were piloted among CHPs using fictional examples. There was moderately good agreement among CHP answers (Krippendorff's alpha=0.775); CHPs erred on the side of caution and referred for evaluation at PHCC when not necessary. CHPs were also trained on symptoms, transmission, and prevention; KOBO data collection tool; and respectful communication in December 2022 with refresher trainings in late February/early March 2023. Expanded CBS reporting began in early March 2023 and remains underway through at least September 2023, with summary surveillance data available weekly. Ongoing phone surveys seek to understand CBS acceptability among camp residents and their experiences with the program.

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SCALABLE DISTRIBUTED MANUFACTURING OF POINT-OF-CARE MOLECULAR DIAGNOSTICS IN THE GLOBAL SOUTH

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As climate change and land-use changes increase the risk of environmentally mediated infectious diseases in the Global South, innovative solutions that synthesize policy, economics, and bioengineering are necessary to ensure that equitable and quality healthcare reaches low-resource settings (LRS). Currently, to diagnose and monitor vector-borne and transmissible pathogens, LRS are forced to rely on foreign supply chains to deliver expensive, proprietary consumables. The lack of autonomy and agility of LRS to respond to outbreaks is partially due to inequitable distribution of diagnostic manufacturing capacity, which is concentrated in the Global North. Commercial molecular diagnostics rely on expensive, proprietary reagents and highly technical processes, providing a barrier to local manufacturing of diagnostics in LRS-a crucial requirement for building and maintaining healthcare capacity affordably in any region. To completely transform access to sensitive molecular diagnostics, build capacity for infectious disease surveillance, and reduce carbon-intensive cold-chain shipments, we propose a decentralized model for commerce known as distributed manufacturing. We are developing a circular manufacturing pipeline that requires minimal infrastructure and will yield open-access room-temperature stable reagents for loop-mediated isothermal amplification (LAMP). The reagents are integrated into a point-of-care, sample-to-answer modular molecular diagnostic device called SnapDx, which does not require electricity or external equipment. SnapDx can detect SARS-CoV-2 in patient saliva samples, with a limit of detection, sensitivity, and specificity of 1875 copies/µL, 82.7%, and 95.8%, respectively. Further, SnapDx is compatible with various biofluid samples and reprogrammable to fit the disease profile of different LRS. Scalable distributed manufacturing of SnapDx will democratize diagnostics, enable surveillance of neglected and emerging infectious diseases, and increase the number of healthy life years globally.

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SOCIODEMOGRAPHIC, CLINICAL AND PROGRESSIVE PROFILE OF CHILDREN FROM 06 TO 59 MONTHS HOSPITALIZED FOR SEVERE ACUTE MALNUTRITION AT THE THE REGIONAL HOSPITAL OF BOUNDIALI.FROM JANUARY TO SEPTEMBER 2022

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Severe acute malnutrition is a major public health problem in several countries around the world & is a priority in the Sustainable Development Goals. Constituting one of the leading causes of morbidity & mortality of children under 5 years of age. In Côte d'Ivoire the prevalence of Severe acute malnutrition has stagnated for more than fifteen years at around 7%. The scale of Severe acute malnutrition in the Bagoué region & the low documentation on this subject in this region led us to conduct this study to determine the sociodemographic, clinical & progressive profile of children from 6 to 59 months hospitalized for Severe acute malnutrition at the Regional Hospital of Boundiali. We have conducted a cross-sectional descriptive study from January to September 2022 on a comprehensive sample of 109 children from 6 to 59 months hospitalized at the Regional Hospital of Boundiali. The mean age was 19.7 months with 76.15% who were between 12 & 59 months old; The sex ratio was 1.1 & 61.4% lived in rural areas. Marasmus was found in 79% & kwashiorkor in 21% & as associated pathology we noted that 28.8% had malaria, 27.1% had acute respiratory infection, 18.6% had severe anemia, 18.6% had diarrhea & HIV infection was noted in 5.08%. The average length of hospital stay was 6 days & Severe acute malnutrition was stabilized at 46.8% & 8.3% had died. In conclusion, severe acute malnutrition in children from 6 to 59 months of age remains a concern in hospital environment. The analysis of the associated factors through subsequent studies will make it possible to better clarify the causes & consequences of this malnutrition.

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PREVALENCE AND FACTORS ASSOCIATED WITH MATERNAL AND NEONATAL SEPSIS IN SUB-SAHARAN AFRICA, A SYSTEMATIC REVIEW AND META-ANALYSIS

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Reducing maternal and newborn mortality is a key component of Sustainable Development Goal (SDG) 3. Sub-Saharan Africa, with a maternal mortality ratio estimated at 542, remains the region with the highest maternal mortality ratio. Maternal and Neonatal sepsis constitute a major cause of mortality and morbidity. In the low- and middle-income countries (LMICs), more than 95% of maternal deaths more than half of neonatal deaths due to sepsis. There is little data on its prevalence and associated factors in Saharan Africa. Understanding these factors will help to guide interventions, and deployment of community-based initiatives to prevent maternal and neonatal sepsis in sub-Saharan African resource constrained context. Using Prisma guideline, we have reviewed studies from different databases from January 2012 to November 2022. After checking and applying the inclusion and exclusion criteria, the selected studies was independently assessed for quality and risk of bias by 2 researchers. Stata 17 was used, and the grouped prevalence was calculated. Heterogeneity was examined using the Q-statistic and the I2-statistic. Thirty-four studies were included in this systematic review and meta-analysis. The global prevalence of maternal and neonatal sepsis in sub-Saharan Africa was respectively 71% and 56% respectively 70%. However, a heterogeneity of prevalence was observed. For maternal factors, the highest prevalence was

observed for urinary tract infection (90.5%) and the lowest prevalence was observed for caesarean delivery (58.3%). For neonatal factors, the highest prevalence was observed for intrapartum fever (80.8%) while the lowest prevalence was observed for caesarean delivery (37.7%). The prevalence of maternal and neonatal sepsis in sub-Saharan Africa is high. There was a variability on the prevalence depending on the factors. The scarcity of data and studies may explain the heterogeneity.

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IMPACT OF COVID-19 INFECTION ON PREGNANCY AND NEONATAL OUTCOMES EVIDENCE FROM A SUB-COHORT OF PREGNANT WOMEN FROM THE AMANHI-COVID-19 STUDY

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The full extent of the effects of COVID-19 on maternal and fetal health is not yet fully understood. Some studies suggest pregnant women with COVID-19 may be at higher risk for certain complications, including preterm birth, preeclampsia, and cesarean delivery. The AMANHI-COVID-19 study aimed to determine the incidence and factors associated with adverse outcomes among COVID-19-positive pregnant women or recently delivered women in a suburban area of Karachi. From March to December 2021, 410 women (pregnant or delivered within 60 days) were enrolled. Detailed information was collected on prior and concurrent pregnancies and illnesses, along with anti-SARS-CoV-2 antibody testing. Monthly information was collected on COVID-19 symptoms, pregnancy complications, and hospital records. Women were visited within 10 days of the end of gestation to ascertain outcome, peripartum details and collection of blood samples. Roche Elecsys immunoassay was used to detect anti-SARS-CoV-2 antibodies in the samples. The prevalence of COVID-19 among pregnant women was 57.3%. Pregnant women who were seropositive for COVID-19 had higher rates of miscarriage (18.1%) and stillbirth (3.6%) compared to non-reactive women (10.7% and 1.5%, respectively). The results of the study suggest that there may be a possible association between exposure to COVID-19 and adverse birth outcomes. Specifically, the odds of being seropositive and having a miscarriage were 1.9 times the odds of having a live birth (95% CI: 1-3.8). The odds of stillbirth among those exposed to COVID-19 were 1.8 times greater than having a live birth (95% CI: 0.5-7.5). This study found no significant association between socioeconomic status, age, education and parity. The study demonstrated that seropositivity during pregnancy increases the risk of adverse pregnancy outcomes. They must adhere to recommended guidelines to mitigate their risk of contracting the virus, including social distancing measures, face masks, and vaccination to reduce the likelihood of infection.

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DEVELOPING LABORATORY INFRASTRUCTURE AND TECHNICAL CAPACITY TO ADDRESS INFECTIOUS DISEASES IN EQUATORIAL GUINEA

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The increasing prevalence of emerging and re-emerging infectious diseases in Equatorial Guinea necessitates the establishment of high-quality clinical research laboratories. This study outlines the process of developing and strengthening the Baney clinical research laboratory on Bioko Island, with the goal of creating a gold standard, reference laboratory for infectious diseases in the country. Inaugurated in early 2019, the Baney Lab was initially built to conduct malaria clinical trials but had to pivot due to the COVID-19 pandemic. Through a collaboration between MCD global, Sanaria Inc, Ifakara Health Institute, Swiss Tropical and Public Health Institute, and the Equatorial Guinean government, the laboratory infrastructure and staff technical capacity were significantly improved. Key methods included the installation of advanced molecular biology analyzers, development of standard operating procedures, and staff training. The Baney Lab demonstrated remarkable adaptability and resilience by swiftly transitioning from malaria research to addressing COVID-19 and other infectious diseases, becoming a testing reference lab for all of Equatorial Guinea and gaining WHO certification as a regional reference laboratory. This study shares the experiences and challenges faced during the transformation of a basic laboratory into a high-quality, internationally recognized research facility, highlighting the importance of developing robust laboratory infrastructure and technical capacity to effectively and rapidly address diverse infectious diseases in Equatorial Guinea.

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USING SOCIAL LISTENING METHODS TO UNDERSTAND COVID -19 VACCINATION IN THE DEMOCRATIC REPUBLIC OF CONGO

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Social media creates opportunities to stay informed, but has also enabled and amplified the current infodemic that continues to undermine the COVID-19 response and vaccination campaign in the Democratic Republic of Congo (DRC). As of 5 March 2023, 12.7% of the Congolese population has received a COVID-19 vaccine. With the increasing influence of social media platforms like Twitter and Facebook, social media interactions concerning COVID-19 vaccination topics have increased remarkably. This work aims to assess COVID-19 associated posts and track rumors related to vaccination utilizing social listening techniques. Social media posts on Facebook and Twitter were analyzed from 04 September 2021 to 02 September 2022, using Brand24 and 10 keywords (e.g., "Covid-19", "Astrazeneca") associated with COVID-19 vaccination to measure engagement, sentiment (i.e positive, neutral, negative) and frequency of COVID-19 related themes in DRC. A total of 9,326 posts were identified and coded by overall theme (e.g., suspicion about vaccine/COVID-19 information, perception of COVID-19 risk). The suspicion of COVID-19 vaccine posts included any post in which a respondent was suspicious of the vaccine, safety, origin, intention to vaccinate or any information about COVID-19. The perception of COVID-19 risk post included any discussion of the severity of COVID-19 related risk of infection, death or any negative outcome. The majority of posts came from Facebook (78.4% vs 21.6% on Twitter). Facebook had more negative posts compared to Twitter (78.7% vs 55.2 %). Nearly three-quarters of all posts were negative (73.6%), while 21.2% were positive and 5.2% were neutral. The most common theme identified on Facebook was COVID-19 information and vaccine suspicion (21.1%). The most common theme identified on Twitter was the perception of COVID-19 risk (16.4%). Given the vast reach of social media worldwide, this novel social listening methodology is an innovative way to identify public sentiment related to health emergencies to inform response activities and campaigns to address misinformation and boost public confidence in health responses.

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GLOBAL HEALTH CHALLENGES OF INFLUENZA SENTINEL SURVEILLANCE COLLABORATION NETWORK

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Developing effective health protection surveillance is critical for enhancing global health. The Armed Forces Research Institute of Medical Sciences (AFRIMS) has coordinated and enabled collaborations with international partners to expand a network of influenza surveillance throughout South and Southeast Asia since 2005. These sites provide the capability to rapidly identify influenza and quickly disseminate information among partners. In order to develop baseline data to more fully understand the current epidemiology situation, determine the seasonal and regional genotypes of influenza disease, and enhance outbreak response capability. AFRIMS established a network for influenza disease surveillance in Bhutan, Cambodia, Nepal, the Philippines, and Thailand. More than 100 field locations collected data and samples from patients meeting criteria for influenza-like-illness. Rapid testing for influenza A and B is performed in the field as the first step followed by real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) for influenza A (pdmH1, H3) and B. Some samples were transported to AFRIMS, where confirmation of all rRT-PCR was performed with virus sequencing performed as warranted. In addition, sequencing and drug resistance analysis is provided to all surveillance station and regional partner collaborators giving participating healthcare providers feedback on the influenza viruses circulating. Including surveillance activities from JAN 2009 through DEC 2022, AFRIMS partners collected and tested a total of 75,141 patients. To date, 37.4% of these samples tested positive for influenza A and/or B. Influenza A was the most common type accounting for 67.2% of the influenza positive samples. Sub-typing of influenza viruses detected 9,783 (13.0%) A/H3; 9,016 (12.0%) A/H1; 46 (0.1%) A/Unsubtyped; 9,123 (12.1%) B; and 94 (0.1%) Co-infected A and/or B. AFRIMS and its collaborating partners in South and Southeast Asia continue to contribute to global knowledge of influenza infections via sample collection, laboratory testing, storage, surveillance and performing and disseminating epidemiological studies.

6600

COMPARISON OF PLAQUE REDUCTION NEUTRALIZATION TEST AND MULTIPLEX ARBOVIRUS IGG DETECTION TEST FOR DETECTION AND DIFFERENTIATION OF IGG RESPONSE TO ZIKV AND DENV

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Arthropod-borne viruses (Arboviruses) cause many emerging and re-emerging diseases. The window of detection for many of these viruses using molecular assays is short, and hence serology plays a vital role in diagnosis and surveillance. The serological methods are limited due to cross-reacting antibodies; therefore, the PRNT is the gold standard for antibody detection. We have validated an 18-plex arbovirus IgG detection assay that detects antibodies to ten arboviruses using 38 PRNT-positive samples. The multiplex arbovirus IgG assay uses optically coded magnetic microspheres to immobilize NS1 and envelop protein antigens from 10 different arboviruses, namely, Zika (ZIKV), Dengue all four serotypes (DENV 1- 4), West Nile (WNV), Japanese Encephalitis (JEV), Yellow Fever (YFV), Tick-Borne Encephalitis (TBEV), and Chikungunya (CHIKV), to interrogate IgG responses in exposed serum or plasma. This 18-plex assay also includes five internal controls that assure the assay and reagent performance. The 38 samples included 17 serum samples, of which 10 were convalescent dengue samples collected between 2009 to 2015 from returning travelers. We also tested 21 plasma collected during the ZIKA pandemic of 2016. These samples were also tested using a 7-plex SARS-CoV-2 IgG multiplex panel. We found 100% agreement between the two tests qualitatively for DENV. The PRNT serotyping results matched in 8/10 samples. The PRNT titer positivity to ZIKV NS1 antigen was negative in these samples, although the envelop protein reactivity was positive in all ten samples. A serology assay based on whole virus particles or envelop protein from ZIKV may give false positive reactivity with DENV-infected samples. In these samples, no PRNT results for ZIKV were available. In 28 ZIKV-positive samples, the PRNT and multiplex assay matched in 27/28 samples completely. One instance was discrepant as it was found reactive with one out of three ZIKV antigens used in this assay. Multiplex SARS-CoV-2 IgG tests shows100%. In conclusion, this limited validation of the 18-Plex arbovirus IgG assay shows excellent agreement with PRNT.

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US SURVEILLANCE OF NEGLECTED TROPICAL DISEASES - A MISSED OPPORTUNITY FOR SURVEILLANCE OF NEGLECTED TROPICAL DISEASES

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Neglected tropical diseases (NTDs) are a grouping of diseases common in low-income populations of Africa, the Americas, and Asia. Some NTDs are associated with significant morbidity and mortality and have a severe impact on communities and economies. These diseases are neglected in part becuase they are not considered major concerns in wealthy countries; however, conducting research is often challenging in high-prevalence low and middle income countries due to poor infrastructure, lack of electronic health systems, etc. Surveillance of NTDs in developed countries, such as the U.S., is often irregular, despite the prevalence of disease, health burden, and outbreak potential. The Centers for Disease Control and Prevention (CDC) list 17 NTDs. We conducted a review of state department of health (DOH) websites to describe surveilance of CDC-defined NTDs and case numbers from available. Our review identified nationally reportable 4 NTDs (human cases reported to the CDC in 2019: chikungunya n=192, dengue n=1414, Hansen's disease n=77, rabies n=0). 6 other NTDs were reportable to 1 DOH (Chagas disease in 8 states; cysticercosis/teniasis in 6 states; scabies in 3 states; soil-transmited helminths in 1 state; echinociccosis in 1 state; African tryptanosomiasis in 1 state). Based on the review of available data, the case counts in 2019 include Chagas n=35; cysticercosis n=31; teniasis n=3; echinococosis n=1; soil-transmitted helminths n=14. DOHs varied widely in reportable NTDs; some states explicitly specified diseases, whereas others may report NTDs under categories such as 'diseases of public health importance'. Public-facing data availability was variable; some DOHs presented surveilance data in downloadable format for easy analysis. Others report cases in PDFs, while some states' data were only available upon request under the Freedom of Information Act, i.e. echniococcosis in Idaho. The lack of reporting requirements for NTDs, with only 4 of 17 reportable nationally and 10 reportable nowhere, is a missed opportunity to better understand NTDs, conduct research, and prepare for future outbreaks.

6602

SCALE UP FOR IMPACT IMPROVING COVID-19 ANTIGEN RAPID DIAGNOSTIC TESTING IN NIGERIA

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Continuous testing of people is essential to preventing the spread of the coronavirus disease 2019 pandemic, In Nigeria, only 1.6% of the population had been tested for COVID 19 since the pandemic commenced in Nigeria, staggering low compared to other countries in Africa and across the globe and below the WHO benchmark for testing of 200,000 per week. Despite collective enormous investment and effort by the Government of Nigeria and partners, testing remains suboptimal in Nigeria due to lack of access to testing. Rapid scale-up of testing capacity for COVID 19 is therefore crucial at all levels of the health care system. A total of 280 volunteers were recruited across eight states in Nigeria to scale up testing in communities and health facilities using COVID 19 Ag Rapid Diagnostic Test. The volunteers were trained on safe sample collection using RDT kits, handling of positive samples, testing workflow and interpretation of test results. We ensured aavailability of adequate and appropriate biosafety measures including waste management and infection prevention and Control measures. Strategies for testing includes mobile outreach testings, religious centers, community testing and facility-based testing. At all points quality assurance measure were put in place and test results were captured real time using the electronic case investigation forms and integrated real time into the National surveillance data base. Overall, total of 394,000 COVID 19 antigen rapid diagnostic test was conducted with 146 positive samples giving a test positivity rate of 0.04%. Genomic sequencing conducted on positive samples revealed 100% omicron variant. Timely and accurate testing is an essential tool in preventing the spread of COVID 19 and must be implemented strategically. This finding reveals the impact of leveraging resources to strengthen the country's capacity for detection of COVID 19 and other epidemic prone diseases.Key words: Scale up, COVID-19 prevention, Antigen Rapid testing, Nigeria

6603

FILLING THE INFORMATION GAP: FIND MPOX TEST DIRECTORY AND PERFORMANCE EVALUATIONS

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The 2022 global mpox outbreak spurred rapid development of commercial diagnostics. However, there was no central location where users could access information on the availability of mpox diagnostic tests. Furthermore, limited data on test performance, particularly for tests suitable in decentralized settings, posed a barrier to implementation. FIND aimed to fill this information gap through development of a global mpox test directory and independent performance evaluations of point-of-care (POC) diagnostics. From August 2022, FIND gathered information on mpox diagnostics through landscape review of various sources. We also put out a call for expressions of interest (EOI) to identify POC-appropriate antigen lateral flow tests (LFAs) and nucleic acid tests (NATs) for performance evaluation, selecting suppliers based on reported analytical and clinical performance, ease of use, and distribution in low- and middle-income countries (LMICs). As of 19 February 2023, we registered 119 commercially available mpox tests in the test directory: 87 (73%) NATs and 32 (27%) immunoassays (IAs) targeting mpox antigen (n=18), mpox antibodies (n=13), or mpox antigen + antibodies (n=1). Thirty-two (27%) tests are considered POC, including 18 antigen-based IAs, 11 antibody-based IAs, 1 antigen + antibody-based IA, and 2 NATs. In response to the EOI, we received 50 eligible submissions (33 LFAs and 17 NATs); 3 POC LFAs and 2 near-POC NATs were selected for evaluation. For performance evaluations, which will start in early 2023, we engaged qualified sites in Central Africa (n=2) and Europe (n=1) and established protocols for analytical and clinical evaluation of selected tests compared to laboratory-based PCR on skin lesion specimens. Results are expected in the end of 2023. Information on test availability and performance evaluations are essential to controlling outbreaks such as mpox, with POC tests especially important for diagnosis in decentralized settings in LMICs. The FIND mpox test directory and ongoing POC test evaluation will enable us to generate and share performance data on mpox diagnostics with the global community.

6604

PRELIMINARY INVESTIGATIONS OF THE MICROBIAL INTERACTIONS IN THE GUT OF POTENTIAL VECTORS OF LEISHMANIA CHANCEI IN GHANA

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The endosymbiotic relationship in the insects' gut microbial community contributes to the insects' physiology and vectorial competence. This has the potential for disease control in vectors. Cutaneous leishmaniasis (CL) in Ghana is caused by a new species Leishmania (Mundinia) chancei and has been endemic in the Volta Region of Ghana since 1999 with unknown vectors. Previous laboratory investigations showed that L. (Mundinia) chancei colonizes and replicates in the gut of Culicoides sonorensis, but could not persist beyond the blood meal stage in the gut of Lutzomyia longipalsis. This study sought to investigate endosymbionts present in the guts of Culicoides biting midges and sandflies caught in the CL endemic communities in Ghana that may promote or prevent the survival of Leishmania parasites and contribute to disease transmission and cutaneous lesion exacerbation. A total of 135 sandflies and 410 biting midges were caught by light traps in leishmaniasis endemic communities in Ghana. Flies were pooled in groups of 5 for sandflies and 10 for biting midges and further subjected to DNA extraction. Using both universal and specific 16S bacteria primers, the extracted DNA was subjected to PCR screening for bacteria (Wolbachia, Ochrobactrum, Ehrlichia, Tsukamurella). Of 27 pools (135) of sandflies, 5 (19%), 27 (100%) and 3 (11%) were positive for Wolbachia, Ehrlichia and Tsukamurella respectively. Out of 41 pools (410) of midges, 5 (12%), 11 (27%) and 6 (15%) were positive for Wolbachia, Ehrlichia and Tsukamurella respectively. The Leishmania parasite DNA was amplified in 37% of sandfly pools and 7% of the biting midges' pools. Further genomic analysis such as the sequencing of amplicons is being carried out to provide sufficient data to support this study of the gut microbial community and to ascertain the relationships between the insect and its microbiome.

6605

SAND FLY SURVEILLANCE IN LEISHMANIASIS ENDEMIC AREAS IN CENTRAL HONDURAS

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Leishmaniasis is a serious health problem in Honduras where cutaneous and atypical cutaneous cases are predominant, yet visceral cases are also present. Information about sand fly vector species is limited, particularly in the central region of Honduras. The aim of this study was to identify sand fly species found in leishmaniasis-endemic areas in central Honduras, and screen them for infection with Leishmania parasites. Sand flies were collected in Comayagua (17 sites), Francisco Morazán (2 sites) and Cortés

(1 site) departments from 2018-2022 using CDC light traps. Specimens were identified using taxonomic keys at the U.S. Naval Medical Research Unit No. 6 Entomology Laboratory on Soto Cano Air Base in Comayagua. Females were processed using a modified protocol that allowed for molecular testing and males were clarified with 20% KOH, eugenol-lactic acid (1:1). Unfed females were pooled (1-10 /tube) and PCR-screened for Leishmania minicircle kinetoplast (kDNA). Lutzomyia DNA was confirmed by 12S ribosomal PCR. A total of 978 sand flies (686 males, 292 females) belonging to 13 species were collected: 485 from Comayagua (14/trap), 474 from Francisco Morazán (59/trap) and 19 (19/trap) from Cortés. The most abundant sand fly species in Comayagua and Francisco Morazan were Lu. longipalpis (61.3%) and Lu. evansi (26.3%); Lu. (Coromyia) spp., and Lu. cruciata were also recorded in both departments (<4%). Lutzomyia panamensis was the only species collected in Cortes and was also present in Comayagua. A sub-set (28-100%) of female sand flies (112 unfed, 28 blood-fed) from each department was screened for Leishmania DNA; all samples were negative. We recorded for the first time the presence of Lu. longipalpis, the main vector of L. infantum, and the secondary vector Lu. evansi in 7 and 4 sites in Comayagua department, respectively. Atypical cutaneous leishmaniasis cases reported by the Honduran Ministry of Health in Comayagua suggest the presence of L. infantum in this region. Future studies will further characterize sand fly vector species, Leishmania clinical isolates and potential reservoirs in Comayagua department.

6606

TOWARDS A HOST-TARGETED INSECTICIDE STRATEGY: TRYPANOSOMA CRUZI INFECTION AND HOST FEEDING PATTERNS OF TRIATOMA DIMIDIATA IN A REGION WITH PERSISTENT CHAGAS DISEASE

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Chagas disease, caused by Trypanosoma cruzi, affects 6 to 7 million people worldwide. The goal is to eliminate transmission of this neglected disease by 2030. The main vector in Central America is Triatoma dimidiata, an insect that can be found from Mexico to the north of Peru. Studies in Guatemala show that vector control interventions, including plastering and residual indoor insecticide applications, decreased household infestations of T. dimidiata, but did not eliminate populations. There are regions where vectors persist despite multiple interventions. During June-August 2022, we conducted entomological surveys in 76 households from a region with persistent infestation in Comapa, Department of Jutiapa, Guatemala. Indoor walls and floors were swabbed to detect parasite and triatomine DNA as an independent metric of infestation. For sampled communities, the triatomine infestation index (presence of any life stage) was 26.3%, and the colonization index (presence of immature insects) was 18.4%. Of 86 triatomines, we found that 66% were recently fed. We will characterize the infection prevalence and circulating discrete typing units of T. cruzi using multiplex real-time PCR. We will identify the triatomine host feeding patterns by amplifying the vertebrate cytochrome B gene followed by amplicon deep sequencing. Previous PCR-based blood meal studies of T. dimidiata in Guatemala reveal the predominant hosts included chickens, rats, mice, dogs, ducks, and humans. Our study aims to provide complementary information regarding hosts and transmission cycles in this region. In a One Health approach, we intend that these studies will form the basis for deployment of host-targeted insecticides to the highly utilized vertebrate hosts (e.g., dogs, chickens) to suppress vector populations and protect human health.

6607

ASSESSING KNOWLEDGE ABOUT TICKS AND TICK BORNE DISEASES AMONG INDIANA HEALTHCARE PROVIDERS AND EXTENSION PROFESSIONALS

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The risk of tick-borne diseases (TBDs) has increased with the expanding geographic range, altering seasonal activity, and introduction of invasive ticks in Indiana. When tick control and prevention are underserved, prompt and proper diagnosis and treatment can reduce the TBD threat and disease severity, making it important for authorities, especially healthcare professionals, to stay informed about the tick vectors, associated diseases, and TBD diagnoses and treatment options in their locality. However, there is currently a lack of information about the knowledge of ticks and TBDs and diagnostic proficiency of Hoosier healthcare and extension professionals. To address the gap, we conducted an anonymized Qualtrics survey, distributed via emails to subscribers of 'Purdue University Agricultural Extension Educators' and 'Indiana State Department of Health Physician Network' distribution lists. Our survey comprised 24 discrete or ordinal questions, and one open-ended question, and received responses from 597 participants. We used chi-square and ANOVA tests to assess for significant differences in knowledge scores among demographic groups. Further analysis to identify important predictors of knowledge score gaps is ongoing. Results, to date, shows that while 87.6% of respondents recognized the importance of early removal of ticks to reduce TBD transmission and the association of 'bulls eye' with Lyme disease, only a small percentage correctly identified tick species capable of transmitting diseases in Indiana (25.6%); describe the geographic distribution of Lyme disease and Ixodes scapularis within the state (29.3 and 40.4%, respectively); and name all the endemic TBDs in the state (1%). Aggregate knowledge scores varied significantly based on factors such as respondents' credentials, area of specialty, years of experience, self-identification as a tick expert, and use of online resources to obtain information about ticks and TBD diagnosis. Our findings indicate the need for education and training interventions to improve the knowledge and preparedness of healthcare professionals in Indiana to mitigate the threat of TBDs.

6608

TICK AND INSECT CELL LINES FROM THE TICK CELL BIOBANK FACILITATE ISOLATION OF WOLBACHIA AND OTHER OBLIGATE INTRACELLULAR BACTERIA ORIGINATING FROM MULTIPLE VECTOR SPECIES

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Research into obligate intracellular bacteria in vectors faces particular challenges associated with the need for suitable host systems, whether in vivo (live vertebrates and/or arthropods) or in vitro (cell culture). The Tick Cell Biobank houses the world's largest collection of tick cell lines, as well as a growing collection of new insect cell lines, representing many taxa of importance to tropical medicine. This allows us to conduct studies on the susceptibility of a variety of arthropod cell lines to intracellular bacteria of diverse origins. In general, such bacteria can grow in cells of a much wider range of host species in vitro than in vivo, encompassing cells from both natural hosts and arthropods unlikely to be encountered in nature. Here we present two examples. (1) The genus Ehrlichia contains several tick-borne human or veterinary pathogens including Ehrlichia ruminantium. In vitro, E. ruminantium grows in cell lines derived from not only its vectors, Amblyomma spp., but also multiple other non-vector species (e.g., Dermacentor and Ixodes spp., and the one-host tick Rhipicephalus microplus, which was recently reported to support transovarial transmission of E. ruminantium). (2) Wolbachia symbionts are found in around half of all known terrestrial arthropods in which they are best known as reproductive parasites causing cytoplasmic incompatibility and other phenotypes. Wolbachia is not confirmed to infect ticks; detection in ticks is usually

associated with the presence of parasitic wasps or nematodes. However, tick cell lines support growth of several strains of Wolbachia originating from insects. We summarise how insect and tick primary cultures and cell lines have been used to isolate Wolbachia strains wPip and wPap from Culex pipiens mosquitoes and Phlebotomus papatasi sandflies, respectively, and wCfeF and wCfeJ from Ctenocephalides felis fleas (vectors of bartonelloses and rickettsioses). Moreover, we report use of diverse arthropod cell lines to separate a mixture of wCfeF and wCfeJ from an originally co-infected tick cell culture, allowing the successful generation of complete genome assemblies for both strains.

6609

IMPROVING DISTRIBUTION MODELS OF SPARSELY DOCUMENTED DISEASE VECTORS BY INCORPORATING INFORMATION ON RELATED SPECIES VIA JOINT MODELING

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A key component of understanding the risk of exposure to vector-borne diseases is accurate classification of the spatial distribution of their vectors. Standard species distribution models are applicable to vector species that are well-documented, but may produce biased or inaccurate results for species for which data are limited. In light of global change, vectors that are currently not well-documented, due to either a lack of established presence or lack of current public-health relevance, could become increasingly important. Therefore, it is vital that we have tools to estimate the spatial distributions of these vectors. A key assumption that allows us to leverage additional information on sparsely sampled vectors is that the environmental niches of evolutionarily related species are not completely independent, nor are the spatial distributions of vectors and the pathogens they transmit. One tool that allows us to exploit these relationships is joint hierarchical modeling. In this work, we evaluate whether joint hierarchical models of multiple vectors and human diseases improve distribution estimates of sparsely sampled vectors. Further, we aim to determine if there is an optimal taxonomic level to pool vector species within our modeling framework. We first fit our models to an empirical dataset of ticks and tick-borne disease within Florida, then utilize simulations to test the generalizability of our results and our understanding of their underlying causes. When fit to empirical data, the average accuracy of the estimated distributions for a sparsely-sampled species was 0.691 for the pooled models, compared to an accuracy of 0.364 in the single model. When fit to simulated data, the average R2 between the true and estimated distributions of a sparsely sampled species was 0.38 in the pooled models, compared to an R2 of 0.01 in the single model. While we could not detect a definitive optimal level of taxonomic pooling, current results demonstrate that, via limiting overfitting, joint hierarchical models improve distribution estimates of sparsely sampled vector species.

6610

ANALYSIS OF BLACK FLY ENTOMOLOGICAL SURVEILLANCE FOR ONCHOCERCIASIS ELIMINATION IN SEVEN NIGERIAN STATES

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Entomological surveillance is critical to onchocerciasis elimination. WHO criteria to stop mass drug administration (MDA) in endemic areas requires 6000+ Simulium damnosum sl black flies with an Onchocerca volvulus-infection prevalence significantly <0.05%. Collections by human landing catch (HLC) and Esperanza Window Traps (EWT) are labor and resource intensive. The Carter Center partnered with State and Federal Ministries of Health to collect black flies in seven states in central and southeastern Nigeria at sites selected by the National Onchocerciasis Elimination Committee (NOEC) and supplementary prospected sites. We analyzed fly data from stop-MDA assessment or post-treatment surveillance (PTS) from 2014-2022 to determine the most productive methods and seasons of captures. At least one month of adult black fly data was reported for 314 sites: 2,765 monthly counts from HLC and 1,742 monthly counts from EWTs, which were introduced in 2016. Despite most sites being selected as high-risk first-line villages near rivers supporting breeding, no Simulium flies were ever captured at the majority (n=166, 52.9%) of sites. At productive sites, the number of flies per month was right skewed, with an average of 69.0 flies/month (range 0-2938, s.d. 240) but 0 flies in 52.3% of monthly collections. EWTs were less productive than HLC; in sites and months where both were used, HLC produced 2.0 times as many flies as EWTs. Earlier years targeted rainy season months (~June to November); the NOEC later recommended 12 full months for more comprehensive analysis. Flies were thus collected from July 2021 to June 2022. The average count from productive sites dipped to a minimum of 37 in January but peaked in February and March at 130 and 134 flies, respectively. In 2021-2022, only 82 (35.5%) of 231 sites across 5 states were productive, and 56.0% of 56,762 total flies were captured at just 4 sites. These results reveal extreme variability in black fly yields from predicted high risk sites. Understanding the ecological predictors of the most highly productive sites could improve both the representativeness and efficiency of fly collection for program monitoring.

6611

EFFICACY OF A PERSONAL INSECT REPELLENT KIT PERIMETER CONFIGURATION AGAINSTIXODES SCAPULARIS FEMALE TICKS IN AN ENCLOSED PEET GRADY-STYLE CHAMBER

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Tick-borne diseases (TBDs) are a burden for human and animal health. Prevention of TBDs relies mainly on the prevention of tick bites. Effective tick-bite prevention methods such as EPA-approved topical repellents, permethrin-treated clothing, and thorough tick checks are currently available. However, there is limited user compliance; thus, new bite-prevention technologies are needed. Furthermore, there are no commercial passive spatial devices for area protection against tick bites. To fill this gap, Widder Brothers developed the Personal Insect Repellent Kit (PIRK), a passive, lightweight device containing transfluthrin. In 2018, we started our collaboration with Widder Brothers to test the PIRK against three tick vectors of public health importance, Ixodes scapularis, Dermacentor variabilis, and Amblyomma americanum. Our previous studies demonstrating the contact and short-range spatial efficacy of the PIRK against Ixodes scapularis ticks will be briefly reviewed. In this study, we tested the capability of a PIRK perimeter configuration to act as a tick barrier in an enclosed Peet Grady-style chamber. In this assay, ticks are placed close to the PIRK perimeter and exposed for two hours. Tick behaviors and location in the test arena were recorded during exposure, and ticks were assessed for KD and mortality post-exposure. More than 90% knockdown was obtained at 1 and 2hrs post-exposure, and 90% mortality at 48hrs post-exposure. These data indicate the potential of a PIRK perimeter configuration to protect an area from ticks when at a close distance from the device. Ongoing studies to investigate the dimension of the area protected by the device and assess the perimeter device under semi-field conditions and determine suitability as a limited outdoor device, will be discussed.

6612

ADAPTING VECTOR SURVEILLANCE SURVEYS USING BAYESIAN EXPERIMENTAL DESIGN: AN APPLICATION TO AN ONGOING TICK MONITORING PROGRAM IN THE SOUTHEASTERN UNITED STATES

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Recent decades have seen an expansion of medically important ticks and their associated pathogens throughout North America. A critical step in the prevention of tick-borne diseases is establishing the geographic and temporal extent of host-seeking ticks. However, such data are generally incomplete or entirely lacking in many areas, particularly when considering a spatio-temporal scale which is fine-grained enough to meaningfully establish risk of human exposure. Unfortunately, local vector-control agencies frequently lack the awareness and resources to perform the regular, systematic surveillance that such data demands. While statistical modeling can help address gaps in tick distribution maps, these models require sufficient high-quality data to reduce prediction uncertainty to an acceptable level, in order to reliably assess risk and inform policy. Here we demonstrate the promise of Bayesian Experimental Design to maximize the effectiveness of surveillance and control programs given limited resources. Using previous surveillance data as input, this framework allows us to identify future survey times and locations which minimize the uncertainty in current tick distribution maps. We apply our methods to an ongoing tick surveillance program in South Carolina state parks, and propose novel design criteria specifically tailored to public-health priorities. Our design analyses are complemented by an extensive model comparison study, where competing mixed-effects models widely used in the literature are evaluated based on model complexity and goodness-of-fit.

6613

INDOOR RESIDUAL SPRAYING HAS REDUCED SANDFLY ABUNDANCE AND INCIDENCE OF VISCERAL LEISHMANIASIS IN THE INDIAN SUB-CONTINENT

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Control efforts towards reaching elimination of visceral leishmaniasis (VL) on the Indian sub-continent mainly consist of detection and treatment of cases and indoor residual spraying (IRS). While IRS constitutes over 3/4 of the overall control budget, its impact on vector abundance and VL transmission has not been conclusively established. To address this, we analysed indoor vector abundance data collected from 8 endemic blocks in India (2016-2022), block-level VL case numbers from the KAMIS registry (2013-2021), and IRS quality assurance data as measured by high-performance liquid chromatography (2017-2019). Using statistical and mathematical modelling, we investigated whether sandfly abundance in sentinel sites in India changed as a result of IRS, and whether the decline in VL case numbers was in line with trends in sandfly abundance, accounting for changes in case detection rate over time. Between 2016 and 2022, a total of 229,896 sandflies were caught in CDC light traps, situated in 913 indoor living spaces across 50 villages and 8 blocks. Across the 165,189 data records (up to 4 per month per trap), vector abundance showed a declining trend over the years and was highly seasonal, typically peaking around July. In 4 blocks where IRS was started or stopped during the study period (as part of the national control program), IRS reduced sandfly abundance by 27% (95%-CI: 21%-33%) on average. In 3 of these blocks, this reduction ranged from 27% to 34%; in the fourth block, the reduction was not significantly different from zero. Concentrations of insecticides on walls were not significantly associated with the degree of reduction in vector abundance. Model-predicted trends in VL case numbers, which accounted for trends in vector abundance and case detection delays, closely followed reported case numbers. In conclusion, IRS is very likely to have contributed to reductions in sandfly abundance, although there was a strong secular declining trend in sandfly abundance across all blocks, regardless of IRS status. Trends in vector abundance explain observed declines in VL case numbers, even when correcting for temporal changes in case detection rate.

6614

DISTRIBUTION OF FRESHWATER SNAILS VECTORS FOR THE TRANSMISSION OF URBAN SCHISTOSOMIASIS IN THE ABUJA, FEDERAL CAPITAL TERRITORY, ABUJA, NIGERIA

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Freshwater snails belong to the class of highly infective flukes of medical and veterinary importance. The infections caused by them are widespread and prevalent in ponds, streams, marshes and lakes contaminated by faeces or urine of infected humans and animals where they breed. We determined the presence and distribution of freshwater intermediate snail hosts of schistosomes in an endemic urban area of Abuja, the Federal Capital Territory (FCT), Nigeria. Eight sampling locations in four districts [Area 1 and 2 (Garki district), Jahi 1/2 (Kado district), Karu 1/2 and City College (Nyanya district) and Central Mosque river (Central Business district] were sampled. Snails were prospected for and processed using standard techniques. Identification was done to species level based on the shell morphology using the identification keys of Brown Kristensen (1993). Each species was counted to determine the number collected in time and space. A total of 1,225 freshwater snails belonging to eight species in four families were collected. members of the family planorbidae (60.6%) with B. truncatus (24.8%) were most abundant. Freshwater snail species were found in all the water bodies in this study but the Central Business District recorded the highest number (40.0%). More Freshwater snail species were collected from streams 1,018 (82.4%) than ponds 207 (17.6%). Fresh aquatic leaves and stems (46.3%) were preferred attachment surfaces in this study. This study shows that Freshwater snail intermediate hosts of trematodes are present in urban Abuja in FCT and suggests possibility of high cases of human and animal schistosomiasis in the area; this calls for an urgent need for adequate environmental management, behavioural change modifications and snail control measures in Abuja alongside mass administration of Praziquantel.

6615

CLIP RNAI SCREEN: UNVEILING THE PROTEASE NETWORK THAT REGULATES HUMORAL IMMUNITY IN ANOPHELES GAMBIAE

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The mosquito immune system is required for mosquito survival and limits vector competence. To optimize mosquito fitness, the immune system is tightly regulated to balance resistance to pathogens and limiting self-harm. To fight pathogens that invade their body cavity, mosquitoes activate humoral immune responses such as opsonization, melanization, and antimicrobial activity via Toll pathway activation. In insects, these immune reactions are regulated by proteolytic activity through cascades of Clip-domain containing serine proteases (cSPs) and their non-catalytic homologs (cSPHs), together known as CLIPs. In this study, we developed a functional genetic analysis pipeline to assess the impact of 90 of the 109 annotated CLIPs on hemolymph antimicrobial activity and melanization in Anopheles gambiae mosquitoes. A zone of inhibition assay (ZOI) coupled

with RNAi was used to identify the contribution of CLIPs to hemolymph antimicrobial activity after Micrococcus luteus challenge. We combined this assay with established protocols that assess the contribution of CLIPs to melanization by quantifying melanotic mosquito excreta, allowing us to measure the impact in these two immune responses simultaneously. With this screen, we identified six CLIPs required for, and two CLIPs as inhibitors of antimicrobial activity. Furthermore, we identified 13 CLIPs required for and five CLIPs as inhibitors of melanization, confirming published results and expanding the canon of melanization regulators by seven CLIPs. Among the identified regulators, a single protein (CLIPB10) was required for both melanization and antimicrobial activity, suggesting limited crosstalk between the pathways controlling these immune responses. Importantly, this study demonstrated for the first time that CLIPs are involved in regulating antimicrobial activity in An. gambiae. Together, our results unveil an unprecedented complexity of immune regulation by proteases, suggesting that protease cascades in An. gambiae mosquitoes form a complex regulatory network with little redundancy and distinct sub-networks upstream of individual types of immune responses.

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IMPACT OF ARBOVIRUS INFECTION ON THE HOST-SEEKING BEHAVIOUR OF AEDES AEGYPTI MOSQUITOES

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Vectorial capacity can be defined as the efficiency of a mosquito to transmit a pathogen. It relies on several factors, including vector competence, feeding preference, survival, and host-seeking behaviour of mosquitoes. Arbovirus infection can (in-)directly impact these factors. Previous studies have shown that Aedes aegypti mosquitoes infected with dengue virus increase probing and locomotor behaviour. However, the impact of arbovirus infection on host-seeking behaviour is poorly understood. Earlier work showed that West Nile virus decreases host-seeking behaviour of the Culex pipiens mosquito, but we do not know whether this is a common phenomenon for other interactions among mosquito and arbovirus species. Therefore, the objective of this study was to unravel the effect of alphavirus (chikungunya and Mayaro viruses) and flavivirus (Zika virus) infection on the host-seeking behaviour of Ae. aegypti mosquitoes. To test this, we injected Ae. aegypti mosquitoes with chikungunya, Mayaro and Zika virus and incubated them for 8-10 days. Next, we released these mosquitoes in a one-port olfactometer in our BSL3-facility. After having exposed mosquitoes to human odour cues in this set-up, saliva samples were collected, and infection rates and transmission rates were calculated. In addition, we simultaneously ran a survival experiment, investigated the mosquito's propensity to feed, and evaluated time spent in flight to test effects of arbovirus infection on these parameters as well. Altered vector behaviour can have a major impact on disease transmission risk, and depending on its precise effects, either under- or overestimate the transmission of arboviruses.

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METATRANSCRIPTOMIC APPROACH TO CHARACTERIZE MICROBIOTA AND BLOODMEALS IN ANOPHELES DARLINGI FROM COLOMBIA

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Mosquitoes are holobiont organisms harboring diverse microorganisms which may play a role in host biology. Little is known about the microbial composition of malaria vectors from the Neotropics. The emergence of the next generation sequencing allowed obtaining sequence data from the mosquito, its microbiota and even identify its bloodmeal sources. This study aimed to characterize the bacterial and fungal communities, in addition to bloodmeals in the main malaria vector Anopheles darlingi using a metatranscriptomic approach. The mosquitoes were collected in three malaria endemic regions of Colombia, Bajo Cauca (BC), Pacific (PAC) and Amazon (AM). The An. darlingi were grouped into pools. RNA was extracted and cDNA libraries were prepared. RNA-seq was performed on the Illumina Nova Seq 6000 platform. Sequencing quality was determined with FastQC and host reads were excluded from analysis, contigs were assembled in MetaSPAdes. BLAST against SSU and LSU SILVA database was performed to identify bacteria and fungi, and against vertebrate COI and Cytb database to identify bloodmeal sources. Identification results were confirmed in NCBI non-redundant database. A total of 303 contigs were assigned to bacteria and 29 to fungi. The Proteobacteria (58.09%) and Actinobacteria (16.50%) phyla were the most abundant. Some of the sequences detected include, Moraxella osloensis, Serratia marcescens, Asaia bogorensis, Asaia krungthepensis and Thorsellia anophelis, which have been previously reported in mosquitoes. Regarding the fungi, the Ascomycota and Zoopagomycota phyla were the most abundant. The blood meal analysis identified sequences from Homo sapiens and Canis familiaris with more than 99% of nucleotide identity. These results indicated the utility of the metatranscriptomic approach for identifying the microbiota composition and bloodmeal source in a single assay and the information obtained could be useful in public health.

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CAN THE ANOPHELES FUNESTUS FEEDING RATE IMPROVE ON AN ARTIFICIAL MEMBRANE FEEDING SYSTEM?

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Malaria is the most severe vector-borne disease caused by the Plasmodium parasites and transmitted by Anopheles mosquitoes. Laboratory-reared anophelines are essential to advance research to reduce or eliminate malaria. The success of laboratory rearing as well as studies on parasite-mosquito transmission are advanced by using artificial membrane feeding systems. This will require the optimisation of mosquito feeding which will ensure that an optimal number of mosquitoes feed to maximise research sample sizes available for analysis. In this study, various parameters such as age of the mosquito, duration of starvation, method of starvation, volume of blood meal, duration of feeding, type of artificial membrane and feeding in the light or dark were evaluated to determine their impact on the feeding rate in a main African malaria vector, Anopheles funestus. By optimising the artificial membrane feeding parameters, an increase in the feeding rate of the An. funestus mosquitoes was observed. The results obtained from these parameters increased the feeding rate of the An. funestus above 50%. However, feeding rates were not significantly increased by the mosquito density, the addition of lactic acid to the blood meal, duration of feeding or the volume of blood. Furthermore, this study allows for successful adult feeding during laboratory rearing as well as opens research revenues that are dependent on blood feeding such as transmission-blocking studies, endectocide studies, etc.

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REVEALING FUNCTIONS OF HEMOCYTES AFFECTING PLASMODIUM FALCIPARUM INFECTION IN ANOPHELES GAMBIAE

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Malaria is one of the most devastating human diseases. However, in the last few decades, a significant decrease in the number of cases and deaths has been achieved, largely thanks to strategies focused on vector control. Mosquitoes have an efficient immune system, which protects them

against a variety of pathogens, including Plasmodium. Hemocytes are considered super immune cells because they can eliminate microorganisms through cellular and humoral mechanisms, and they are responsible for the production of several anti-Plasmodial factors. However, most of the research on hemocyte's role in fighting Plasmodium has been conducted using rodent malaria models. In the current research, we studied the function of An. gambiae hemocytes against the human malaria parasite P. falciparum. We found that hemocyte depletion results in a reduction in the number of oocysts in the mosquito midgut. In addition, we observed a high mortality rate of hemocyte-depleted mosquitoes upon infection, which is linked to blood feeding. Interestingly, hemocyte depletion increases the bacterial load in the midgut (microbiota), which, however, is not causing the high mortality. We do observe a loss in the midgut epithelium integrity independent of microbiota upon hemocyte depletion, which could result in uncontrolled cell death. We hypothesized that hemocytes are a key factor in controlling midgut epithelium integrity, which is important for the establishment of infection and development of P. falciparum. Here we present evidence that suggests new roles of hemocytes in the midgut physiology of mosquitoes, that could indirectly impact the permissiveness of mosquitoes to P. falciparum. A better understanding of hemocytes' function in human pathogen infection could allow the development of new strategies for the control of vector-borne diseases by using genetic engineering technologies.

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EFFECT OF SPERMATHECAL PROTEINS ON SPERM SURVIVAL AND FUNCTION IN THE YELLOW FEVER MOSQUITO AEDES AEGYPTI

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As the primary vector of Zika, chikungunya, yellow fever and dengue viruses, the Aedes aegypti mosquito affects the lives and livelihoods of millions globally. Control of these disease vectors is compromised by the increasing prevalence of chemical insecticide resistance. Strategies to replace or reduce populations through release of modified males show promise, but their success relies heavily on a complete understanding of mosquito mating biology. For Ae. aegypti, a successful mating provides females with enough viable sperm for a lifetime of producing offspring. Disruption of the mechanisms of sperm transfer and storage provides a tantalising target for novel mosquito control interventions. Here, we used RNA-seq data to screen for molecules putatively involved in promoting sperm survival and performed functional assays using RNAi-mediate gene silencing and CRISPR-based gene knockouts on the most promising candidates. Analyses of the post mating response showed that disruption of key serine proteases had a major effect on female mating phenotypes.

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NEUROPEPTIDE REGULATION OF FEMALE MATING BEHAVIOR IN AEDES AEGYPTI MOSQUITOES

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Female Aedes aegypti mosquitoes are the primary vectors of human disease-causing viral pathogens throughout the world. Methods to control disease rely on disrupting mosquito mating and reproduction to reduce population size. However, the signaling pathways and neural circuits that regulate female mating behavior in this species remain poorly understood. Female Ae. aegypti generally only mate once. During mating, the male transfers seminal fluid peptides and proteins to the female that act on cognate receptors in the female to suppress her mating receptivity, ensuring she rejects mating attempts from all subsequently-encountered males and only produces offspring from the first male. Our group previously identified a male-derived neuropeptide, Head Peptide I (HP-I), and cognate G protein-coupled receptor, NPY-like Receptor 1 (NPYLR1), capable of enforcing short-term (<24 hours post-mating) mating receptivity suppression. Our work focuses on identifying the cells that express npylr1 and testing the functional necessity and sufficiency of these cells in suppressing mating receptivity at the behavioral level on both short and long timescales. Using a genetic approach, we are anatomically mapping the cells that express npylr1 and determining if constitutively silencing and optogenetically activating these cells is capable of modifying female mating receptivity. The relationship between short-term and lifetime suppression of mating receptivity is poorly understood, and our experiments will provide the first map of female mating circuitry and insight into whether short and long-term changes in mating receptivity utilize shared neural circuits. Understanding the basic mechanisms of mating regulation is critical for creating new mosquito control methods and ensuring the continued efficacy of existing methods.

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EXPLORING NON-CODING RNAS FOR PATHOGEN BLOCKING IN MOSQUITOES

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Mosquitoes are vectors of a variety of pathogens that they transmit to humans via biting, and mosquito-borne diseases threaten more than 40% of the global population. Malaria caused by Plasmodium parasites is transmitted to humans by Anopheles mosquitoes, while Aedes species transmit viral pathogens, such as dengue and zika virus. Due to the lack of vaccines, effective therapies and emerging insecticide resistance, transmission blocking in the mosquito is emerging as a promising additional approach to encounter this threat. Apart from their physical barriers, mosquitoes rely on their innate immune system to confront pathogens. Multiple key players of the immune signaling pathways act as restriction factors during the infection cycles in the mosquito, while some mosquito genes serve as host factors facilitating pathogen infection. The main defenses are orchestrated by signaling pathways which result in various responses including lysis, encapsulation, melanization, phagocytosis and anti-microbial peptide production. Non-coding RNAs (ncRNAs) including the small non-coding RNAs (sncRNAs, <200nt long) such as siRNAs, miRNAs and piwiRNAs and the long-non-coding RNAs (lncRNAs, >200nt long) regulate gene expression, hence adding an extra layer of complexity to vector competence. They may regulate immune defenses against pathogen infection, as indicated by their differential expression upon pathogen infection. LncRNAs in particular regulate many biological processes, with existing evidence for their implication in D. melanogaster antiviral immunity. We have shown that several lncRNAs modulate ZIKV infection and reproduction, and could therefore play roles in regulating immunity-reproduction tradeoffs. In our quest to explore the use of non-coding RNAs for disease control, we have also assessed the potential of small activating RNAs (saRNAs) to augment immune responses to pathogen infection. Non-coding RNAs have not been extensively explored with regards to vector-borne disease control, and we show that they represent useful tools to be harnessed for pathogen transmission blocking strategies of public health significance.

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NEW ASPECTS OF SPOROZOITE AND ANOPHELES SALIVARY GLAND INTERACTIONS

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Here, we investigate the interaction between the Plasmodium parasites and mosquito salivary glands. Using high-resolution label-free proteomics, we compared the salivary gland protein landscape of P. berghei-infected and non-infected Anopheles gambiae, as well as the composition of saliva collected from non-infected and P. berghei- or P. falciparum-infected mosquitoes. In the salivary gland proteome, we found that sporozoite infection upregulated proteins across multiple functional families, including lipid and iron transport, metabolism, and immunity, particularly within the melanization pathway. Interestingly, the melanization of sporozoites inside

the salivary glands has never been reported, suggesting that the parasite evades melanization through an unknown mechanism. Conversely, the saliva proteome showed that sporozoite infection depletes certain groups of proteins, remarkably immune proteins. Using confocal and transmission electron microscopy, we observed that some of these immune proteins are expressed in the salivary gland cells and accumulate on the surface of sporozoite bundles in the gland secretory cavities. Moreover, we observed profound morphological changes in the saliva confined into the infected secretory cavities, which could impact the secretion and activity of salivary gland proteins. Overall, this work sheds light on new aspects of a still poorly understood step in the parasite life cycle.

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ANALYSIS OF THE GENITALIA ROTATION IN THE MALE MOSQUITOES CULEX PIPIENS

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Culex pipiens is a major vector of arbovirus and other human diseases. This species' populations have developed insecticide resistance, necessitating the development of alternate vector control strategies, such as the sterile insect method (SIT). This approach requires an understanding of the physiological factors behind male Culex pipiens sexual development, such as the rotation of their genitalia. The objective of this study was to qualitatively and quantitatively examine genital rotation in male Cx. pipiens, since it is an essential indicator of sexual maturity. The genital rotation rate was significantly affected by temperature variations (either 18°C, 22 °C or 25°C), with the rate increasing as the temperature rose. This research contributes to our understanding of the male biology of Cx. pipiens. Understanding and controlling the pace of sexual maturation in males has implications for the timing of the release of sterile males, which is essential for the sterile insect approach.

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IN SILICO DATA MINING REVEALS IMPRESSIVE DIVERSITY OF ANTIMICROBIAL PEPTIDE-CODING GENES IN MALARIA VECTOR ANOPHELES GAMBIAE

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Malaria remains a major concern in global public health. The extent of malaria worldwide, thelimitations of current control methods, and the urgent need for new chemoprophylactic andchemotherapeutic agents foster the investigation of new drug pipelines that improve or evenreplace current treatment strategies. Antimicrobial peptides (AMPs) have shown to be promisingcandidates to target malaria parasites due to broad diversity of mechanisms of action, plasticity totune activity through amino acid substitutions and the existence of distinct methods for generatinga diverse range of analogs. AMPs can also be envisioned to target parasites within mosquito hosts.Upon Plasmodium infection, dozens of host effectors are recruited to inactivate parasites,including different families of naturally encoded AMPs. Although a few classes have beendescribed to inhibit sporogonic stages of Plasmodium in mosquitoes, our understanding of themolecular diversity and function of AMPs in the major malaria vector An. gambiae is largelylacking. We have initiated a study on the discovery of novel mosquito AMPs through acomprehensive in silico survey. Data mining on publicly available An. gambiae genome revealedan impressive diversity of over 30 potential novel gene-encoded AMPs, including at least 8multigenic families. Spatial-temporal transcript distribution was analyzed by qPCR in distinctmosquito tissues and developmental stages, along with their response to bacterial stimuli and to P.falciparum infection. Additionally, the participation of AMPs during parasite infection wasstudied in vivo by RNAi-mediated gene silencing. To reveal their biological functions, 12 peptideswere selected for in vitro activity testing against a panel of bacteria, fungi, viruses, and distinctPlasmodium stages. The discovery of new classes of AMPs was further supported by theidentification of ortholog genes in at least 5 mosquito species. Our study provides the first steptowards the expansion of AMP repertoire in medically relevant mosquito species and paves theway for the development of novel strategies to mitigate the impact of vector-borne diseases.

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IDENTIFICATION OF METABOLOMIC PROFILE OF MOSQUITOES ANOPHELES SPECIES DIET BY ULTRA HIGH PERFORMANCE LIQUID CHROMATOGRAPHY MASS SPECTROMETRY TECHNIQUE IN LIMA PERU

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Malaria is an infectious disease transmitted by mosquito vectors of the family Culicidae of the genus Anopheles. The mosquitoes need a source of nutrients such as carbohydrates, lipids, amino acids to develop physiological activities like parity, longevity, survival and vectorial capacity. The mosquito's crop is part of the digestive system, which plays an important role as a reserve prior to the digestion of consumed sugars. In Peru, the research about the nectarivores diet is limited and does not exist data about the metabolomic profile of the Anophelines species by Ultra High Performance Liquid Chromatography Mass Spectrometry which can separate chemical compounds and identify metabolites with high sensitivity, resolution and accuracy. The aim of the study was to identify and create a metabolomic database of the mosquitoes Anopheles species' diet. The samples were mosquitoes' crop of An. pseudopunctipennis collected in the field, and crops of the bioassay's mosquitoes exposed in a cage to five plants which were Bidens alba, Ludwigia octovalvis, Ludwigia peploides, Bougainvillea spectabilis and Lonicera japónica collected in the field too. Other samples used to compare metabolomic profile and quality control were methanolic extracts of the five plants and internal standards of sugars; the metabolomic profile of the mosquito's crops were analyzed by UHPLC MS technique. The data analysis was performed with the software and libraries MZmine 2.51, Xcalibur 3.1, XCMS 3.7.1., Rstudio 4.2.0, and Metaboanalyst 5.0, HMDB, GNPS and Metlin database. The results obtained show that there is a relationship between the plants' compounds and those found in the mosquito´s crop. Some compounds found were sugars such as glucose, fructose, sucrose, trehalose, cerelose, D-manitol, 10 amino acids, 6 pesticides, 11 lipids, and other compounds. The results will contribute to better understand the feeding ecology of mosquitoes and on the future design more efficient traps based on the sugar preferences of the local mosquitoes' populations for vector control and the secondary metabolites will allow to study metabolism pathways and resistance to pesticides.

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DETERMINANTS OF AEDES AEGYPTI AND CULEX SPECIES LANDING RATES IN NORTHERN ESMERALDAS PROVINCE, ECUADOR: HUMAN LANDING CATCH STUDY JUNE 2021 - JULY 2022

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Mosquitoes vector several infectious diseases; ascertaining what contributes to their biting patterns in distinct contexts enables us to tailor public health interventions. The human landing catch method approximates per-person-time biting rates of mosquitoes and provides a low-cost method to quantify patterns in mosquito behaviour. We aimed to establish the human landing patterns of mosquitoes in a peridomestic context in northern Ecuador and to explore their variability across the year in two communities. Starting in June of 2021, mosquitoes were collected during three-hour periods, thrice daily for five consecutive days each month. Collections occurred in two communities - one smaller, riverine community with less infrastructure (Santa María), while the other had a larger population and

serves as a regional hub for commerce and travel (Borbón). Two collections (one in a semi-enclosed setting and another in an unenclosed setting) were done in each community simultaneously. The semi-enclosed setting used netting to simulate being within a dwelling, while the unenclosed setting was outside but still near a dwelling. We also assessed several environmental variables: temperature, humidity, wind speed, and rainfall. Of the total mosquitoes (n = 18,408), 17,525 (95%) were of the genus Culex, and 354 (2%) were Aedes aegypti. More total mosquitoes were found in Santa María (16,723 or 94%), which was driven by Cx. spp., with 16,691 Cx. mosquitoes collected there. Ae. aegypti preferred Borbón, with 91% (322) of all Ae. aegypti there. There were statistically significant temporal and environmental preferences for both Cx. and Ae. aegypti in Borbón, with Cx. being crepuscular and Ae. aegypti landing throughout the day, and both have distinguishable temperature and humidity variations. Temporal preferences for Cx. spp. do not differ by community; however, insufficient Ae. aegypti were captured in Santa Maria to compare. The differences in mosquito behaviour are relevant in the context of climate change and vector-control programming. Capturing the heterogeneity across diverse communities can inform site-specific interventions.

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MALARIA VECTOR BIONOMICS AND PHENOTYPIC RESISTANCE STATUS TO INSECTICIDES USED IN VECTOR CONTROL IN NDOLA DISTRICT, ZAMBIA

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Malaria is one of the main causes of morbidity and mortality in Zambia contributing to 1.4% of the global burden. LLINs and and IRS are the main malaria elimination strategy. However, the success of vector control is dependent on a good understanding of the bionomics and susceptibility status of the local vectors. Thus, this study aimed at assessing the bionomics and susceptibility status of the local malaria vectors. This study was conducted in Ndola district from July 2021 to October 2021. Mosquito collection was done using CDC - light traps, PSC, Aspiration and Larval Collection. Anopheline mosquitoes collected were morphologically identified and confirmation of malaria vectors was done using PCR. Data analysis was done using Williams's mean for mosquito densities; Kruskall Wallis H test used to compare the distribution of mosquitoes. A negative binomial was used to determine predictors affecting mosquito counts; insecticide resistance testing was done was done using WHO tube and CDC bottle bioassay. The malaria vectors identified were Anopheles funestus s.s and An. gambiae s.s. Anopheles funestus was the predominant malaria vector and exhibited a homogeneous distribution (X2 = 4.717, P>0.05). An. gambiae was found to be highly endophilic and anthrophilic. An. funestus s.s and An. gambiae s.s seeking a blood meal in the urban areas was at least 2.24 and 9 times more respectively in the urban sites than in the rural sites. Indoor resting density of An. funestus s.s in rural site was 1.67 times more than in the urban sites and the indoor resting density of An. gambiae s.s in the urban site was 262 times more than in the rural site. Main breeding sites identified were irrigation trenches (4.67 larvae/dip) and garden ponds (2.72 larvae/dip). Sprayed houses were significantly associated with reduced mosquito numbers (B = -0.956, IRR = 0.384, P < 0.05. An. gambiae s.s was fully susceptible to organophosphates and neonicotinoids but highly resistant to pyrethroids, carbamates and organochlorines. Lastly, the two main vectors in Ndola vary in bionomics and insecticide susceptibility and recommend that control measures must be tailored to these findings.

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A DIGITAL QUESTION-BASED ENTOMOLOGICAL SURVEILLANCE PLANNING TOOL INCREASES KNOWLEDGE ACQUISITION AND SELF-EFFICACY IN USERS

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Stalled progress in malaria control across Africa underscores the need to focus on gaps in protection so that programs can tailor vector control to local drivers of transmission. A paper-based Entomological Surveillance Planning Tool (ESPT) was developed in 2018 to distil normative guidance into an operational decision-support tool to enable cost effective, locally tailored, and evidence-based vector control. Currently, an electronic version of the ESPT (known as eSPT) is being developed to improve access, uptake and use of the paper-based ESPT. To inform its further development, the eSPT's contribution towards question-based entomological surveillance planning was evaluated through exploring knowledge acquisition and retention, and technology acceptability. The evaluation workshops were conducted with target users in Ethiopia and Malawi, with further evaluations currently underway in Mozambique. These users included entomologists and decision-makers from government, and partner institutions in vector-borne disease control. A mixed-methods, uncontrolled, before and after study investigated the impact of the eSPT on knowledge, attitudes, and work practices related to entomological surveillance planning. The evaluation workshops in Ethiopia and Malawi showed that the eSPT significantly increased participants' entomological knowledge acquisition (p = 0.044), and self-efficacy to develop entomological surveillance plans (p = 0.001). These results reveal that the eSPT improves users' entomological knowledge acquisition and self-efficacy to develop entomological surveillance plans.

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FIRST DETECTION OF ANOPHELES STEPHENSI IN ACCRA, GHANA, USING MOLECULAR SURVEILLANCE

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The invasive Anopheles stephensi is rapidly expanding its range in Africa. It was first detected in the horn of Africa but has now spread to many countries in east Africa and subsequently detected in West Africa in Nigeria. Through ongoing studies on urban malaria transmission in Accra, where Anopheles mosquitoes were seen breeding in polluted and unfamiliar habitats including car tyres in sympatry with Aedes mosquitoes, we set up surveillance for An. stephensi in the city of Accra, Ghana. Larval collections were done in and around human habitations in 17 urban and 3 peri-urban sites. Urban sites included sites that were closer to the Kotoka International Airport and the Tema seaport. Larvae were raised into adults and identified morphologically. PCR was done on suspected An. stephensi samples that could not be fully morphologically identified. PCR unamplified samples were sent for sequencing of the ITS2 region. Sequencing revealed some of the unamplified samples from two different areas of Accra to be An. stephensi. The other samples turned out to be An. coluzzii and An. pretoriensis. More

samples are being screened by PCR and subsequently by sequencing. The malaria situation in the areas with An. stephensi will be discussed. This study confirms the rapid expansion of the invasive An. stephensi in Africa. Increased surveillance to understand the extent of the spread of this vector is important to inform vector control measures for An. stephensi.

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ANOPHELES STEPHENSI - SIGNIFICANCE OF ITS UBIQUITOUS PRESENCE IN URBAN AND RURAL SETTINGS; IMPACT ON VECTOR CONTROL AND MALARIA ELIMINATION IN INDIA

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Anopheles stephensi is the primary vector of urban malaria and has been widely incriminated in metropolitan cities in India with the detection of gland and gut infections. The vector breeds in clear water habitats such as overhead tanks, wells, cisterns, barrels/drums, sumps (underground tanks), roof gutters, curing pits in construction sites, fountains, ornamental tanks and also in lesser examined rain-fed habitats. An. stephensi breeds and co-exists with other disease vectors like Aedes aegypti in water storage containers and is a risk if vector control operations are targeted disease-specific. The increasing urban agglomeration of human populations and inadequacy in protected piped water supplies necessitates an increase in water storage containers, consequently increasing the breeding potential of An. stephensi which has a longer flight range and maintains a high degree of contact with the human population. So even at low densities, it can transmit infection and with high population density in urban areas, the chances of being bitten are comparatively high. The adult vectors in urban areas predominantly rest in cattle sheds with close proximity to human dwellings. In recent years, the vector has been observed predominantly in rural areas in India owing to the increase in water storage containers and have outnumbered the earlier known malaria vectors. Hence, An. stephensi is not only a problem to urban areas but also a threat to rural settings. Considering the invasive nature of the vector in African countries and WHO cautioning to many other countries, its presence in rural settings in India along with the existing vectors would delay the progress of elimination and warrants effective surveillance mechanism to control the spread of the vector.

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FOREST COVER AND THE DYNAMICS OF PEAK BITING TIME OF INFECTED NYSSORHYNCHUS DARLINGI IN RURAL COMMUNITIES OF THE BRAZILIAN AMAZON

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Deforestation, changes in land use, availability of blood-meal hosts, and human mobility are major drivers of malaria risk. Environmental changes can influence the peak biting time of Nyssorhynchus darlingi. This study aimed to test the effect of forest cover percentage on the peak biting time of infected Ny. darlingi females in Amazonian rural communities where malaria transmission is continuous with API (> 30). Human landing catch (HLC) was performed outdoors from 18:00 to 00:00 h, in the peridomestic environment of 78 houses, and Shannon traps with HLC in the forest fringe, in 12 municipalities of Acre, Amazonas, Pará, and Rondônia states, amounting to 942 collections hours. Deforestation was measured as the percentage of forest cover, the sum of forest edges, and the distance of each house from the drainage network in each location sampled. A generalized linear mixed (GLM) model was employed to examine the association between forest cover and peak biting time of infected Ny. darlingi. In total, 11,810 Ny. darlingi females were tested for Plasmodium, 110 were infected in peridomestic and 3 in forest fringe (81 with P. vivax and 32 with P. falciparum). The GLM model showed a significant positive association between infected females and landscapes with 25% ¬ 45% forest cover percentage at 21:00-22:00 h and 22:00-23:00 h, whereas in those with forest cover percentage > 75% the peak occurred at 18:00-19:00 and 19:00-20:00 h. We showed that deforestation can affect the peak biting time of Ny. darlingi females infected with P. vivax and P. falciparum. These results provide new insights into the variation observed in the peak biting time of Ny. darlingi across multiple anthropogenic landscapes in the Brazilian Amazon.

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IMPACT OF NEW GENERATION INSECTICIDE TREATED NETS AND INDOOR RESIDUAL SPRAYING ON ENTOMOLOGICAL INDICATORS OF MALARIA TRANSMISSION IN RWANDA

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Insecticide treated nets (ITNs) and indoor residual spraying (IRS) are the core malaria control interventions in Rwanda. However, since 2013, widespread resistance to insecticides has been reported threatening the effectiveness of these vector control interventions in Rwanda. As part of the insecticide resistant management strategy, Rwanda introduced the use of non-pyrethroid insecticides in 2017 for IRS and new generation nets in 2020, following a stratified map of interventions, endemicity of malaria and insecticide resistance. IRS with Actellic 300CS was implemented in Ngoma district, Karongi district received interceptor G2 (IG2) nets and Kicukiro district received piperonyl butoxide (PBO). Entomological indicators of malaria transmission that included sporozoite infection rate (SIR), entomological inoculation rate (EIR) and vector composition was monitored, one year before (2019) and two years after (2020-2021) the deployment of these interventions. The SIR before and after the deployment of interventions were 0.2% vs 0% in Ngoma district (IRS),1.2% vs 0.7% in Karongi district (IG2 nets), 1.05% vs 0.1% in Kicukiro (PBO nets), respectively. The EIR per person per year before and after the deployment of intervention was 5.47 vs 0 in Ngoma (IRS), 3.94 vs 2.04 in Karongi (IG2 net) and 19.16 vs 1.97 in Kicukiro district (PBO net), respectively. Prior to the interventions the predominant species was An. gambiae sensu stricto (s.s.), making up to 75.4%, 90.4%, and 94.8% of the An. gambiae complex, in Ngoma, Karongi and Kicukiro districts, respectively. After the interventions, the proportion of An. gambiae s.s. dropped drastically to 3.9%, 56.9%, and 58.8% in Ngoma, Karongi and Kicukiro, respectively. The deployment of IRS and new nets decreased the SIR and EIR in all sites. These changes were also accompanied by a shift in vector species composition from An. gambiae s.s. to An. arabiensis, with the highest shift occurring in Ngoma (IRS).

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ASSOCIATION BETWEEN LANDCOVER CHARACTERISTICS AND AQUATIC HABITATS OF THE MALARIA VECTORS, ANOPHELES FUNESTUS DURING THE DRY SEASON

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Anopheles funestus can sustain malaria transmission during the dry season due to its use of larger and more permanent aquatic habitats. Ability to predict where An. funestus larval are most likely to occur during the dry season would facilitate their targeting by larval control. Here we investigated the land use and environmental factors associated with An.

funestus breeding in the dry season and used results to develop a habitat suitability models for predicting the distribution of An. funestus habitats in southern Tanzania. A systematic survey was conducted in 19 villages in the dry season to identify all water bodies and test for An. funestus larvae. Water bodies were characterized based on type, size, and the presence of emergent vegetation. Multiple logistic models were used to associate the proportion of different landcover types within 300m, physical characteristics of habitats and the presence of An. funestus. Significant predictors of An. funestus habitats were used to develop a habitat suitability model for this species in the dry season. Thirty percent of 1466 aquatic habitats surveyed had An. funestus larvae: majority being streams (73%), large ponds (15%), and human created habitats (5.5%). Anopheles funestus habitats were characterized by permanent clear water, slow moving with emergent vegetation. The proportion of forest within 300m buffer was the most important land use predictor of An. funestus occurrence (positive association). Conversely, the proportion of built area within 300m was negatively associated with An. funestus presence. Other terrain variables including elevation and slope were retained in the model but had lower relative importance. The suitability of An. funestus aquatic habitats across the study area was predicted to vary between 0.22-0.82 with the accuracy of 83%. The results suggest that in the dry season, An. funestus larvae are most likely to be found in aquatic habitats, often under trees, and permanent clear water. The habitat suitability map generated from these criteria could be useful to prioritize where larval control should be targeted in the dry season of southern Tanzania.

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THE IMPACT OF POLARIZED LIGHT AND PHYSICAL-CHEMICAL WATER BODIES PARAMETERS ON OVIPOSITION SITE SELECTION IN ANOPHELINE MOSQUITOES

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It is vital to comprehend oviposition site selection to strengthen vector control strategies, such as larval source management. The detection of water during the oviposition still needs to be better understood. Although some aquatic mosquitoes use horizontally polarized light and chemical cues to detect potential breeding sites to lay their eggs, their roles in Anophelines mosquitoes remain unclear. This study aims to better understand Anopheline oviposition behavior and the environment by analyzing chemical-physical properties and light polarization in water surfaces. We sampled 115 breeding sites across Lima, Peru, between 2020 and 2021. We used an in vivo and in vitro quantitative analysis of the physical-chemical parameters of water samples from breeding sites. In the field, we used a camera with a lens multiple wavelength polarized filter to recreate the mosquito vision. We then run a statistical analysis for the statistics of water physical-chemical parameters and polarized light patterns.Our findings align with recent studies that suggest the spread of mosquitoes in uninhabited areas and the survival of larvae in polluted breeding sites. According to the results, some chemicals, such as total dissolved solids, pH, alkalinity, phosphate, and nitrate, significantly impacted larval abundance. While there was not enough evidence to imply the positive role of the polarization effect on oviposition site selection, larval density and pH showed significance when captured by the circularly polarized light. These findings suggest a constrained polarotaxis, which could critically affect mosquito egg-laying and repellent studies.

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EFFECTS OF INSEMINATION AND BLOOD-FEEDING ON LOCOMOTOR ACTIVITY OF WILD-DERIVED FEMALES OF THE MALARIA MOSQUITO ANOPHELES COLUZZII

Behavioural shifts in the canonical location and timing of biting have been reported in natural populations of anopheline malaria vectors following the implementation of insecticide-based indoor vector control interventions. These modifications increase the likelihood of human-vector contact and allow mosquitoes to avoidinsecticides, both conditions being favourable to residual transmission of the malarial parasites. The biting behaviour of mosquitoes follows rhythms that are under the control of biological clocks and environmental conditions, modulated by physiological states. In this work we explore modifications of spontaneous locomotor activity expressed by mosquitoes in different physiological states to highlight phenotypic variability associated to circadian control that may contribute to explain residual transmission in the field. The F10 generation progeny of field-collected Anopheles coluzzii from southwestern Burkina Faso was tested using an automated recording apparatus (Locomotor Activity Monitor, TriKinetics Inc.) under LD 12:12 or DD light regimens in laboratory-controlled conditions. Activity recordings of each test were carried out for a week with 6-day-old females belonging to four experimental treatments, representing factorial combinations of two physiological variables: insemination status (virgin vs inseminated) and gonotrophic status (glucose fed vs blood fed). Chronobiological features of rhythmicity in locomotor activity were explored using periodograms, diversity indices, andgeneralized linear mixed modelling. The average strength of activity, onset of activity, and acrophase were modulated by both nutritional and insemination status as well as by the light regimen. Inseminated females showed a significant excess of arrhythmic activity under DD. When rhythmicity was observed in DD, females displayed sustained activity also during the subjective day. Insemination and gonotrophic status influence the underlying light and circadian control of chronobiological features of locomotor activity. Overrepresentation of arrhythmic chronotypes as well as the sustained activity of inseminated females during the subjective day under DD conditions suggests potential activity of natural populations of A. coluzzii during daytime under dim conditions, with implications for residual transmission of malarial parasites.

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EXPOSURE TO MALARIA VECTOR BITES IN RELATION TO HUMAN SLEEPING PATTERNS IN RURAL MALAWI

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Many primary malaria vector species commonly bite people indoors at night. Insecticide-treated bednets (ITNs) exploit this behavior to protect individuals while asleep. However, mosquito behaviors such as increased outdoor biting may result in gaps in protection for ITN users. Likewise, human outdoor activity during late evening or early morning can result in exposure to mosquito bites and malaria risk. We assessed people's sleeping and waking up time and location in relation to mosquito biting profiles to quantify exposure to malaria vectors and malaria risk. Human host-seeking mosquitoes were sampled using the human landing catch technique. From September 2020 through February 2021, mosquitoes were collected every hour from 6pm to 10am both indoors and outdoors at study sites in two rural districts of southern Malawi. A questionnaire was also administered to household heads to record self-reported sleeping and waking up times. A total of 1,501 Anopheles mosquitoes were collected consisting of 80% An. gambiae s.l. (13% indoors and 67% outdoors), 14% An. funestus s.l. (10% indoors and 4% outdoors) and 6% other anopheline species (6 indoors and 80 outdoors). The majority of participants (84%, n=26,672) reported going to sleep within an hour or two after sunset, between 6-8PM. In contrast, 16% of participants reported being awake during the same period during which 4% of vectors were caught biting. Likewise, 49% (n=26,674) of respondents woke up at sunrise or within an hour after sunrise (5-6AM), followed by 44% (n=26,674) who woke up one to three hours after sunrise (6-8AM). During the same periods, 21% of vectors were caught biting. We conclude that while a good proportion of study participants reported being indoors when 75% (n=1126) of mosquito bites took place, 25% (n=375) of bites occurred when nearly 93% of people

were already awake and thus potentially exposed to bites. The results suggest that many people were either outdoors, or not under an ITN while Anopheles vectors were biting. Thus, risk of malaria could be lowered by using personal protection while outdoors or indoors outside an ITN, particularly in the evening and early morning hours.

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NON-RESIDENTIAL SPACES AROUND HOUSES ARE IMPORTANT SOURCES OF AEDES AEGYPTI MOSQUITO VECTORS IN WESTERN AND COASTAL KENYA

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Aedes aegypti is an important vector of dengue, Zika and chikungunya and other arboviruses. Non-residential spaces close to human dwellings are rarely targeted during vector control activities due to the endophilic and anthropophilic behavior of this vector. The current study assessed the importance of non-residential spaces in production of Ae. aegypti in two cities in Kenya: Ukunda (coastal Kenya) and Kisumu (Western Kenya). The two study sites were divided into eight 200x200 meter zones. Mosquitos were collected in each of the zones using BG traps and Prokopack aspirators from October 2020 through January 2022. Trapping by BG traps was done once every two months in each of the 8 zones per study site. Prokopack was done monthly in each of the 8 zones per study site. In total, 2,887 and 4,148 Ae. aegypti mosquitoes were collected by BG traps and Prokopack, respectively. BG traps collected significantly more Ae. aegypti mosquitoes in non-residential spaces (P<0.0001) compared to residential spaces. Prokopack collected significantly more mosquitoes in residential spaces (P<0.0007) compared to non-residential spaces. In residential spaces and for both traps, abundance of Ae. aegypti mosquitoes was positively associated with houses with higher number of rooms (>8) and negatively with houses with surrounding vegetation. The number of Ae. aegypti mosquitoes trapped by Prokopack were negatively associated with having a cemented floor and absence of domestic animals. BG traps placed in yard shops and gardens trapped significantly more mosquitoes compared to uninhabited houses. In Prokopack traps, presence of trees was positively associated with abundance of Ae. aegypti mosquitoes while presence of short grass and wet drainage channel were negatively associated mosquitoes in the non-residential spaces. Our results indicate substantial contribution of non-residential spaces to Ae. aegypti mosquito abundance. Presence of vegetation and the type of non-residential spaces influences mosquito abundance. Non-residential spaces near human dwellings are important targets for vector suppression interventions.

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ENTOMOLOGICAL SURVEILLANCE AND COMMUNITY KNOWLEDGE ON MOSQUITOES AND DENGUE RISK IN THE GALAPAGOS ISLANDS, ECUADOR

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Spread by the Aedes aegypti mosquito, dengue presents an ongoing threat to community health, even in places like Ecuador's Galapagos Islands, located 1,000 km west of the mainland. Known for their unique biodiversity and Darwin´s theory of evolution, Galapagos has a population of over 30,000 people distributed in 5 islands, two of which (Santa Cruz and San Cristobal) are endemic for dengue fever. Dengue cases are reported almost every year with the first significant outbreak occurring in San Cristobal in 2010 and since then, smaller outbreaks approximately every five years. Here, we report results from a mixed-methods study with entomological surveillance and qualitative research through KAP related to the mosquito and dengue. BG-sentinel traps and Prokopack aspirators were used to collect mosquitoes in and around houses in 2017 and 2018. A total of 1,929 adult and immature mosquitoes were collected from 419 houses in Santa Cruz, San Cristobal, Isabela, and Floreana islands. Of these, 532 specimens (27.6%) were identified as Ae. aegypti which was found in all collection periods revealing its year-long presence and in 121 of 419 (28.9%) of surveyed residences. Although not found in Floreana, Ae. aegypti was confirmed on Isabela, indicating its recent expansion to this island; a subsequent first dengue outbreak on Isabela was reported in 2020. Five focus group discussions with a total of 41 participants revealed that residents know about dengue and understand its transmission by mosquitoes, but they did not consider it as an important health threat, despite 65 dengue cases were notified in the 2017-2018 period and increased to 205 cases between 2020-2021 during the COVID-19 pandemic. Vector control efforts by governmental agencies are sporadic and often ineffective. Abatization and mosquito control is done at blind and thus most likely increase insecticide resistance in local mosquito populations, which needs urgent investigation. Establishment of a year-long mosquito surveillance program with community involvement may help to prevent dengue or other vector-borne diseases in the Galapagos in the future.

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DEFINING THE CONTRIBUTION OF COMPLEMENTAL MALARIA VECTOR ANOPHELES COUSTANI S.L. TO PLASMODIUM FALCIPARUM SPOROZOITE INFECTION IN A HIGHLY ENDEMIC REGION IN UGANDA.

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Entomological surveillance and assessment of the impact of vector control interventions, targets primary malaria vectors; Anopheles gambiae s.s, An. arabiensis, An. funestus and an. coluzzii. Rarely is the contribution of secondary malaria vectors examined. This study aimed to underscore the role of An. coustani s.l. in Plasmodium falciparum sporozoite infection in Adjumani district, a highly endemic area. Mosquitoes were collected for 21 months (May 2021-January 2023) indoors using CDC light traps (CDC LT) and pyrethrum spray collections (PSC). Additionally, the human baited double net (HBDN) method was used for indoor and outdoor catches. Overall, 58,351 mosquitoes were collected. Of these, 21.8% (12,741/58351) were An. gambiae s.l; 69.2% (40,387/58351) were An. funestus s.l and 9% (5223/58351) were An. coustani s.l. CDC light traps, PSC and HBDN accounted for 74.5%, 23.8% and 1.6% of all collections respectively. Whilst, CDC LT collected significantly more An. funestus s.l (31,419 vs 8,773, CI: 0.006-0.0035, P=0.006) compared to PSC; An. coustani s.l. accounted for 61% of all HBDN collections with similar proportions to An. gambiae s.l in PSC (18.9% vs 18.1%). An. coustani constituted 72.4% (indoor) and 61.3% (outdoor) of HBDN collections. A subset of indoor catches including An. gambiae s.l. at 30% (1545/5085), An. funestus s.l. at 40% (2019/5085) and An. coustani s.l. at 30% (1521/5085) were examined for P. falciparum sporozoites. Overall, the sporozoite infection rates were 1.9% in An. gambiae s.l, 1.5% in An. funestus s.l and 0.1% in An. coustani. However, evaluation of monthly sporozoite rates showed that in December 2021, An. coustani s.l. sporozoite rate (0.18%) was higher (not significant) than that of An. funestus s.l (0.0%). In February 2022, the An. coustani sporozoite rate (0.2%) was higher than An. gambiae s.l (0%) though not statistically significant. Of note, the contribution of An. coustani as a malaria vector exhibiting both indoor and outdoor biting may be underestimated. The requisite for understanding the contribution of this species to outdoor malaria transmission remains relevant.

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CHARACTERIZATION OF MOSQUITO BITE EXPOSURE IN HUMAN USING NOVEL BITE DIARY APP AS A NEW PARADIGM LINKING SOCIO-ENVIRONMENT AND MOSQUITO-BORNE DISEASE TRANSMISSION

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Mosquito-borne diseases are an increasing threat to global public health. Despite the key role that human-mosquito contact rates lay in driving mosquito-borne disease transmission, disease risk has been primarily studied through the lens of mosquito abundance and overlooks human-mosquito contact dynamics. As a result, we continue to have a limited understanding on how human-mosquito contact rates are influenced by socio-environmental and human behavioral factors that drive mosquito-borne disease transmission. To fill this gap, we used a novel mobile-app based bite survey instrument (Bite Diary) to characterize and quantify human exposure to mosquito bites in Florida. Research participants initially participated in a workshop to learn about the research project, mosquitoes, and mosquito-borne diseases. They then monitored mosquito bites they may receive in their normal daily lives for a period of seven days, and entered any bite-associated data in the Bite Diary app in a real-time fashion. They also participated in an online survey at the end of the bite monitoring period to provide data related to demography, knowledge, attitude and practice. Our study showed that bite exposure was highly heterogeneity with a small portion of participants experienced relatively higher number of mosquito bites than others. The bite exposure rate was influenced by human behaviors such as outdoor activity level, as well as environmental factors such as weather conditions associated with season. We also investigated relationship among mosquito bite reaction, bite tolerance, protective behavior (e.g., repellent usage), and the reported bite exposure rate. We emphasize the practicality of using surveys to investigate human-mosquito contact rate in relation to human behaviors, and the importance of a model-driven study design that produces field-quantified parameters which can be readily applied in mathematical models. Our focus on human-mosquito contact dynamics contributes new insights into the mechanisms behind mosquito-borne disease spread and emergence, and guides future research directions to inform disease prevention and control.

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DEVELOPMENT OF SEMI-AUTOMATED SYSTEMS TO GENERATE MOSQUITOES FOR VECTOR-BORNE DISEASE RESEARCH

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Malaria is a global health burden that is caused by the Plasmodium parasite and is spread by Anopheles mosquitoes. In order to comprehensively study malaria, live mosquitoes are needed. Obtaining and handling mosquitoes precisely and safely using traditional methods is laborious and time consuming and does not meet current research needs. We have developed several devices that partially automate the rearing and handling of Anopheles stephensi mosquitoes, including separating pupae from larvae and aspirating female mosquitoes. Our insectary raises approximately 50,000 mosquitoes a week, which requires rearing in over 100 pans where the pupae are separated from larvae daily before the pupae emerge into adult mosquitoes. To streamline this process, we developed the Pupation Station, which is a semi-autonomous system that aids in the daily draining and separation of larvae and pupae. It consists of an array of 6 large aluminum pans with fixed electronically actuated values that aid in the draining and filling of the pans. It simplifies the larva rearing process, reduces physical taxation, increases consistency, and maximizes mosquito yields compared to manual methods, reducing the amount of time needed for the separation process by 66%. Once adult mosquitoes emerge, females need to be separated from males as only females blood feed and transmit the Plasmodium parasite. We have developed an Automatic Aspirator to transfer mosquitoes between cartons, replacing the need for a traditional mouth aspirator. Together, these systems have increased the robustness, reproducibility, and efficiency of mosquito rearing. We anticipate that they could be extended to other mosquito species and scaled to other laboratory or manufacturing settings to enhance vector-borne disease research.

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VECTOR PROFILES AND RISK FACTORS AMONG EARLY EVENING VERSUS OVERNIGHT MOSQUITO COLLECTIONS IN THE HIGH MALARIA TRANSMISSION SETTING OF NCHELENGE DISTRICT, ZAMBIA

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Communities in Nchelenge District, Zambia experience intense residual malaria transmission despite existing interventions such as indoor residual spraying (IRS), bed net distribution, and integrated community case management. To further understand exposure to vectors capable of transmitting malaria parasites, mosquitoes foraging in 24 households were captured between the hours of 16:00-22:00 and 22:00-06:00 during two weeks of August 2019, resulting in 1048 female anophelines captured indoors including Anopheles funestus (94%), An. gambiae (2%), and other understudied anophelines (4%). Differences in mosquito counts in the early evening (N=466) versus overnight hours (N=582) were not statistically significant, and a more diverse population of mosquitoes was captured in the early evening hours. DNA from mammalian hosts was detected and the human blood index (HBI) of blooded anophelines was 97.1%. Plasmodium falciparum-specific CSP proteins were detected within anopheline head/thoraxes, revealing almost 2% (N=18) of the collected An. funestus (N=17) and An. gambiae (N=1) harbored sporozoites. Data from household surveys including household structural characteristics and intervention coverage suggest greater anopheline abundances in homes made with natural materials rather than manufactured products or finished structures, and more mosquitoes were found in homes with less IRS and bed net coverage. These studies suggest exposure to vectors occurs in both the early evening hours, when residents are not protected by bed net barriers, and overnight, with some mosquitoes actively feeding on humans and harboring infectious parasites. Given these results, further investigation into the settings where malaria transmission may occur, the magnitude of indoor biting, and how to refine methods of prevention in Nchelenge is warranted.

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ANTIBODY RESPONSE TO AEDES SPP. MOSQUITO SALIVARY PROTEINS AS A MARKER FOR EXPOSURE: A SYSTEMATIC REVIEW AND POOLED ANALYSIS

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Arboviruses, especially those transmitted by Aedes spp. mosquitoes, are responsible for a massive global burden of disease in humans. Additionally, hypersensitive/allergic humans can suffer from debilitating symptoms upon bite exposure. As current methods can be costly and cumbersome, more efficient mosquito surveillance, which can accurately examine bite exposure (and possible arbovirus exposure), is needed. One such promising alternative is the use of ELISA technology to quantitatively measure exposure to mosquito bite. Using PRISMA guidelines, a systematic review

and pooled analysis were performed to assess the efficacy of detection of human antibody response to mosquito salivary proteins as presented in the literature. A total of 1353 studies were screened by two reviewers; 99 articles were included in the qualitative synthesis. The pooled analysis included 20 papers that met our inclusion criteria, provided individual level human IgG response to MSP via ELISA, and explicitly stated how OD scores were reported. We assessed how subject age, Aedes spp. mosquito, antigen type, collection season, population level of mosquito exposure, Köppen-Geiger climate, and OD reporting method impact OD values in separate univariate analyses as well as a multivariate analysis. Furthermore, five studies from the pooled analysis included individual level IgG response data to endemic and non-endemic Aedes spp.; these underwent receiver operator curve (ROC) analysis. We found that OD values correlated positively with antigen complexity, population level of mosquito exposure, and wherein climates permitted year-round mosquito activity. The area under the curves from the ROC analysis indicate that there is a distinct signature for human exposure to endemic versus non-endemic Aedes spp. While there is considerable variation between studies (ICC=0.12), using human IgG holds promise in complimenting more traditional mosquito surveillance methods as a proxy for individual and population exposure to Aedes spp. mosquitos.

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INVESTIGATION OF MEDICALLY IMPORTANT ARBOVIRUSES AND INSECT-SPECIFIC VIRUSES IN THE SYLVATIC AND URBAN VECTORS OF YELLOW FEVER VIRUS COLLECTED IN THE BRAZILIAN AMAZON

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Culicids are important vectors and viral reservoirs of arthropod-borne viruses and insect-specific viruses (ISVs), respectively. Mosquitoes of the genera Aedes, Sabethes, and Haemagogus comprise species of great epidemiological relevance since they are involved as vectors in transmission cycles of arboviruses, such as yellow fever. From May 2021 to June 2022, mosquito collections were carried out at the Adolpho Ducke Forest reserve bordering Manaus, Amazonas state, Brazil. Mosquitoes morphologically identified as species of Aedes, Sabethes, and Haemagogus genera are being investigated in this work. So far, 284 pools from the Haemagogus genus and 26 pools from the Aedes genus have been macerated, and the supernatant obtained was used for viral isolation in vitro and molecular investigation for flaviviruses, alphaviruses, and insect-specific viruses such as PCLV, HTV, GUAPV, CxFV, and AeFV. All pools tested for medically important arboviruses were negative. HTV was detected in 25 pools (8.8%) of Haemagogus (Hg. janthionomys, Hg. leucocelaenus, and Hg. baresi). PCLV was detected in 13 pools (4.5%) of Haemagogus (Hg. janthionomys, Hg. leucocelaenus, and Hg. baresi) and in six pools (23%) of Aedes (Ae. aegypti, Ae. albopictus, and Ae. scapularis). We also detected GUAPV in two pools (7.7%) of Aedes (Ae. albopictus, and Ae. argyrothorax). We sequenced the PCR products by the dideoxy method, confirming the presence of HTV and PCLV Haemagogus spp. In addition, we had 19 pools (6.7%) of Haemagogus and five pools (19.2%) of Aedes positive for flavivirus. The isolation of HTV and PCLV was confirmed in C6/36 cells by end-point PCR. Next, we aim to confirm our results by sequencing and for the positive samples: genomic characterization, biological characterization, and electron microscopy. This finding reinforces how little we know about ISVs circulation and the importance of entomological and viral surveillance in Brazilian mosquitoes, especially in the Amazon Rainforest, a hotspot of circulation and maintenance of arboviruses.

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HUMAN BEHAVIORAL DETERMINANTS OF RISK OF EXPOSURE TO ANOPHELES AMONG SEASONAL MIGRANT WORKERS AND RESIDENT POPULATIONS IN LOWLANDS AND THE GENERAL POPULATION IN THE HIGHLANDS, NORTHWEST ETHIOPIA

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In northern Ethiopia, regular population movement from highlands to malaria endemic lowlands may be a barrier to malaria elimination that calls for tailored vector control strategies. In this study, we assessed the entomological and human behavioral drivers of malaria exposure among seasonal migrant workers and resident populations in lowlands and the general population in the highlands. In each setting 4 sites were selected. During the high transmission season, October-December 2022, hourly CDC light trap (CDC LT) collections coupled with human behavior observations (HBOs) were conducted for 52 nights from 18.00 to 06.00 hrs. In the highlands, per site 4 houses with recent malaria cases and 4 controls were selected. In the lowlands, 8 households/farm structures were sampled per site. Vector and human behaviors were quantified and compared with and without bed nets. In the highlands, 4,127 mosquitoes belonging to 13 species with both indoor and outdoor biting behaviors were captured. Based on morphology, Anopheles gambiae sensu latu (s.l.) was dominant (41.8%, 1726) followed by An. demeilloni (24.7%, 1018) and An. cinereus (11.3%, 467). The Anopheline mean capture rate for highland sites was higher in indoors (14.0) than outdoors (5.8). In the lowland sites, 2,553 mosquitoes belonging to 18 species were captured with mean capture rate 6.0 for indoors, and 6.2 for outdoors. An. gambiae s.l. (36.2%), An. pretoriensis (24.3%) and An. demeilloni (20.2%) were the most abundant. Human behavior adjusted capture rates suggested that the highest risk of being bitten was early in the evening (18.00-20.00 hrs.) for both highland and lowland sites. In highlands, most exposure (88.4%) occurred indoors (awake or asleep without bed nets) but outdoors in lowland sites (70.0% among seasonal migrants and 70.7% among the residents). These gaps in protection call for tailored interventions: in the highlands, indoor residual spraying (IRS) and human behavioral communication may be useful in reducing man-vector contact. In the lowlands, high outdoor exposure will require alternative interventions to address these gaps.

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CLOSE-KIN MARK-RECAPTURE METHODS TO ESTIMATE DEMOGRAPHIC AND DISPERSAL PARAMETERS OF MOSQUITOES

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Close-kin mark-recapture (CKMR) methods have recently been used to infer demographic parameters such as census population size and survival for fish of interest to fisheries and conservation. These methods have advantages over traditional mark-recapture methods as the mark is genetic, removing the need for physical marking and recapturing that may interfere with parameter estimation. For mosquitoes, the spatial distribution of close-kin pairs has been used to estimate mean dispersal distance, of relevance to vector-borne disease transmission and novel biocontrol strategies. Here, we extend CKMR methods to the life history and population structure of mosquitoes. We derive spatial kinship probabilities for mother-offspring, father-offspring, full-sibling and half-sibling pairs, where an individual in each pair may be a larva, pupa or adult. A pseudo-likelihood approach is used to combine the marginal probabilities of all kinship pairs. To test the

effectiveness of this approach at estimating mosquito demographic and dispersal parameters, we develop an individual-based model of mosquito life history which labels each individual with a unique identification number. Using the dengue vector Aedes aegypti as a case study, we find the CKMR approach can provide unbiased estimates of adult census population size, adult mean dispersal distance, and adult and larval mortality rates for logistically feasible sampling schemes. Considering a simulated population of 3,000 adult mosquitoes, estimation of adult parameters is accurate when ca. 40 adult females are sampled biweekly over a three month period. Estimation of larval parameters is accurate when adult sampling is supplemented with ca. 120 larvae sampled biweekly over the same period. The methods are also effective at detecting intervention-induced increases in adult mortality and decreases in population size. As the cost of genome sequencing declines, CKMR holds great promise for characterizing the demography and dispersal of mosquitoes and other insect vectors of human diseases.

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ADVANCEMENTS OF ARTIFICIAL INTELLIGENCE (AI) IMAGE RECOGNITION FOR USE IN VECTOR SURVEILLANCE OPERATIONS

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Mosquito surveillance, the monitoring of vector abundance, distribution, and diversity, is a critical step to assess mosquito-borne disease risk. Despite its importance, few vector control organizations have access to expert taxonomists with the capacity to evaluate the significant quantities of specimens collected by routine vector surveillance programs. As a result, organizations must rely on seasonal staff with minimal taxonomic expertise to guide important downstream intervention strategies. Convolutional neural networks (CNNs) for image recognition, a deep learning method, have emerged as a promising modality with the capability to visually differentiate between species. The IDX is a system consisting of a controlled optical configuration integrated with algorithms that continue to evolve and improve based on representative specimen image data contributed by partners. In the most recent iteration, the system performed with an accuracy of 97.75±0.06% across 21 species in lab testing. In a test of the deployed algorithm performance on IDX, data from a California vector control district was analyzed, and achieved a macro averaged recall of 97.1% across the top five species. These advancements demonstrate translation of these algorithms from the lab to field practice. In the next phase of work, data collection and testing will be conducted with a wider range of partners in operational scenarios.

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EVALUATION OF MYRISTICA FRAGRANS ESSENTIAL OIL AS A POTENTIAL BIOPESTICIDE FOR THE CONTROL OF AEDES MOSQUITOES IN JAMAICA

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The use of synthetic insecticides to control Aedes mosquitoes continue to be a significant challenge in Jamaica's fight against arboviruses due to rising resistance in mosquito populations. As a result, novel control methods are urgently required. As the use of plant extracts as mosquitocidal agents is currently being investigated worldwide, we therefore sought to assess the potential efficacy of Myristica fragrans (nutmeg), as a natural biopesticide. The nutmeg essential oil was screened against different life stages of laboratory and field Ae. aegypti mosquitoes. We discovered that the oil had significant efficacy against the third larval stage, with LC50 values of 7.18 ppm for the Rockefeller laboratory strain and 15.82 ppm for the Jamaican field strain. Interestingly, the oil displayed modest activity against the less commonly targeted pupal stage, with LC50 values of 1090.00 ppm and 965.90 ppm for laboratory and field strains, respectively. Future studies will focus on further evaluations against the larval stage using additional laboratory and field strains as well as conducting adulticidal assays. Additionally, chemical analysis of the oil and mechanistic studies will be done to identify the constituent (s) responsible for the observed mosquitocidal activity and to determine how the oil is producing this activity. If the oil is found to be highly efficacious, then preliminary field studies will be performed, and formulations of the oil may be studied for prospective use as a biopesticide in Jamaica. Keywords: Biopesticides, Aedes mosquito, Jamaica

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INTERIM EFFICACY REPORT OF ECO BIOTRAPS IN DHARAVI, MUMBAI, INDIA

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We had previously presented an introductory note on the use of a green ovitrap device – Eco BioTrap for an innovative adjunct integrated vector management for vector control. This longitudinal cohort study was carried out in two areas Kumbharwada and Rajiv Ganghi Nagar covering approximately 100,000 population in 10,000 households of Asia's largest slum Dharavi, Mumbai, India. Dharavi is endemic for dengue for several years. A set one trial (with mosquito attractant and anti-larval IGR compound (Pyriproxyfen) and control was placed 10 to 15 meter apart in the study sites following the World Health Organization (WHO) guideline for mosquito larvicides. Two teams comprising of two trained health staff each conducted the study with a follow-up period on day 7, day 14, day 21 and day 28, respectively. Data were recorded on excel sheet and thus analysed. The three-month interim deployment study showed that Eco BioTraps are effective (93%) in attracting the gravid female mainly Aedes aegypti for ovipositing to lay eggs and is highly impactful in eliminating breeding as part of Source Reduction/Larval Source Management (LSM). This device can also be used for larval surveillance for evaluating of any intervention. Further study is underway to find out the long-term impact on the mosquito vector burden and dengue.

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EVALUATION OF THE SYSTEMIC INSECTICIDAL EFFECTS OF IVERMECTIN TREATED CATTLE ON AEDES AEGYPTI, VECTOR OF ARBOVIRUSES

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The burden of Aedes-borne viral pathogens has increased over the past two decades. In the absence of specific treatments against the virus, insecticide-based vector control tools remain the best way to decrease transmission. However, the selection and spread of insecticide resistance in Aedes vectors call for the development of complementary vector control tools. In the IMPACT project funded by Unitaid Agency, we evaluated the systemic insecticidal effects of ivermectin injected to calves on the survival and fertility of Ae. aegypti, one of the primary vectors of arboviruses. A total

of 7,005 females of Ae. aegypti from two strains were used, an insecticide susceptible strain “Bora-Bora” and the “Bobo” strain, a recent colony developed from wild larva captured in Bobo-Dioulasso, Burkina Faso. Mosquitoes were directly blood fed on cattle injected with ivermectin at 1 mg/kg and 0.8 mg/kg of body weight. Survival, reproductive parameters were measured and compared between strains and in function of the dose and the delay after injection (DAI) at which blood feeding occurred. Our data show that all parameters but hatching rate were significantly decreased in Bora Bora fed on treated calves, with different magnitude in function of the Ivermectin dose and the DAI: survival decreased by at least 50% until 14-21 days post treatment, mean number of females that laid eggs decreased by 45 to 50%, while the number of eggs laid by the females that remained alive decreased by 65 to 85% until 21 DAI. For the Bobo strain, survival decreased by 15% until 7 DAI for the 1mg/kg dose only, and hatching rate was the only reproduction parameter significantly impacted, with 20 to 40% eggs that were laid that didn’t hatch. These differences in ivermectin toxicity between Bora Bora and Bobo call for ivermectin differential susceptibility between strains. However, in both populations, the impacted parameters have all great importance in determining vectorial capacity. Hence, Ivermectin could contribute to significantly reduce Ae. aegypti populations densities if the toxic effect is sustained over time, notably through the use of Long Acting Ivermectin Formulations.

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UNLEASHING NATURE’S SECRET WEAPON: TACKLING MOSQUITO MENACE WITH STREPTOMYCES SP. KSF103

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The use of environmental-friendly techniques for mosquito control has garnered attention in recent years, and our study aimed to evaluate the potential of Streptomyces isolates for Culicidae control. The insecticidal property of Streptomyces sp. KSF103 ethyl acetate (EA) extract against mosquitoes and non-target organisms; its preliminary mode of action; and its effect on dengue virus 2 replication in mosquitoes were investigated. We used in vitro and in vivo experiments to determine the insecticidal activity of the EA extract. The results revealed that the EA extract exhibited strong cytotoxicity against C6/36 cells and considerable mortality in eggs, larvae and adults of all four important vector mosquitoes, namely Aedes aegypti, Aedes albopictus, Anopheles cracens, and Culex quinquefasciatus. However, it displayed no significant toxicity effect on non-target cellular model human fibroblasts (MRC-5) and non-target organisms such as Chlorella spp. and Odontoponera denticulata. Apoptosis induction was found to be the preliminary mode of action of the EA extract on C6/36 cells as well as the larvae and adults of Ae. aegypti. Moreover, biochemical assays revealed that it inhibited acetylcholinesterase activity, indicating the disruption in the insect nervous system. We also discovered the inhibiting property of the EA extract against DENV-2 replication in C6/36 cells. Pre- and post-treatment assays of the EA extract on C6/36 cells demonstrated significant inhibitions, suggesting the disruptions on virus entry and adsorption on pre-treated cells and intracellular replication of the virus on post-treated cells. Chemical profiling of the EA extract revealed the presence of pentanamide, c17 sphinganine, dichamanetin, dodemorph, and antillatoxin B, which antillatoxin B and dichamanetin were active against DENV NS2B/NS3, NS5, and envelope protein (E) of DENV-2 via in silico study. Our study suggests that Streptomyces sp. KSF103 EA extract can potentially become a promising source of environmentally benign biocontrol agents for mosquito-borne diseases.

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METHODS USED FOR MALARIA AND MOSQUITO CONTROL AT THE HOUSEHOLD LEVEL IN TANZANIA. THE SCHOOL MALARIA AND NUTRITION SURVEY

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Global Technical Strategy for Malaria 2016-2030 is to ensure universal coverage for all people at risk of malaria using effective vector control with either LLINs or other core prevention tools such as indoor residual spraying. These are highly effective methods of vector control, but additional interventions are needed for long-term, sustainable malaria control and elimination. This study aimed to determine factors related to methods used for malaria and mosquito control at the household level in Tanzania. A cross-sectional survey involving primary school pupils was selected for an interview and a random sample of households around the schools was interviewed on malaria prevention, treatment, and control methods. We applied a generalized linear model to determine factors associated with methods used for malaria and mosquito control at the household level. Our study involved 6,018 households from 26 regions in Tanzania. We find that the head of household engaged in business had an AoR of 0.93(CI = 0.87 - 0.99, p = 0.032) times less likely to more methods compared to those who deal with agriculture activities. Head of household who is employed had an AoR of 0.92(CI = 0.84 - 1.01, p = 0.066) times less likely to use methods compared to those who are dealing with agriculture activities. Head of household who is unemployed had an AoR of 0.81(CI = 0.68 - 0.96, p = 0.015) times to use fewer methods compared to those who are dealing with agriculture activities. We found households size between 5-8 members had an AoR of 1.05(CI = 1.00 - 1.11, p = 0.059) times to use more methods compared to a household with people between 1- 4. Household sizes between 9-13 had an AoR of 1.17(CI = 1.09 - 1.26, p = <0.001) times to use more methods compared to a household with people between 1 to 4. We find that households with wood floor structures had an AoR of 0.85(CI = 0.72 - 0.99, p = 0.043) times less likely to use more methods compared to those households with the cement floor structure. Our results highlight the different measure used at household level to control and eliminate malaria cases in Tanzania.

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IMPACT OF CLIMATE VARIABILITY ON VECTOR-BORNE DISEASES (MALARIA) IN THE DEMOCRATIC REPUBLIC OF THE CONGO

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According to the WMO, by 2050, temperatures are predicted to rise by 2-3°C in temperate latitudes, with a 7% increase in average precipitation. In the context of these rising temperatures, there will likely be an increase in vector reproduction and high average temperatures will lead to an increase in malaria cases. In this context, in DRC, efforts have been undertaken by the National Malaria Control Program (NMCP) to understand and mitigate this scenario to identify areas that are at high risk of malaria transmission and implement targeted interventions to prevent and control the spread of the disease. Of these, the development of the integrated malaria dashboard, a visualization tool to monitor the performance of the malaria indicators, have been undertaken since 2021. This captures epidemiological (malaria weekly surveillance cases and deaths from IDES) and malaria transmission factors (including meteorological data). Through those decisions, the evolution of the malaria indicators will be monitored to have a clear picture of the influence of climate variability in the spread of malaria in DRC. The country is also setting up innovative approaches to control and eventually eliminate the disease and providing specialized trainings, to inform healthcare workers and other stakeholders. Finally, advocating for the improvement of water, hygiene and sanitation systems in DRC is an effort

undertaken by the NMCP, as these are responsible for the transmission of malaria, and they are likely to increase with rising temperatures will reduce the breeding sites of mosquitoes. As such, the rise of temperatures in DRC would lead to an increase of malaria burden if all efforts are not put in place. Climate change has the potential to exacerbate the burden of malaria in DRC, the country with the second highest burden of malaria, but efforts are being undertaken by the NMCP to mitigate this scenario and prevent a potential worsened malaria pandemic crisis in the context of changing climate conditions.

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SPATIAL AND TEMPORAL DISTRIBUTION OF ANOPHELES SPECIES ACROSS THREE DIFFERENT ECOLOGICAL ZONES IN GHANA

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Vector management of Anopheles mosquito species in West Africa is challenged by limited data on their distribution, species profile, and lack of reporting mechanisms from sentinel sites. To provide insights into the epidemiology of vector-borne diseases such as malaria and filariasis, this study investigated the distribution and species composition of Anopheles mosquitoes in three ecologically distinct zones of Ghana. We collected adult Anopheles mosquitoes using CDC light traps, UV light traps and Biogents Sentinel (BG) traps, and morphologically identified on monthly basis, between 2017 and 2021. We subsequently performed analysis using R version 4.1.0 and fit a Generalized Linear Mixed Model (GLMM) with a negative binomial distribution to depict the trapping method and month of collection as fixed effects, and the year of collection and site as random effects. Out of a total of 20,222 Anopheles mosquitoes collected, majority were from Navrongo (66.1%), Kintampo (32.1%), and Kumasi (1.8%). The most predominant Anopheles species identified was An. gambiae (67.83%), followed by An. coustani (21.39%), An. rufipes (5.12%), An. pharoensis (4.35%), and An. funestus (0.91%). There was a significant association between season and the collection of An. gambiae ($p < 0.001$). Additionally, significantly higher numbers of An. gambiae were collected in the wet season than in the dry season in Kintampo ($p < 0.001$) and Navrongo ($p = 0.0023$). Furthermore, there was a less likelihood of An. gambiae collected using UV light traps compared to the CDC light traps (IRR = 0.8, 95%CI = 0.67-1.07, $p = 0.0989$). The results of this study will inform the development of evidence-based vector management strategies and contribute to the efforts to reduce the burden of vector-borne diseases in Ghana and West Africa at large.

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RELEVANT DENGUE TRANSMISSION RISK IN NON-HOUSEHOLD ENVIRONMENTS IN KENYAN CITIES CAN LEAD US TO RETHINK THE HOUSEHOLD AS THE FOCUS OF VECTOR CONTROL ACTIVITIES

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Dengue transmission has recently been reported in multiple African countries including Kenya, raising attention as an emerging public health concern. In endemic countries, most vector control activities are applied within households; however, recent evidence suggests that spaces other than households might have a relevant role in dengue transmission in urban areas. To evaluate the role of non-household spaces in dengue risk in Kenya, we conducted analyses based on data from extensive vector sampling carried out in Kisumu and Ukunda, two Kenyan cities with documented dengue virus circulation. Four sampling strategies targeting different vector stages were used to collect mosquitoes in both household and non-household environments. Data were analyzed to assess the differential proportion of spaces from both environments with presence of the vector and the number of individual vectors per structure. Further, taking these data as input, we simulated total vector and human populations to estimate the difference in vectorial capacity for household and non-household environments based on m, the vector-to-host density. The proportion of sampling sites with vectors present was similar in household and non-household environments. The number of vectors was higher in non-household environments in Kisumu and similar in households and non-households in Ukunda. Mirroring vector density, vectorial capacity was higher in non-households in Kisumu and similar in both environments in Ukunda, suggesting an important entomological risk in non-household environments in both cities. Our results highlight the importance of including non-household sites in vector control activities to improve city-wide disease control efforts.

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MEASURING THE LONG-TERM PUBLIC HEALTH IMPACT AFTER CITY-WIDE WMEL DEPLOYMENTS IN YOGYAKARTA

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A cluster randomised trial of wMel Wolbachia-infected mosquito releases in Yogyakarta City, Indonesia, in 2018-2020 showed a 77% reduction in dengue incidence and 86% reduction in dengue hospitalisations in wMel-treated areas. Yogyakarta now represents the first dengue-endemic setting in which wMel has been established at a high level at a city-wide scale (~400,00 people), since releases were completed throughout untreated areas in January 2021. The incidence of dengue notified to the hospital based passive surveillance system was lower in 2021 and 2022 than any two-year period in the past 20 years, but not zero. It is unknown what proportion of these remaining clinically-reported cases are true dengue cases and resident in Yogyakarta. We established a prospective enhanced dengue surveillance study in 13 primary health clinics in January 2023, to test the feasibility of achieving local dengue elimination in Yogyakarta following area-wide Wolbachia deployment. Patients aged 3-45 years with 1-4 days of undifferentiated fever and resident in Yogyakarta City are enrolled and tested for virologically-confirmed dengue (VCD) by dengue virus RT-PCR and NS1 ELISA. History of travelling outside of the city within the 14 days prior the illness onset is captured through interview. The hypothesis is that enhanced clinical surveillance will demonstrate an absence of locally-acquired virologically-confirmed dengue within 5 years post-intervention (2025). Aggregate data on notified hospitalised dengue patients from the routine surveillance system is obtained on a monthly basis and interrupted time-series analysis of notified dengue cases will be used to evaluate the long-term public health impact of Wolbachia. In January to March 2023, we have enrolled 549 participants, 2 VCD cases were found from 440 tested blood samples. This showed a low prevalence of dengue case during the dengue season. We will present the design and first 9 months of results from the enhanced dengue surveillance study, and results of the interrupted time series analysis showing the impact of Wolbachia on notified dengue incidence 2.5 years after city-wide releases.

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MODELING THE EFFECTIVENESS OF ATTRACTIVE TARGETED SUGAR BAITS IN REDUCING CLINICAL MALARIA

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Attractive targeted sugar baits (ATSBs) are a novel vector control intervention that have shown promising results of mosquito population reduction in semi-field and field studies. Randomized control trials are currently ongoing in Kenya, Zambia and Mali to determine the effectiveness of ATSBs in reducing clinical malaria. We use an individual-based simulation model of malaria, OpenMalaria, to estimate the effectiveness of ATSBs in reducing clinical malaria incidence in children aged 1-14 in settings based

on western Kenya and western Zambia. Our results suggest that even with relatively high pre-existing coverage of insecticide-treated nets (ITNs), ATSBs can be very effective in reducing clinical malaria. Even relatively low daily probabilities of mosquitoes feeding on an ATSB, that lead to modest reductions in mosquito densities, can lead to a 30% reduction in clinical incidence in children. Our results suggested a greater effectiveness in reducing clinical malaria in Kenya than in Zambia, assuming equivalent coverage of sugar sources with ATSBs; and similarly suggested higher effectiveness when the main vector species was An. gambiae rather than An. funestus. Our results were most sensitive to assumptions on baseline transmission intensity (ATSBs were more effective in low transmission settings); assumptions on frequency of sugar feeding (ATSBs were less effective when mosquitoes only sugar-feed while host-seeking); and on the duration of the host-seeking stage - which is especially difficult to measure in the field (ATSBs were less effective when mosquitoes found hosts quickly). Overall, our results support the optimism behind ATSBs but suggest that settings where they are deployed should be carefully considered and particular importance should be paid to estimating the time mosquitoes require to find and feed on blood hosts.

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INSECTICIDE TREATED RESTING STATIONS REDUCE PARITY RATE OF THE ENZOOTIC MOSQUITO VECTOR OF EEE VIRUS, CULISETA MELANURA

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Laboratory and field experiments were conducted to develop and test the concept of insecticide-treated, resting stations to reduce the vectorial capacity of Culiseta melanura for eastern equine encephalitis (EEE) virus. Of four commercial insecticides applied to the inner surfaces of resting stations (black-painted, durable molded fiber containers used in the greenhouse industry) and presented to adult Cs. melanura, the microencapsulated formulation of lambda cyhalothrin Demand CS showed the highest mortality and longest duration of effect (more than 98% mortality for 5 weeks). Mosquito density in treated boxes was nearly nil in the field, compared to untreated boxes. A field evaluation was implemented at six bog sites in southwestern Michigan with natural populations of Cs. melanura and history of EEE activity, where three sites each received 300 boxes treated with Demand CS and distributed at bog perimeters, and three control sites had no treated boxes. Mosquitoes were sampled once weekly for 9 weeks from mid-July to mid-September from 75 untreated boxes at each site. Results showed a statistically significant decrease in the percentage of parous, female Cs. melanura at treatment compared to control sites following distribution of treated resting boxes, with up to 50% reduction in parity rate during the course of the experiment (3,185 dissected), and further revealed a shift towards a younger population age structure when considering unfed, blood fed, half gravid, and gravid physiological categories. Survival analysis suggested that the vectorial capacity of Cs. melanura populations at the treatment sites was reduced meaningfully with regard to control of EEE virus transmission. Blood meal analysis showed an avian host selection profile, with northern cardinal, American robin, and blue jay as the most commonly selected hosts. Overall, the results of the study support a proof of concept for use of insecticide treated resting stations for targeted control of EEE virus transmission.

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IN WITH THE NEW AND OUT WITH THE OLD: INITIAL OBSERVATIONS OF THE EXTENT OF LONG-TERM USE OF OLD LLIN DESPITE THE AVAILABILITY OF NEW NETS DURING THE 2020 MASS CAMPAIGN IN BENIN

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From 2011 to 2020, there were four mass distribution campaigns and ancillary continuous distribution of Long-Lasting Insecticide-treated Nets (LLINs) in Benin. Although new LLINs are freely available across malaria-endemic countries, there are anecdotal and empirical reports of continued use of old LLINs, despite likely diminished bio-efficacy against malaria vectors. To quantify the number of old nets in use despite the availability of newly distributed LLINs, households were surveyed to determine which nets were hanging and the integrity of those nets after the 2020 LLIN campaign in Benin. Household surveys of 2902 randomly selected houses were conducted in 24 randomly selected villages in Benin. Observation of nets and information on the net origin, utilization, and physical integrity were recorded using a survey form on Open Data Kit (ODK) loaded on tablets. A mosquito net that was hanging over a bed was classified as in use. A total of 7576 nets were found in the surveyed houses. An average of 95% of LLINs that were hanging or lying on or near the bed were in use of which 48% of these were torn. The origin of most LLINs (71%) found in households was from the 2020 mass campaign (n=5384). A total of 11% (n=809) of LLINs were from 2011, 2014, and 2017 campaigns, and 14% (n=1036) were from either purchase, routine distribution, or other sources. Approximately 95% (765 of 809) of LLINs found in the house from 2011, 2014, and 2017 mass campaigns were still in use. Only 5% (n =347) of households saved their new 2020 LLINs for later use. This study provides initial insights into the persistent use of old LLINs despite the availability of new LLINs. Retaining old LLINs in the presence of new LLINs does not seem to be common practice as most people hung their new nets. However, nets from 2011 were still found hanging after the 2020 mass campaign. Still, this assessment only provides provisional results. More evaluation is needed to understand the factors leading to the persistent use of old nets to develop strategies and policies that promote maximum usage of new LLINs.

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INTEGRATED VECTOR MANAGEMENT IMPLEMENTED TO REDUCE DENV-1 POSITIVE CASES IN HUMANS AND MOSQUITOES IN MAYAGÜEZ, PUERTO RICO, 2022

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In September 2022, following the passage of Hurricane Fiona through Puerto Rico, cases of DENV increased areas of Puerto Rico (PR), including the western part of the island. The Puerto Rico Department of Health (PRDH) began to report elevated DENV-1 human cases in the municipality of Mayagüez and classified this area as critical area. At that time, there were approximately 54 human cases. Most confirmed cases occurred within public housing complexes of this municipality. The Puerto Rico Vector Control Unit (PRVCU) established entomological surveillance using nearly 100 Autocidal Gravid Ovitraps (AGO) distributed over seven zones of active DENV1. The PRVCU deployed additional AGOs to control the mosquito population through saturation trapping. Our surveillance traps captured 8,773 females Aedes aegypti females, the principal vector of dengue, Zika and chikungunya in Puerto Rico. All these females were tested for dengue,

Zika and chikungunya viruses, yielding a total of 42 mosquito pools were positive for DENV-1, but no other serotypes were found. Neither were there any pools positive for chikungunya or Zika viruses. The PRVCU attempted to treat each of the seven zones with our standard regimen of Wide Area Larvicide Spraying (WALS). However, due to major security challenges, we could only complete about 1/3 of the total larvicide applications although one zone did receive all required applications. In that zone, other control strategies were also used such as community outreach, distribution of educational materials and repellents, installation of control traps, etc. The number of trapped female Ae. aegypti decreased in all treated zones but the decrease was greater in the zone with the largest number of treatments. In that zone, the number of female Ae. aegypti was reduced by about 70%, falling from a pre-treatment average of 17.5 of female Ae. aegypti mosquitoes per trap per week to 5.1/trap/week. Given that Ae. aegypti in Puerto Rico has very high insecticide resistance, this was an important success here. The results are encouraging, and we hope to be able to implement this approach in other, more secure areas of Puerto Rico in the future.

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THE SPREAD OF CHIKUNGUNYA VECTORS: A POTENTIAL THREAT TO GLOBAL HEALTH

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Chikungunya is a viral disease caused by the chikungunya virus (CHIKV), a re-emerging arthropod-borne virus transmitted to humans through infected Aedes aegypti and Aedes albopictus mosquitoes. Chikungunya is characterized by acute febrile polyarthralgia and inflammatory arthritis, the latter of which can be severe, debilitating, and long-lasting. This targeted literature review was performed to identify evidence on CHIKV vectors and their role in the global spread of the disease. CHIKV was first identified in Tanzania in 1952 and isolated in Africa and Asia over the following decades, causing occasional outbreaks in those regions. Since 2004, CHIKV has spread to over 110 countries throughout Africa, Asia, the Americas, and Europe. CHIKV often causes large explosive outbreaks with high attack rates. One of the most recent major outbreaks occurred in Colombia in 2014, affecting roughly 106,000 people. As of 2014, CHIKV cases have been identified among U.S. travelers returning from areas at risk of transmission. Furthermore, because of globalization and international trade, CHIKV vectors can cover vast distances in a short time. The rapid spread of CHIKV is also influenced by global climate change. Temperature and precipitation changes, in particular, affect the proliferation, survival, and abundance of Aedes mosquito vectors, ultimately increasing the worldwide spread of habitable regions for the Aedes genus of mosquitos. Consequently, this increase exposes more areas to the risk of local autochthonous transmission if the travelers should import the virus, as observed in Italy over the last 15 years, where outbreaks occurred within 10 years of vector introduction. All in all, climate change and an increase in globalization will cause distributional shifts, and likely expansion, in the climatically suitable areas for CHIKV transmission. This has global public health implications and highlights the need for a preventive vaccine against chikungunya.

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HOST PREFERENCES OF ANOPHELES GAMBIAE S.L AND THEIR IMPLICATIONS FOR MALARIA TRANSMISSION IN FOUR INDOOR RESIDUAL SPRAYING INTERVENTION DISTRICTS IN GHANA

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The risk of exposure to infections transmitted by mosquitoes is influenced by their host preference. In Ghana and other parts of sub-Saharan Africa, Anopheles gambiae s.l is a significant vector of malaria, with a high propensity to feed on humans. The AngloGold Ashanti Malaria Control program implemented indoor residual spraying (IRS) in sixteen (16) districts of Ghana in 2021. As part of broader entomological surveillance activities to track the impact of the indoor residual spraying on the local vector populations, pyrethrum spray collections were carried out from January to December 2021, to sample indoor-resting mosquitoes from randomly selected houses at four (4) sentinel sites located in Obuasi, Wa, Lawra, and Sissala East. Mosquito samples were identified morphologically and also tested for the source of blood-meal using direct enzyme-linked immunosorbent assays (ELISAs). A total of 451 Anopheles species were collected from the sentinel districts, out of which 85% (n=383) were morphologically identified as An. gambiae s.l. Two hundred and twenty-six (226) of the An. gambiae s.l were blood-fed and were tested for the source of blood-meal. The results showed that across the four (4) IRS districts, An. gambiae s.l fed on five (5) different hosts that comprised of human blood-meal (55-89%), bovine (3.6-5%), goat (1.8-2.8%), pig (1.4-3.6%) and dog blood-meals (1.4-3.6%). There were also mixed blood-meals of two sources recorded at all the sites. Human blood-meal was the predominant source in all districts, with Obuasi having a human blood index (HBI) of 0.76, Wa 0.87, Lawra 0.91 and Sissala East 0.88. These findings have important implications for malaria transmission and the design and implementation of vector control measures. The high level of anthropophagy observed indicates that the vectors have a strong preference for human blood-meal. Therefore, targeted interventions that focus on reducing human-vector contact could be effective in tackling the transmission of malaria in the study areas.

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OPTIMAL CONTROL OF DENGUE WITH EXISTING AND FORTHCOMING INTERVENTIONS

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Progress towards controlling dengue has proven to be difficult, with clear examples of successful control being few and far between and typically not sustained over time. At the same time, evidence from trials indicates that a range of interventions should be capable of reducing transmission. This contradiction raises the possibility that there is scope to improve how interventions are used. We addressed this possibility using a mathematical model of seasonally varying dengue virus transmission in nearly 2,000 cities. The model was informed principally by Aedes aegypti occurrence maps, temperature and its effects on mosquito and virus traits, and spatial estimates of dengue virus force of infection. We applied optimal control theory to models for each city, resulting in estimates of the frequency with which each of several interventions should be deployed if cost-effectiveness is to be maximized. While our results indicate that some combinations of interventions may be more cost-effective than others, especially in some settings, there are challenges that all interventions face. Namely, limits to intervention coverage impair effectiveness, and increased intervention effort is required over time to counterbalance the effect of rising susceptibility, particularly for more effective interventions. We also found that cities with more seasonally marginal levels of transmission and higher costs incurred

by dengue morbidity and mortality have greater scope to engage in cost-effective control programs. Our results offer a novel piece of information that decision makers could use to inform rational choices about efforts to control dengue within their communities.

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CHANGING ASSUMPTIONS ABOUT MOSQUITO HABITAT AVAILABILITY DRIVE VARIATION IN SEASONAL DENGUE DYNAMICS WHEN BEHAVIORAL CONTROL IS PRESENT

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Though vector control strategies for dengue can vary significantly in efficacy and scale of implementation, human behavior is an important component of their success. Behavior can influence compliance patterns with spraying campaigns and participation in mosquito habitat reduction, namely the elimination of standing water. The nature of the relationship between that influence and the outcomes we observe in behavioral studies is difficult to pinpoint, though, since several factors influence the presence of standing water in a home besides behavioral control alone. Specifically, the connection between rainfall and mosquito habitat availability is uncertain, as increased rainfall has been associated with both greater and lesser habitat availability—while it can directly increase standing water presence outdoors, it can also discourage intentional water storage. To explore the possible consequences that this relationship may have on the efficacy of behavioral interventions, we developed a deterministic, coupled-contagion model for the spread of dengue virus and associated container-management behaviors. Preliminary analyses suggest that the effects of changing assumptions regarding rainfall are most notable under temperate climate regimes, where mosquito population dynamics are subject to more seasonal variation than in tropical climes. In a temperate setting, when mosquito habitat availability is positively correlated with monthly rainfall patterns, we observe a higher, later seasonal peak in dengue incidence than when there is an inverse relationship between habitat availability and rainfall. This effect is dampened by the transmission of container control behaviors, driven by mosquito presence, disease incidence, and social conformity, which produce a mosquito population that is more stable over time. In this work, we found that the impact of dengue control behaviors is largely dependent on assumptions about what drives mosquito reproduction in a given setting, and suggest this as a focus when tailoring interventions to community-specific conditions and concerns.

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INFLUENCE OF THERMAL AND INSECTICIDE GRADIENTS ON IMMATURE AEDES AEGYPTI PERFORMANCE

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Mosquito-borne diseases are ubiquitous, with mosquitoes vectoring parasites, arboviruses, and bacteria to wildlife, domestic animals, and humans. Temperature is a well understood, fundamental factor that influences both mosquito and pathogen traits, altering Rθ, an important proxy for the population growth rate of pathogens. Consequently, global climate change is expected to alter incidence and seasonal dynamics of many mosquito-borne diseases, and ecologically relevant predictive models are essential to mitigating these changes to disease risk. In recent years, eight mosquito and pathogen traits have been shown to exhibit unimodal responses with temperature, and these thermal performance curves (TPCs) have been implemented into a generalized Rθ equation. Temperature is the sole abiotic factor considered, however, and little is known how other abiotic factors, such as insecticides, impact each parameter. To begin understanding the extent to which insecticides fit into the temperature-dependent Rθ equation, we implemented a response-surface design on Aedes aegypti mosquitoes in temperature-controlled incubators to examine if temephos (a widely used organophosphate larvicide) interacts with temperature to influence larval and pupal mortality and development time and adult body size. Initial analysis using generalized additive models show a significant interaction between temperature and temephos dose for larval and pupal mortality and pupal development time. These results demonstrate the significance of incorporating abiotic gradients into temperature-dependent Rθ models to better understand disease spread and implement vector control.

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FROM THE LAB TO THE FIELD: LONG-DISTANCE TRANSPORT OF STERILE MALE MOSQUITOES

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Pilot programmes of the sterile insect technique (SIT) may rely on importing significant and consistent numbers of high-quality sterile males from a distant mass-rearing factory. As such, long-distance mass-transport of sterile males may contribute to meet this requirement if their survival and quality are not compromised. This study therefore aimed to develop and assess a novel method for long-distance shipments of sterile male Aedes aegypti mosquitoes from the laboratory to the field. In addition, different types of mosquito compaction boxes and a simulated transport of marked and unmarked sterile males was assessed in terms of survival rates/ recovery rates, flight ability and morphological damage to the mosquitoes. The novel mass-transport protocol allowed long-distance shipments of sterile male mosquitoes for up to four days with a non-significant impact on survival (> 90% for 48h of transport and between 50 and 70% for 96h depending on the type of mosquito compaction box), flight ability and damage. In addition, a one-day recovery period for transported mosquitoes post transport increased sterile male escape ability by more than 20%. This novel system for long-distance mass-transport of mosquitoes may therefore be used to ship sterile males worldwide for journeys of two to four days. This study demonstrated that the protocol can be used for standard routine mass-transport of marked or unmarked chilled male mosquitoes required for the sit or other related genetic control programmes.

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BACTERIAL COMMUNITIES ASSOCIATED WITH ANOPHELES GAMBIAE LARVAL HABITATS IN SOUTHERN GHANA.

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Mosquito breeding habitats is an ecosystem that comprises of a complex, intimately associated micro-organisms. Understanding the bacterial community structure, and its dynamics on mosquito larval productivity is a pre-requisite for comprehending mosquito habitat selection for oviposition. Sequencing of the 16S rRNA using Oxford Nanopore's MinION platform was used to identify and compare the bacterial communities in Anopheles positive breeding habitats (productive and semi-productive habitats) and negative habitats (non- productive) from Southern Ghana. A total of 12 bacterial taxa were identified in all the samples tested. Significantly, mosquito positive breeding habitats (productive and semi-productive) had more bacterial diversity compared to mosquito negative habitats (non- productive). Comparisons of bacterial composition revealed that Epsilonproteobacteria was more common ($P < 0.05$) in

unproductive habitats, Gammaproteobacteria, Actinobacteria and Sphingobacteria were more common ($P < 0.05$) in productive habitats, and Gammaproteobacteria, Betaproteobacteria, and Alphaproteobacteria were the most abundant bacterial class in Anopheles larvae. Only two taxa, belonging to the phyla Gammaproteobacteria and Betaproteobacteria were common to both larvae and mosquito positive breeding habitats. These results suggest a higher bacteria composition may play a role in Anopheles mosquitoes' attractiveness to a breeding habitat. These findings contribute to the understanding of which bacteria, directly or indirectly, can be linked to absence or presence of mosquitoes larvae in breeding habitats, and set the basis for the identification of specific bacterial taxa that could be harnessed for vector control in the future.

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A VOLATILE PYRETHROID SPATIAL REPELLENT (VPSR) USING TRANSFLUTHRIN AS AN INTERVENTION FOR REDUCING OUTDOOR MALARIA TRANSMISSION

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Presently, the most common malaria control tools - i.e. long lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS) are limited to targeting indoor biting and resting behaviors of Anopheles mosquito species. Few interventions are targeted towards malaria control in areas where transmission is driven or persists due to outdoor biting behaviors. A volatile pyrethroid-based spatial repellent (VPSR) using a transfluthrin active ingredient was designed to address this gap in protection. A collection of one semi-field and three field trials were conducted in communities vulnerable to outdoor biting in Zambia and Indonesia, assessing the protection provided by the VPSR in outdoor spaces where biting is known to occur. The product provided significant protection to users during semi-field trials by preventing host-seeking activity by roughly 40% per night and increasing mortality among exposed mosquitoes. Host-seeking was significantly reduced in structures protected by the VPSR device across the remaining three field trials, with significant nightly reductions of around 70% observed in these trials. Individual hourly protection between 60% and 80% was observed across each trial. This study aims to compare the results of these VPSR trials and leverage additional information from the study areas - possibly including household density, road networks, and surveyed human behavior - to further assess the efficacy and cost-effectiveness of the VPSR intervention in each study area and across possible scenarios. Both nightly and hourly protection were considered based on the transmission setting and in terms of possible improvements to semi-field trial design to measure possible repellency or mortality effects on mosquitoes in a confined space.

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EVIDENCE-BASED DESIGN OF ENHANCED VECTOR SURVEILLANCE FOR LARVAL SOURCE MANAGEMENT ON BIOKO ISLAND, EQUATORIAL GUINEA

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From 2004-2018, sustained intensive vector control on Bioko Island reduced malaria prevalence from over 40% to around 10%, but since 2018 there has been a resurgence in prevalence despite continued vector control. To supplement the core interventions of indoor residual spraying and insecticide-treated net distributions, larval source management (LSM) was added to the intervention package. LSM has been implemented on a small scale on Bioko Island at various times from 2013-2021, and in 2022 a breeding site survey was conducted to support an expanded LSM implementation in 2023. However, to enable evaluation of the impact of LSM, it was necessary to enhance the vector surveillance system on Bioko. Since 2004, human landing catch (HLC) in 14 sentinel surveillance sites has been the primary vector surveillance activity, but expanding HLC to evaluate LSM impact is cost-prohibitive. In 2017, CDC light traps were also placed indoors in sentinel sites, but especially since 2018 have been highly inefficient in capturing Anopheles mosquitos. Thus, two new trapping methods were selected to implement for LSM evaluation in 2023 based on their operational suitability and cost: resting sticky boxes (RSB) and oviposition traps (OT). Sites for trap placement were selected primarily based on the 2022 larval habitat survey data. For each 1km x 1km grid cell targeted for LSM, at least five sites were selected for RSB and at least one for OT. Site selection was based on a statistical analysis of the breeding survey data, which incorporated information about breeding site characteristics and environmental covariates to rank potential site locations. Final sites were selected from a subset of the highest ranked potential sites based on operational considerations such as accessibility, trap integrity and frequency of trap revisit in relation to the LSM deployment. The resulting surveillance framework continues HLC in sentinel sites for historical comparison, while implementing a spatially broad network of traps to monitor adult mosquito density in an urban area.

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COMBINING A SCHOOL-BASED AND COMMUNITY-BASED EDUCATIONAL INTERVENTION IN URBAN KENYA FOR LARVAL SOURCE REDUCTION

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Aedes aegypti mosquitoes are the primary vectors for many arboviral diseases including chikungunya (CHIKV) and dengue (DENV), and they primarily breed in domestic containers. Previous studies have shown that there is a severe lack of knowledge about non-malaria arboviral diseases in Kenya, so we proposed a household and school-based educational intervention in Urban Kenya to determine whether it could bring about long-term improvements in knowledge, attitudes, and behaviors related to source reduction of Ae. aegypti vectors. In this cluster-randomized controlled trial, there were 243 households from five control villages and 249 households from five intervention villages. In each household, at least one child (11-14 years) and his/her primary caregiver were enrolled. The intervention used printed informational posters, live demonstrations, and videos to focus on source reduction techniques for the most productive mosquito breeding sites found in urban Kenya. Data on the participants' knowledge, attitudes, and behaviors were collected at baseline, 3-, and 12-months post-intervention as well as counts of immature mosquitoes in containers in the participants' households. Caregivers in the intervention group significantly outperformed the control group in the knowledge and behavior questions at the 3- and 12-month follow-up ($p<0.01$). Children in the intervention group showed similar performance to the control group in knowledge and behavior questions at the 3-month follow-up, but at the 12-month follow-up, the intervention group significantly outperformed the control group ($p<0.01$). Although the total number of immature mosquitoes did not differ between the control and intervention groups, there was significantly less mosquito breeding in intervention household containers - a focal point of the intervention - at the 12-month follow-up compared to baseline (26.19% to 1.93%, $p<0.01$). Paired educational interventions at the school and household level can bring about positive changes in knowledge, attitudes, and behaviors that protect against arboviral diseases and may be relevant in other urban Kenyan communities.

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ADVANCEMENTS TOWARD COMMERCIAL-SCALE PRODUCTION OF YEAST RNAI INSECTICIDES FOR MOSQUITO CONTROL

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The development of new mosquito control interventions, such as RNAi-based yeast insecticides, is a multi-staged process. Efforts to move RNAi yeast technology from the bench to the field began with proof of concept experiments to demonstrate yeast efficacy and modes of action in the lab. These studies, which were performed with a laboratory yeast strain, were followed by semi-field and small-scale field trials that involved the development of delayed-release formulations, as well as scaling yeast production from shake cultures to bioreactors. The pursuit of large-scale field trials and ultimately the global deployment of a commercial product requires substantial scale-up of yeast production and the transition from laboratory yeast strains to more robust commercial-ready strains suitable for scaled fermentation. Cas-CLOVER, an RNA guided dimeric nuclease system, was used in combination with piggyBac transposase to generate a robust yeast strain containing multiple integrated copies of an insecticidal shRNA expression cassette. This enabled production of shRNA that targets a sequence which is conserved in mosquito Shaker genes, but which is not found in non-target organisms, during yeast propagation. The yeast performed well in laboratory trials conducted on Aedes spp., Culex spp., and Anopheles gambiae larvae. Delivery of the yeast to adult mosquitoes as an attractive targeted sugar bait (ATSB) also induced high levels of adult mortality. Large-scale fermentation facilitated kilogram-scale production of the yeast, which was subsequently heat killed and dried. LD90 levels for the yeast insecticide produced at scale, which correlated with shRNA levels that were several-fold higher than laboratory yeast strains, were reduced with respect to the lab strains. Efforts to begin to evaluate the yeast in additional species of mosquitoes, including Anopheles stephensi, a substantial threat to malaria prevention, and to confirm the efficacy of the yeast in field trials will be discussed. These studies indicate that yeast RNAi insecticide production can be successfully scaled for large field trials and global product distribution.

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SHOULD WE BE SPRAYING 80% OF THE HOUSES? AN OPERATIONAL, CLUSTER RANDOMIZED TRIAL ON BIOKO ISLAND TESTING THE NON-INFERIORITY OF A LOWER COVERAGE

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Indoor residual spraying (IRS) has been used annually on Bioko Island for 20 years. By 2023, 30 rounds had been completed for high coverage. Throughout IRS's history, the question of what constitutes high coverage and how to balance it with limited resources has arisen. We present an operational, cluster randomized trial of IRS investigating the non-inferiority of 50% coverage against the canonical 80% recommended. The alternative hypothesis of non-inferiority posits that the effect size of 50% coverage is at least as large as the effect size of 80% coverage. Two arms of 37, randomly allocated clusters were sprayed for two consecutive years. Malaria indicator surveys were used as benchmarks to measure malaria prevalence at baseline (2020) and following each of the two rounds (2021 and 2022). The outcomes of interest were malaria infection at individual level and malaria prevalence and change in prevalence at the cluster level compared to the baseline. The intervention (50%) arm proved challenging given that IRS cannot be denied to the population, resulting in over spraying (above the target) of some rural clusters. In the control (80%) arm, spray teams struggled with under spraying (below the target), particularly in urban areas where achieving high coverage is challenged by low adherence and high numbers of houses to spray. Analyses were conducted in both intention-to-treat (74) and per-protocol clusters (27 clusters in the control and 23 in the intervention arm, after exclusions given by over and under spraying) using cluster-level summaries and mixed effects logistic regression models. Spillover effects were handled in two ways. First, analyses were conducted only at cluster cores, which were separated from the boundaries by a distance of 300 m. Second, coverage was estimated at each house within the cores by Using 100, 200 and 300 m circular buffers around it and dividing the number of neighboring houses that were sprayed by the total number within each buffer. The question at hand is critical given IRS is labor intensive and resource expensive, and support of a non-inferiority hypothesis would open new possibilities for vector control programs.

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<CHARACTERIZATION OF ANOPHELINES WARMS DURING THE DRY SEASON ALONG THE NIGER RIVER, MALI

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Previous studies in Mali have implicated riverbeds as malaria hotspots during the prolonged dry season. These Anopheline populations found on riverbeds sustain malaria transmission throughout the dry season. They also serve as inoculums for both the transmission and the spread of insecticide resistance in surrounding areas at the onset of the rainy season. Mosquito swarm physical destruction is an alternative control intervention to reduce insecticide-resistant vector population density. This study aims to characterize the swarming behavior of Anopheline populations during the dry season. This is in the prelude to their physical destruction as a control intervention along the Niger River in Mali. We conducted an active search for Anopheline swarms, starting 30 minutes before sunset during 3 successive days in and around each fishing hamlet located along the Niger River. For each detected swarm, the following characteristics were recorded: type of marker, height, size, and coordinates of the markers. In the fishing hamlets along the river, there were 84 swarming places. The main type of swarm markers was related to anthropogenic activities and included bundles of wood for cooking (30.8%), bare ground (29.1%), piles of garbage (12.8%), walls (12.8%), latrines (5.1%), and brick (4.3%). The mean number of Anopheles specimens per swarm was 31.5 (Min = 5; Max = 120). Most of the swarms were located outside human settlements. The mean height of swarming was 2.0 meters (Min = 1m, Max = 3.5m) above the ground. This study showed that most of the swarming markers were created by anthropogenic activities and were located outside of human dwellings making them easily accessible for destruction.

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FORECASTING WEST NILE VIRUS WITH GRAPH NEURAL NETWORKS: HARNESSING SPATIAL DEPENDENCE INIRREGULARLY SAMPLED GEOSPATIAL DATA

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In our work, we present a graph neural network model to forecast the location of mosquitoes positive for West Nile virus (WNV), a disease that has become endemic in much of North America over recent decades. The number of annual deaths across the United States alone has occasionally

reached the hundreds, highlighting the urgent need for improved measures to curb WNV transmission. Certain species of mosquitoes, primarily Culex, serve as vectors to transmit WNV from birds to humans. Effective targeting of mosquito eradication techniques such as insecticide, larvacide and bug traps remains challenging, and judicious selection of deployment location is one way to improve their effectiveness. Therefore, accurate short-term forecasting of WNV disease can aid mosquito control efforts. Machine learning methods have seen increased application to geospatial environmental problems, such as precipitation nowcasting, haze forecasting, and crop yield prediction. However, many of the machine learning methods applied to mosquito population and disease forecasting do not inherently take into account the underlying spatial structure of the given data. We apply a spatially-aware graph neural network model consisting of GraphSAGE layers to forecast the presence of West Nile virus in Illinois, which may aid mosquito surveillance and abatement efforts within the state. More generally, we show that graph neural networks applied to irregularly sampled geospatial data can exceed the performance of a range of baseline methods including logistic regression, XG-Boost, and fully-connected neural networks.

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TARGETING OF VECTOR CONTROL INTERVENTIONS TO MOBILE, MIGRANT, ETHNIC, AND VULNERABLE POPULATIONS IN MALARIA ELIMINATION SETTINGS: A COMPARISON OF APPROACHES IN THE GREATER MEKONG SUBREGION AND MESOAMERICA REGION

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Vector control is a key component to malaria control and elimination. About 78% of all clinical cases averted in Sub-Saharan Africa from 2000 and 2015 have been attributed to ITNs and IRS. Compared to high burden settings, Greater Mekong Subregion (GMS) and Mesoamerica Region are approaching malaria elimination, share similar socio-economic statuses, and have increasingly focalized transmission in hard-to-reach areas among mobile, migrant, ethnic, and vulnerable populations (MMEVPs). While the GMS is an early adopter of a mix of ITNs and novel interventions, contrastingly, deployment of ITNs is relatively nascent in the Mesoamerica Region. This presentation compares how GMS and Mesoamerican countries target vector control interventions to MMEVPs differently, and explores potential factors that contribute to these differences. In the GMS, alternative ITNs and novel interventions are deployed to protect MMEVPs against malaria, especially in outdoor settings. Cambodia is distributing forest packs containing LLIHNs (hammock nets) and topical repellents to forest-goers, while Vietnam is targeting LLIHNs to MMEVPs in the forested Central Highland (Pf hotspot) and single-sized LLINs to their counterparts in the mountainous North (Pv hotspot), accounting for 25.7% and 30.5% of populations in targeted communes, respectively. In the Mesoamerica Region, Panama is distributing LLIHNs to indigenous populations, Dominican Republic is covering Bateyes inhabited by migrant agriculture workers with LLINs, and Honduras is conducting IRS for Garifuna communities with proven poor LLIN use. Meanwhile, Guatemala is faced with the challenge of covering all active foci with LLINs due to limited funding and registered products. Moving forward, both regions are looking to continuously improve targeting of vector control interventions by addressing similar challenges. These include complex logistics for reaching unsafe or hard-to-reach malarious areas, inadequate protection against outdoor biting, and insufficient monitoring and evaluation among MMEVPs in order to optimize ITN usage and to select the most suitable interventions.

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EFFECTIVENESS OF DUAL-ACTIVE INGREDIENT LONG-LASTING INSECTICIDAL NETS (LLINS) ON PRIMARY MALARIA VECTORS: A SECONDARY ANALYSIS OF A THREE-YEAR CLUSTER-RANDOMIZED CONTROLLED TRIAL IN RURAL TANZANIA

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We performed a secondary analysis of entomological data from a four-arm, cluster-randomised controlled trial carried out to evaluate the effectiveness of three dual-AI LLINs, compared to standard pyrethroid-LLINs (PY-LLINs) against pyrethroid-resistant malaria vectors in rural Tanzania. Between January 2019 and December 2021, we conducted indoor mosquito collections using the Centres for Disease Control light trap (CDC light trap), quarterly in eight houses across 84 study clusters in Misungwi district, north-western Tanzania, followed by molecular laboratory analysis. Entomological outcomes were assessed based on the intention to treat, and the effect of the three dual-AI LLINs was compared to the standard PY-LLINs at the household level. Dual-AI LLINs had the greatest impact on Anopheles funestus s.l., the most efficient vector in the study area, with a comparatively weak effect on An. arabiensis. An. funestus density was 3·1 per house per night in the PY-LLIN arm, 1.2 in the chlorfenapyr-PY LLIN arm (p-value less than 0.0001), 1.4 in the piperonyl butoxide (p = 0.0012), and 3.0 in the pyriproxyfen-PY LLIN arm (p = 0.1453); malaria transmission intensity was also significantly lower in the chlorfenapyr-PY arm: 0.01 vs. 0.06 infective bites/household/night in the PY-LLIN arm (p less than 0.0001). Chlorfenapyr-PY LLINs were the most effective intervention against the main malaria vector An. funestus s.l. over three years of community use while the effect of PBO-PY LLIN was sustained for two years. The other vector An. arabiensis was not controlled by any of the dual-AI LLINs.

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HOT SPOTS AND BLIND SPOTS - ESTABLISHING A SURVEILLANCE BASELINE FOR TICKS AND TICK-BORNE PATHOGENS OF WEST AFRICA FROM 1901 TO 2022

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High quality tick surveillance data is crucial for developing risk assessments for tick-borne diseases and effective mitigation strategies to minimize exposure. Despite ongoing tick research in West Africa, there is a need for a comprehensive review to compile all available tick surveillance data from literature. VectorMap is an online database that characterizes the geographic distribution of arthropod vectors of veterinary and medical importance. To establish a baseline dataset of tick surveillance coverage within West Africa, a systematic literature review was conducted. This review included seven West African countries – Algeria, Morocco, Niger, Nigeria, Senegal, Sierra Leone, and Tunisia. Nineteen search terms and corresponding MeSH terms were used to capture literature from PubMed, Scopus and Web of Science search engines and published between 1901–2022. Over 4,180 articles were captured through our initial searches.

Articles were then filtered by removing duplicates, after which the title and abstracts underwent an eligibility check for inclusion in the review. Eligible articles contained mappable tick collection data, such as descriptions of collection event localities, map-displayed data, or GPS coordinates. Remaining papers then underwent a data extraction process. Additional sources were captured from reference sections of extracted articles representing articles which were not captured with the initial search terms. Information extracted from articles included tick and host taxonomy, geographic collection information, and pathogen detection information. Each unique collection event was georeferenced using the point-radius method and uploaded to VectorMap (vectormap.si.edu). The final novel dataset product consisted of data extraction events from nearly 300 articles, representing ticks from numerous genera, including Amblyomma, Aponomma, Argas, Carios, Dermacentor, Haemaphysalis, Hyalomma, Ixodes, Margaropus, Ornithodoros and Rhipicephalus. This data provides an oversight into surveillance coverage within the region, while also allowing for initial disease acquisition risk mapping.

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SPOTLIGHT REPORT: TICK SURVEILLANCE IN NIGERIA

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A systematic literature review was conducted to establish a baseline dataset of tick surveillance coverage of Nigeria within the VectorMap online database. The literature review made use of nineteen search terms, using PubMed, Scopus, and WOS search engines to capture articles published between 1901–2022. Over 2,000 articles were initially captured with these search terms, after which article titles and abstracts were assessed for relevance to tick and tick-borne disease surveillance. A total of 150 articles met the final inclusion criteria, while 53 additional articles were sourced from searches of the reference sections of articles that met the final inclusion criteria, for a total of 203 articles that underwent data extraction. Information captured during the data extraction process included tick genera and species, tick collection source, collection location, and instances of microbial species detection. Ten genera of ticks were reported within Nigeria, including Amblyomma (11 unique species/subspecies), Aponomma (1), Argas (3), Dermacentor (3), Haemaphysalis (11), Hyalomma (14), Ixodes (5), Margaropus, Ornithodoros (2), and Rhipicephalus (28). The majority of the collection records were ticks removed from vertebrate hosts (94.1%), of which domestic animals accounted for 89.3%. Wildlife hosts included various bird, rodent, and snake species, elephants, monitor lizards, duikers, hyena, sitatunga, and pangolin. Numerous tick-borne pathogens were detected in surveyed ticks, including Anaplasma spp., Babesia spp., Borrelia spp., Coxiella burnetii, Ehrlichia spp., Rickettsia spp., Theileria spp., Crimean-Congo hemorrhagic fever virus (CCHFv), Dugbe virus, and Jos virus. These results demonstrate that great efforts have been made in the characterization of Nigeria's tick fauna. Future studies may focus on ticks collected from the environment, ticks collected from wildlife, and further testing of ticks for tick-borne pathogens with particular emphasis on tick-borne viruses.

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SPOTLIGHT REPORT: TICKS AND TICK-BORNE DISEASE THREATS IN TUNISIA

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A systematic review was implemented to establish a dataset with tick geographic distribution within Tunisia. Establishing this dataset allows for it to be incorporated into VectorMap and potentially be used to inform vector-borne disease risk assessments. Over 1,070 peer-reviewed articles from 1901-2022 were systematically screened to meet the inclusion/exclusion criteria. A total of 35 articles met final inclusion criteria with data extraction and geo-referencing, before being combined into a single database. Tick species identified were from seven different genera including five hard ticks (Dermacentor, Haemaphysalis, Hyalomma, Ixodes and Rhipicephalus) and two soft tick genera (Argas and Ornithodoros). Eight species of Hyalomma ticks were reported, followed by 5 different species of Rhipicephalus ticks. The most commonly survey tick species were Hyalomma dromedarii (Koch, 1844) and Ixodes Ricinus (Linnaeus, 1758), with approximately 52% of articles detecting these species; with Hyalomma marginatum (Koch, 1844) and Hyalomma excavatum, (Koch, 1844), detected in 46% of studies. However, Rhipicephalus turanicus, Pomerantsev, 1936, was detected only in approximately 20% of studies. There were 21 pathogens were reported in Tunisian tick records, including: species of Anaplasma, Borrelia, Coxiella, Ehrlichia, Francisella, Rickettsia, Theileria and Trypanosoma. A lone record of Tick-borne encephalitis virus (TBEV) was also recovered. Hyalomma and Rhipicephalus ticks were the most reported genera with confirmed pathogens. The data collected from this systematic review provides valuable information on the diversity of tick species and can be used in part with surveillance to examine transmission of tick-borne diseases within Tunisia.

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SUCCESSFUL BARTONELLA HENSELAE INFECTION BY AN INCIDENTAL VECTOR IN IMMUNOCOMPROMISED AND IMMUNOCOMPETENT MOUSE MODELS

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The role of ticks in the transmission of Bartonella spp. has become an important topic in understanding Bartonella infections. The overlap of Bartonellosis diagnoses and Lyme disease patients implicates the black-legged deer tick (Ixodes scapularis) as a possible vector. Additionally, the identification of Bartonella spp. in wild I. scapularis with and without the presence of Borrelia spp. requires a systematic approach to determining vector competence. In this study, we compare the frequency and dissemination of bacteria in immunocompetent and immunocompromised mouse models by evaluating a wide variety of tissues for infection using nested PCR. The ability of Bartonella to infect and persist in the tick vector was determined using artificial and natural forms of infection[EME1] . Pathological findings of the liver, kidney, brain, and heart were examined using H&E staining. The data give insight into the role of I. scapularis as a vector of B. henselae as well as perspective on the requirements for infection and animal model development.

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SPOTLIGHT REPORT: HISTORICAL RECORD OF TICK DIVERSITY IN ALGERIA

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Tick-borne diseases remain a concern to the well-being of wildlife, livestock, and humans yet often lack essential data pertaining to tick diversity and distribution within countries. Conducting a systematic review allows for the geographic characterization of tick distribution within a country which can be helpful inform about potential pathogen presence and provide a dataset for VectorMap, an online collection database. Utilizing PubMed, Scopus, and WoS databases, MeSH terms were used to capture literature. A total of 711 peer-reviewed articles from the years 1901-2022 were systematically screened for data meeting the specific inclusion and exclusion criteria. After removing duplicates and filtering based on title, abstract and relevant data, 63 articles qualified for extraction and geo-referencing. Nine different genera were identified, hard tick species included (Amblyomma, Dermacentor, Haemaphysalis, Hyalomma, Ixodes and Rhipicephalus) and soft tick species included (Argas, Carios and Ornithodoros). There most species records were in Hyalomma spp. (n=14) which were followed by Rhipicephalus spp. (n=8). Rhipicephalus sanguineus (Latreille, 1806), Ixodes ricinus (Linnaeus, 1758) and Hyalomma impeltatum (Schulze and Schlottke, 1930) were the most species with individual records. From the collection records with host information, 76% of tick collection events were linked to animals, of which 84% were from livestock. There were 34 reported pathogens, which included Crimean-Congo hemorrhagic fever, Anaplasma spp., Babesia spp., Borrelia spp., Ehrlichia spp., Rickettsia spp., and Theileria spp. This systematic review provides important information about tick diversity and distribution within Algeria over the past 100 years. Additionally, this data can be utilized to assist with surveillance and help identify research knowledge gaps on ticks and tick-borne diseases in Algeria through manipulation of this geographic dataset.

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SPOTLIGHT REPORT: TICKS AND TICK-BORNE DISEASES OF NIGER

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Despite ticks and tick-borne diseases continuing to be a threat to the health of humans and livestock throughout West Africa, there continues to be a lack a of data for adequate risk assessment within the country of Niger. Determining the distributions of various tick species and identifying associated pathogens can provide valuable information regarding at risk areas for TBDs. To supplement tick collection data already documented in VectorMap, a systematic review of literature published between 1901 and 2022 was conducted. Over 300 articles were pulled from three databases, PubMed, Web of Science, and Scopus. Standardized search terms were used, and the resulting articles went through a series of title, abstract, and final review focusing on our inclusion criteria. This was followed by extraction and georeferencing of relevant data. Of the articles found, 40 met the inclusion criteria for Niger and six contained extractable data. A total of 22 individual species were identified from six genera, with Rhipicephalus most frequently reported. Pathogens in two genera were also documented including several newly sequenced genotypes of Ehrlichia and Rickettsia. Hyalomma truncatum (Koch, 1884) and Amblyomma variegatum (Fabricius, 1794) were found to be the most common hosts of pathogens. The current dataset, while limited, identify ticks as disease vectors in Niger and highlights the need for expanding current surveillance efforts. Further examination and analysis of these findings may aid in the selection of future sampling sites.

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ECTOPARASITES OF DOGS IN RURAL GUATEMALA COMMUNITIES AND INFECTION WITH ZOONOTIC AGENTS

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The peridomestic environment creates a receptive environment for the maintenance and amplification of zoonotic vector-borne disease causing agents. Domestic animals can serve as bloodmeal hosts to ectoparasites or other hematophagous arthropods, or function as reservoir hosts for zoonotic agents of disease. Detecting agents circulating in the enzootic cycle among domestic animals and ectoparasites is necessary to identify vector-borne disease threats to humans living in these environments. In June-August 2022, we conducted surveys of ectoparasites infesting domestic dogs and domiciles in rural communities in the municipality of Comapa, Department of Jutiapa, Guatemala. Of 77 homes inspected, 78% had at least one dog. Of the 133 dogs sampled, 46 (34.6%) were parasitized by ticks, primarily Rhipicephalus sanguineus, with a mean intensity of 4 (range 1-31), 91 (68.4%) had fleas with a mean intensity of 4.8 (range of 1-24), and one dog was infested with dog lice. Two homes had off-host Rhipicephalus sanguineus detected on the floors or walls. Overall, 83.5% of the dogs had at least one ectoparasite, and 64.9% of the homes had parasitized dogs. We used a combination of morphological and molecular identification to confirm ectoparasite species. Ectoparasites were tested for Rickettsia sp. and other pathogenic bacteria using PCR. These high infestations with ectoparasites that also feed on humans highlight the potential for spillover events of zoonotic vector-borne disease agents circulating in these rural communities that are currently not recognized by local ministries of health. These data also help to establish baseline surveillance for agents of vector-borne disease to inform future research evaluating host-targeted insecticides as an intervention to control vectors and reduce the incidence of human disease.

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ENHANCING EHRLICHIOSIS RISK DETERMINATION THROUGH THE SOUTHEASTERN TICK-BORNE EMERGENT PATHOGEN SURVEILLANCE (STEPS) PROGRAM IN TENNESSEE

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Ehrlichiosis is a tick-borne disease caused by bacteria of the genus Ehrlichia and transmitted by the lone star tick (Amblyomma americanum), an aggressive human-biter widespread in the southeastern United States. This illness accounts for a substantial burden of tick-borne disease cases in Tennessee. Field collections of questing ticks were conducted in the summer of 2021 in thirteen Tennessee counties with varying ehrlichiosis incidences to evaluate the utility of tick pathogen prevalence data to augment reported human disease incidence data to enhance understanding of tick-borne disease risk. Two sites per county were sampled by a dragging method 2-3 times between June and August, resulting in over 1,400 ticks collected. Samples were identified, pooled, processed, and tested for relevant human pathogens by real-time PCR: A. americanum ticks were tested for Rickettsia spp., Rickettsia rickettsii, R. parkeri, Ehrlichia chaffeensis, E. ewingii, Panola Mountain Ehrlichia sp., Bourbon virus, and Heartland virus; Dermacentor variabilis ticks were tested for Rickettsia spp. and R. rickettsii; Amblyomma maculatum ticks were tested for R. parkeri;

Ixodes scapularisticks were tested for Borrelia spp., B. burgdorferi s.s., and Anaplasma phagocytophilum. All A. americanum (n=1,307) were collected from four Middle Tennessee counties surveyed. Thirteen percent of A. americanum tick pools were positive for an Ehrlichia spp.; E. ewingii and the novel Panola Mountain Ehrlichia species (PME) were detected at higher rates than expected. Counties with higher ehrlichiosis incidences generally had higher infection rates of Ehrlichia spp. in A. americanum ticks. Based on our findings in tick populations, more ehrlichiosis cases may be due to E. ewingii infection than are being reported. Physicians should consider testing for E. ewingii in addition to E. chaffeensis when ehrlichiosis is suspected. The human pathogenicity of PME is uncertain, but the high prevalence of this pathogen in host-seeking ticks supports the need for further study to determine the public health risk posed.

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EFFECTIVENESS OF FLURALANER TREATMENT REGIMENS FOR THE CONTROL OF CANINE CHAGAS DISEASE. A MATHEMATICAL MODELING STUDY

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Canine Chagas disease is caused by the protozoan parasite Trypanosoma cruzi and transmitted by insect triatomine vectors known as kissing bugs. The agent can cause cardiac damage and long-term heart disease and death in humans, dogs, and other mammals. In laboratory settings, treatment of dogs with systemic insecticides has been shown to be highly efficacious at killing triatomines that feed on treated dogs.We developed compartmental vector-host models of T. cruzi transmission between the triatomine and dog population accounting for the impact of seasonality and triatomine migration on disease transmission dynamics. We considered a single vector-host model without seasonality, and model with seasonality, and a spatially coupled model. We used the models to evaluate the effectiveness of the insecticide fluralaner with different durations of treatment regimens for reducing T. cruzi infection in different transmission settings. In low and medium transmission settings, our model showed a marginal difference between the 3-month and 6-month regimens for reducing T. cruzi infection among dogs. The difference increases in the presence of seasonality and triatomine migration from a sylvatic transmission setting. In high transmission settings, the 3-month regimen was substantially more effective in reducing T. cruzi infections in dogs than the other regimens. Our model showed that increased migration rate reduces fluralaner effectiveness in all treatment regimens, but the relative reduction in effectiveness is minimal during the first years of treatment. However, if an additional 10% or more of triatomines killed by dog treatment were eaten by dogs, treatment could increase T. cruzi infections in the dog population at least during the first year of treatment.Our analysis shows that treating dogs every three to six months could be an effective measure to reduce T. cruzi infections in dogs and triatomines in peridomestic transmission settings. However, further studies at the local scale are needed to better understand the potential impact of routine use of fluralaner treatment on increasing dogs' consumption of dead triatomines.

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FLEA-BORNE PATHOGENS IN FLEAS FROM NATURALLY INFESTED DOGS AND CATS IN PRIVATE HOMES IN FLORIDA, USA

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The cat flea, Ctenocephalides felis, is the most common ectoparasite of dogs and cats, and can transmit a variety of pathogens including zoonotic Bartonella and Rickettsia species. The risk factors underlying transmission of these pathogens are incompletely elucidated. The objective of this study was to describe the flea-borne pathogens of fleas from owned cats and dogs and determine associations between flea pathogen carriage and pet and household characteristics. Fleas were collected from pets in 32 homes with flea infestation, in west central Florida, in May 2022. Fleas on each cat and dog were counted using a standardized procedure, then captured and killed by freezing; fleas in the home were also counted using overnight intermittent light traps, then killed by freezing. A survey was used to gather demographic and household information as potential explanatory variables. Fleas were pooled by animal and tested using 16S-rRNA next generation sequencing. Associations between the presence of Bartonella and Rickettsia spp. in fleas with potential explanatory variables were assessed using mixed effects modeling. There were 272 fleas collected from 40 cats in 31 homes, and 98 fleas from 8 dogs in 7 homes. Bartonella clarridgeiae was the most common Bartonella spp. found in fleas from cats and traps (28% and 6% of fleas infected, respectively), and the only Bartonella spp. found in fleas from dogs (4% of fleas infected). Rickettsia spp. were more common than Bartonella spp., found in 84% of fleas from cats, 92% of fleas from dogs, and 90% of fleas from traps. There were few fleas with DNA from other pathogenic bacteria. In conclusion, this study evaluated flea-borne pathogens in fleas from owned pets in their homes, confirming the prevalence of B. clarridgeiae in fleas, and reflecting potential flea-borne disease exposures in this population of pets and pet owners with limited access to veterinary care.

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MOLECULAR DETECTION OF YERSINIA PESTIS AND BARTONELLA SPP. IN RODENT FLEAS FROM PIURA, PERU

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Fleas are arthropod vectors of emerging and re-emerging pathogens, including bacteria of the genus Yersinia and Bartonella. In the Andean region of Piura, sporadic human cases of plague and bartonellosis had occurred. Thus, it is necessary to use vector surveillance to characterize the risk of zoonotic disease transmission. We conducted a cross-sectional study in Piura to determine the presence of Yersinia pestis and Bartonella spp. among fleas infesting rodents. DNA was extracted from 127 fleas collected from 130 rodents. A conventional multiplex PCR targeting the ypo2088 and pla genes was used for Yersinia pestis, while a conventional PCR targeting the gltA gene was used for Bartonella spp. Overall, 5 flea species were taxonomically identified: Xenopsylla cheopis (109), Plocopsylla hector (13), Leptopsylla segnis (3), Pulex irritans (1), and Ctenocephalides felis (1). Of rodents, Akodon mollis was the most abundant (46.1%, 56), followed by Rattus rattus (38.4%, 50) and Mus musculus (13.1%, 17), and four other species. Bartonella spp. DNA was detected in 15.6% (17/109) of Xenopsylla cheopis and 61.5 % (8/13) of Plocopsylla hector. Of the flea samples that were positive for Bartonella, 96% (24/25) were collected from Akodon mollis. Yersinia pestis DNA was detected in two specimens of Xenopsylla cheopis 1.6% (2/127) that were collected from one Rattus rattus and one Akodon mollis. We conclude that the presence of Bartonella spp. and Yersinia pestis in fleas of peridomestic and wild rodents in Piura represent a potential zoonotic risk. The molecular detection of Bartonella spp. in Plocopsylla hector is described for the first time and the need to study its vectorial capacity in the transmission of Bartonella to human populations is highlighted, as well as the role of Akodon mollis

as a reservoir. These pathogens represent important public health risks, especially in rural areas where humans and domestic animals are in close contact with peridomestic and wild rodents. It is necessary to propose ectoparasite control strategies due to the presence of Yersinia pestis in Xenopsylla cheopis because of previous reports in the area of bubonic plague cases.

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CHARACTERIZATION OF EPSTEIN BARR VIRUS INFECTION IN TONSILS OF CHILDREN RESIDING IN MALARIA HOLOENDEMIC REGION OF WESTERN KENYA

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Epstein Barr virus (EBV) is one of the co-factors linked to endemic Burkitt lymphoma (eBL) development, which remains the most common pediatric cancer in sub-Saharan Africa. We have previously shown that children in malaria-endemic areas acquire EBV infection by 6-months of age but there is little knowledge about EBV infection in tonsils, a secondary lymphoid organ in the source of virus transmission. In this cross-sectional study, we characterized EBV infection in blood, plasma, saliva and tonsillar mononuclear cells (TMCs) in children aged 1-14 years undergoing tonsillectomy from western Kenya, a malaria holoendemic region. EBV viral loads and EBV type were determined by PCR in blood, plasma, saliva and tonsillar mononuclear cells (TMCs). We found that the mean EBV viral load in TMCs was significantly higher compared to levels in blood ($p=0.002$). In addition, higher mean EBV viral loads was observed in saliva as compared to mean viral loads in plasma ($p=0.0465$). Although there was no correlation between age and EBV DNA copies in plasma, saliva and blood, a significant negative effect of age on EBV loads was demonstrated in TMCs ($r= -0.6875$, $p<0.0001$), indicating that there is reduction of EBV viral particles as age increases. Children coinfected with both EBV type 1 (EBV-1) and EBV-2 had significantly higher viral loads as compared to those infected with only EBV-1 ($p= 0.0024$) and not EBV-2 in saliva compartment, no difference was observed in the other compartments. This data suggests that, children residing in malaria endemic regions have elevated viral loads in tonsils which decreases as age progresses . In addition, coexistence of both EBV-1 and EBV-2 may favor increase of EBV infected cells hence increase in EBV viral loads.

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RECONCILIATION OF ADVERSE PREGNANCY OUTCOME RISKS BETWEEN FOUR ZIKA VIRUS COHORTS IN LATIN AMERICA

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Although the large ZIKA virus (ZIKV) epidemic in the Americas has now subsided, many disease parameters have yet to be defined, including a precise estimate of the frequency of microcephaly and other congenital anomalies following ZIKV infection during pregnancy. We did a detailed methods comparison of four of the key initial prospective cohort studies that evaluated the risk of ZIKV-related birth defects after maternal infection during pregnancy, using individual patient data meta-analysis to reconcile findings. The studies recruited participants between September 2015 and November 2016 in Brazil and the French Territories in the Americas (Guadeloupe, Martinique, French Guiana). All studies included pregnant women at any gestational age, with confirmed ZIKV infection, and provided systematic follow-up until the pregnancy outcome. However, important methodological differences were identified, including season of enrolment; further inclusion criteria applied; and modes and frequencies of mother and infant examinations. The overall pooled standardized risk estimate of any adverse fetal or infant outcome reported by the studies was 28% [95%CI: 16-41], with high heterogeneity ($I2=91\%$). There was high heterogeneity in pooled risk for many specific adverse outcomes, both overall and by trimester of maternal ZIKV infection diagnosis, such as spontaneous pregnancy loss and clinically apparent abnormalities at birth. We saw agreement ($I2<25\%$) between studies for some adverse outcomes by subgroups, including the risk of structural brain abnormalities after 1st trimester ZIKV infection diagnosis (7%, 95%CI:3-12), and the risk of microcephaly after 1st or 3rd trimester ZIKV infection diagnosis (4%, 95%CI:1-8, & 3%, 95%CI:0-6, respectively). Our study suggests that the variability of initial risk estimates published for adverse fetal and infant outcomes following maternal infection during pregnancy can be partially explained by methodological differences between studies. Standardization of early investigation protocols and pooling of findings in real-time during emerging disease events is recommended.

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EVALUATING BARRIERS AND FACILITATING FACTORS AROUND COVID-19 VACCINATION IN WESTERN UGANDA: A SURVEY OF COMMUNITY MEMBERS

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More than two years since COVID-19 vaccines were first administered, striking global disparities in COVID-19 vaccination rates continue to persist. While media reports have highlighted stagnating COVID-19 vaccination rates in Uganda — where only 28 percent of people have completed the primary vaccination series — specific drivers of low vaccination uptake at the community level remain unclear. We aimed to understand perceived barriers and facilitating factors around COVID-19 vaccination in Mbarara, Western Uganda. A survey (offered in both English and in Runyankole, the local language) was administered to community members 18-years and older passing by temporary COVID-19 vaccination tents set up in public areas. Individuals who approached the tents were invited to participate regardless of their plans to receive COVID-19 vaccination. Chi-square analysis was used to test relationships between prior COVID-19 vaccination status and other variables measured. 1006 community members completed the survey between 30 September 2022 to 11 October 2022. 765/992 (77 percent) had received at least one prior COVID-19 vaccine dose, while 227/992 (23 percent) had never received COVID-19 vaccination. 741/990 (75 percent) of respondents agreed that "A permanent Covid-19 vaccination site is located close to my home or workplace," and 946/990 (96 percent) said they could reach the nearest COVID-19 vaccination site by foot or motorcycle taxi. Previously unvaccinated individuals were more likely to be younger ($p = 0.02$), be male ($p = 0.03$), have never been previously turned away from a vaccination site ($p = 0.0001$), and say that confidence in vaccines should be improved in order to improve local COVID-19 vaccination rates ($p = 0.001$). Although vaccine supply remains a challenge in western Uganda, these results suggest that many community members can conveniently access COVID-19 vaccination sites, and local vaccination programs should prioritize demand creation including among young men.

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DEVELOPMENT OF A SURFACE PROTEIN-BASED MULTIPLEX IMMUNOASSAY FOR MPOX SEROLOGICAL TESTING AND SURVEILLANCE

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The global outbreak of MPOX (MPXV) in 2022 highlights the need to better understand the ecology and distribution of this historically uncommon viral zoonosis. Yet, extensive antigenic cross-reactivity among orthopoxviruses limits specificity of serological assays used to asses MPOX seroprevalence in humans and wildlife. Here, we develop an antigen-based multiplex immunoassay to discriminate MPOX-positive IgG from vaccinia (VACV) and smallpox (VARV). First, 21 MPXV, VACV, and VARV immunodominant surface proteins produced from a variety of sources and expression systems were coupled to magnetic microspheres and tested in multiplex microsphere-based immunoassays with hyper-immunized polyclonal rabbit sera raised against VACV and VARV. To qualify homologous antigens and establish cross-reactions, we tested multiplex panels incorporating homologous MPXV, VACV, VARV surface proteins. Antigen-antibody cross reactions were observed in each of these panels and four MPXV antigens with lower cross-reactivity to VACV polyclonal antisera were identified. Two antigens, A35 and A29L, were selected as potential targets for sensitive binding of MPXV IgG and two antigens, E8L and L1R, were selected as potential targets for specific antibody-binding. Sera from non-human primates challenged with Modified vaccinia Ankara (MVA) were tested with this four-antigen multiplex to further characterize cross-reactions against MVA. Interestingly, A35 and E8L were cross-reactive against MVA while A29L and L1R were less cross-reactive, potentially conferring a higher degree of specificity. The performance of a protein and peptide antigen multiplex panel for specific MPXV antisera detection will be evaluated with convalescent sera from MPOX-infected individuals to further investigate observed antibody-binding patterns. Future work will focus on establishing signal ratios, thresholds for seropositivity, and determining sensitivity and specificity of the assay.

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A SCOPING LITERATURE REVIEW OF GLOBAL DENGUE AGE-STRATIFIED SEROPREVALENCE: ESTIMATING DENGUE FORCE OF INFECTION IN ENDEMIC COUNTRIES

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With half of the world's population at risk of infection, dengue poses a significant public health challenge worldwide. However, its transmission intensity in several endemic countries remains poorly understood, making it challenging to assess the burden of disease and the potential impact of control interventions. The objective of this scoping review was to gain a more comprehensive understanding of the heterogeneity in dengue transmission intensity within endemic countries. We extended a previous review of dengue serological surveys by collating global age-stratified dengue seroprevalence data published in the Medline and Embase databases from 2014 to 2022. These data were then used to calibrate catalytic models and to estimate per-capita risk of infection for a susceptible individual (the force of infection, FOI), which is a key measure of transmission intensity. We found a total of 44 new publications containing 47 relevant datasets from 20 dengue endemic countries. We estimated large heterogeneities in dengue FOI both across and within countries, with FOI estimates ranging from an average of 0.01 in the city of Kaohsiung, Taiwan - specifically in the Nanzih district - to an average of 0.209 in Gressier, Jacmel and Chabin communes of Haiti. Our findings show the geographical distribution of age-stratified serological surveys for dengue and, importantly, highlight regions where gaps in serosurveillance remain. Furthermore, our findings can be used to inform ongoing modelling efforts to improve our understanding of the drivers of heterogeneity in dengue transmission intensity globally, and help guide ongoing efforts to better characterize the global burden of dengue.

6694

DETERMINATION OF REQUIREMENTS TO ENSURE EFFECTIVE INACTIVATION OF POWASSAN VIRUS AS A SURROGATE BIOLOGICAL SELECT AGENTS AND TOXINS (BSAT)

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To ensure BSAT are effectively inactivated, it is imperative to employ best practices in the development, validation, production, authentication, inactivation, traceability, and disposition of the material. Inactivated BSAT should be subject to the highest level of oversight and confirmation testing due to the potential risk of incompletely inactivated pathogens in downstream use under reduced containment. Implementing inactivation provisions and methods for diverse agents has proven challenging since the effectiveness of the inactivation procedures can differ greatly between agent and sample matrix types. In this project, we determined inactivation protocols (inactivation by heat, chemical, or γ-irradiation) and pinpoint critical inactivation parameters for surrogate BSAT pathogen, Langat virus in pilot studies and Powassan virus for validation studies. Inactivation method parameters for Langat virus were then validated by treatment of multiple replicate samples. Parameter set points for the validation study were selected above the minimal effective pilot study parameters using increased dose exposure time, elevated temperature, or chemical concentration. The validated inactivation methods were then tested for effectiveness on Powassan virus (strain LB). Powassan virus, while not a select agent, was used in place of Tick-borne encephalitis virus as a second closely related surrogate in the Flavivirus family. Using the surrogate method validation/verification test approach, we have identified parameters for three different methods of inactivation of Powassan virus. The validated heat inactivation method parameters determined for the Langat strain were successfully transferred and verified on the BSAT surrogate Powassan virus. Formalin inactivation of Langat virus was accomplished using centrifugal filter units for buffer exchange of formaldehyde with PBS following treatment, and the inactivation method was successfully applied to Powassan virus. Finally, γ-irradiation doses were validated with Langat virus and effective parameters were successfully transferred and verified on Powassan virus.

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ASSOCIATION OF FOREST RELATED ACTIVITIES WITH MADARIAGA VIRUS INFECTION IN THE COMMUNITY OF ARUZA IN PANAMA

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Madariaga virus (MADV) is an emerging zoonotic pathogen in Latin America that was first associated with large human outbreak in 2010, in the most eastern province of Darien in Panama. Subsequent studies suggest that

the risk of MADV infection vary geographically within communities the Darién province. For example, MADV risk of infection appears to increase in communities with extensive agriculture and cattle ranching activities, while this risk appears to be dismissed in communities with forest proximity. We intend to evaluate whether livestock or agricultural activities are associated with the seroprevalence of the Madariaga virus in the community of Aruza Panama, the community with the highest MADV seroprevalence. A cross-sectional population serosurvey was undertaken in Aruza during 2019. Characteristics of the study population was obtained. The association with MADV seroprevalence and outcome variable was evaluated at the univariate and multivariate level and expressed as prevalence ratios (PR) using a Generalized Lineal Model (GLM), poisson family Log link function. Independent variables include forest related activities, sex, age, among others. An epidemiological based strategy was used to obtain the most parsimonious model. A total of 251 participants were enrolled in the study, of these, 28.5% reported carrying out livestock or agricultural activities. The estimated seroprevalence of MADV in Aruza was 23.4 %. People who carry out livestock or agricultural activities have a prevalence of MADV of 1.95 (PR=1.95; IC95% 0.58 - 6.55; p=0.282) times compared to those who do not do these activities, adjusting for sex, age and other occupations. Working in the forest has a seropositive for MADV of 4.47 (RP=4.47; IC95% 1.89 - 10.54; p<0.001) times compared to those who do not carry out this type of activity in the forest, adjusting for sex, age and other activities. Our results suggest that people who work in the forest are at higher risk of MADV infection, these results contrasts with previous findings and highlights the need for future evaluations of MADV risk factors.

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DESCRIBING THE IMPLICATIONS OF TEMPERATURE ON THE TRANSMISSION POTENTIAL OF RIFT VALLEY FEVER VIRUS IN CULEX TARSALIS AND AEDES AEGYPTI MOSQUITOES

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Disease-transmitting mosquitoes are constrained by environmental conditions in which they live. The impacts of temperature on mosquito development has been characterized, but few investigations have elucidated the effects of the larval rearing temperature on virus dissemination and transstadial persistence in naturally-infected mosquito vectors. This is of considerable significance as global climate change shifts the habitat boundaries of mosquito vectors, allowing global transmission of infectious diseases to previously unaffected geographical regions. One such emerging infectious disease of concern is Rift Valley fever virus (RVFV), a zoonotic disease endemic to sub-Saharan Africa that is poised for introduction into Europe and the United States due to international trade and travel. Mass abortion storms of livestock and hemorrhagic disease of humans are attributed to RVFV infections. To characterize the impacts of temperature on RVFV transmission in mosquito vectors, we collected adult mosquitoes from Culex tarsalis and Aedes aegypti laboratory colonies. Five to seven days after adult emergence, mosquitoes were provided a RVFV-infected blood meal, derived from wild-type strain KEN128B-15. Mosquitoes were placed at experimental temperatures (28°C, 18°C and 32°C), monitored for oviposition, and provided an uninfected blood meal to induce a second egg-lay. Progeny mosquitoes from this second gonotrophic cycle were reared at the aforementioned temperatures and collected at each life stage to determine RVFV-positivity by plaque assay and to confirm infection status with qRT-PCR. We hypothesize that temperature will drive virus transmission efficiency, and that infection prevalence and transstadial persistence will vary by temperature- and life stage. Preliminary data demonstrate impaired oviposition and larval rearing success at both 18°C and 32°C. Results from these ongoing investigations will be presented.

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PERSISTENCE OF VIRAL RNA IN HOSPITALIZED PATIENTS WITH LASSA FEVER IN LIBERIA

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Lassa virus (LASV) is a persistent regional and global public health threat that causes annual outbreaks in Liberia, Sierra Leone, and Nigeria. Despite the large numbers of individuals infected annually and high rates of mortality among hospitalized patients (25-50%), little is known about viral replication kinetics or the association between host and virus-related factors and clinical outcomes. Plasma samples from patients with suspected LASV infection admitted to Phebe Hospital in Bong County, Liberia were tested for LASV using the semiquantitative Altona 2.0 polymerase chain reaction assay. Among those with confirmed LASV infection serial sampling of a subset of patients occurred on days 3, 5, 7, 10 following diagnosis and 3-, 6-, 9-, and 12-months following discharge along with the collection of demographic and clinical information at each time point. Host- and virus-related factors including sex, age, time from symptom onset and viral loads assessed by cycle threshold (CT) values at the time of diagnosis were compared between patients who survived and died. Clinical data and CT values from 76 patients (mean age 24 years; 50% female; mean 6 days from symptom onset) with confirmed Lassa fever were analyzed including 38 with serial sampling. Of the 76 patients, 66 (87%) survived to discharge. Of 38 patients with more than 1 sample, all of whom received Ribavirin treatment, 90% (26/29) on day 3, 85% (22/26) on day 5, 77% (20/26) on day 7, and 87% (20/23) on day 10 had detectable plasma LASV RNA. The proportion of patients in which LASV RNA was still detectable declined at 3 months post-discharge to 18% (2/11) and 0% (0/7) at 6 months post-discharge. LASV L CT values were significantly greater in survivors (mean CT 31.3) compared with non-survivors (mean CT 26.0; p=0.0184) while LASV GP CT values demonstrated a trend in the same direction (mean CT 30.6 and 27.3 respectively; p=0.059). While PCR positivity indicates that LASV RNA is detectable, it is not known if this represents infectious virus. The persistence of LASV RNA in a large proportion of patients with Lassa fever despite Ribavirin treatment has important clinical and infection control implications.

6698

SIGNIFICANT GAPS IN KNOWLEDGE AND ATTITUDES TOWARDS VACCINATION IN A HIGHLY AFFECTED POPULATION BY THE MONKEYPOX EPIDEMIC: CASE OF KUMBA HEALTH DISTRICT, CAMEROON, SEPTEMBER 2022

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Monkeypox is an infectious disease endemic to West and Central Africa. Despite being endemic in Cameroon, the level of knowledge and prevalence of the disease among healthcare workers (HCWs) is unknown. In December 2021, two confirmed cases were detected in Kumba Health District (KHD),prompting a field investigation during which we evaluated knowledge, attitudes, and practices (KAP) among HCWs and determined seroprevalence among inhabitants. We conducted a KAP study among HCWs in KHD from September 9-14, 2022. We used questionnaires to collect socio-demographic data, knowledge, attitudes toward vaccination

and perceived threat posed by monkeypox. We collected blood in EDTA-tubes from persons visiting health facilities for evaluation of seroprevalence. Samples were tested using an in-house Luminex™ anti-Monkeypox IgG detection kit. We interviewed 104 HCWs (38% nurses, 21% nurse assistants, 9%, laboratory personnel, 4% physicians). Half of them (51/102) had previous knowledge on monkeypox, 13.6% (14/102) had received university or jobsite monkeypox training. The percentage-standardized score for knowledge on prevention, transmission, clinical presentation, and management of monkeypox was 31.2/100. There was no difference between the knowledge scores and vaccination attitudes of the four categories of HCWs studied. Sixty-two percent (63/101) were accepting of monkeypox vaccination, but only 42.4% (42/99) were ready to pay for it. Monkeypox was perceived as less of a health threat than tuberculosis, hepatitis B, HIV, and COVID-19. We tested 166 inhabitants for anti-monkeypox IgG with median age of 25 years (5 months - 73 years) and male/female sex ratio of 0.8. The prevalence of anti-monkeypox IgG was 12.7% (21/166). There were significant knowledge gaps and unsatisfactory attitudes toward vaccination. Monkeypox was overlooked as a serious pathogen. The seroprevalence of monkeypox was high among inhabitants. These findings stress the importance of appropriate training of HCWs and strengthening of the monkeypox surveillance system.

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EVALUATION OF THE LEVEL OF KNOWLEDGE, ATTITUDES, PRACTICES OF PREVENTIVE MEASURES AGAINST COVID-19 DISEASE AMONG MEDICAL STUDENTS AT THE UNIVERSITY OF HEALTH SCIENCES IN GABON

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In Gabon, during the acute phase of the COVID-19 pandemic, medical students were involved in response activities. This has contributed to their exposition to infection. The objective of this study was to assess the level of knowledge, attitudes and practices of preventive measures related to COVID-19 by medical students of Faculty of Medicine, in Gabon. A cross-sectional survey was conducted among undergraduate and postgraduate medical students aged over 17 years, at the Faculty of Medicine, in Gabon from February to June 2022. Socio-demographics characteristics, knowledge, attitude, and practice toward COVID-19 were collected through a self-administered questionnaire under the supervision of the team. The results were analysed using statview 5.0 software and A p-value of <0.05 indicated statistical significance. Of the 711 survey participants, 55.3% were female and the majority were under 25 years of age (63.6%). A majority of medical students had good knowledge (87.9%, n= 625/711), positive attitudes (80.3%; n= 571/711) and only 40.5% (n= 288/711) had good practices. The majority of the participants (n= 683; 96.4%) knew that COVID-19 is a viral disease. More than 85% knew that preventive measures such as wearing mask, frequent hand washing and social distancing are effective. Attitude analysis highlighted that 86.4% of surveyed population considered that COVID-19 is a serious illness and 93% (n= 659) stated that it can be cured. Although 75.3% of the students reported frequent hand washing and 87.9% regularly wore masks, 75.5% reported high frequentation crowded places. Men and those under 25 years had better knowledge, attitudes and practices (p= 0.3). In addition, the rate of good knowledge (96% Vs 86.6%) was higher among postgraduate medical students than upgraduate students. In conclusion, This study demonstrated satisfactory knowledge, positive attitudes regarding COVID-19 among medical student; however, effective good practice was low There is therefore a need to intensify education and to perform training sessions on COVID-19.

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SARS-COV-2 SEROPREVALENCE AMONG INTERNATIONAL TRAVELERS FROM SELECTED DISTRICTS OF THE COPPERBELT PROVINCE OF ZAMBIA

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Like many other countries, Zambia at the peak of transmission, put in place measures to control the spread of SARS-CoV-2 infections including testing of all travellers who were exiting the country. The Tropical Diseases Research Centre (TDRC) was among the main testing facilities in the copperbelt province and the country as whole. The study reports on the characteristics, prevalence and distribution of SARS-CoV-2 infections among international travellers from selected districts in the copperbelt province of Zambia, Chililabombwe, Chambishi, Chingola, Kalulushi, Kitwe, Mufulira and Ndola for the period January 2021 to December 2022. Either Nasopharyngeal or oral samples were collected from travellers who reported to the TDRC testing facility. The samples were processed and tested for SARS-CoV-2 using the Reverse Transcription - Polymerase Chain Reaction methods (RT-PCR). A total of 9616 travellers from whom a complete set of required data was obtained were recorded. The mean age of the travellers was 39.3 years range (3 to 97 years), while only one third of the travellers were female. Kitwe district followed by Ndola district had the highest number of travellers at 36.5% and 25.5% respectively. The overall prevalence of sars-cov-2 was 4.78%. this prevalence was comparable to that of the general population.

6701

DEVELOPMENT AND VALIDATION OF A REAL TIME QPCR FOR YELLOW FEVER VIRUS DETECTION

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Yellow fever virus (YFV) is a re-emerging infectious disease, belonging to the genus Flavivirus. Epidemic cases are reported in Africa and throughout Central and South America even though an effective YF vaccine has been available since 1939. Due to novel circulating strains some reports suggest the mortality could reach up to 60% in some cases. In recent years, there have been several reports of enzootic transmission, and in turn, the increase in unvaccinated people in the area could lead to a change in the epidemiology of YFV transmission and infection. Therefore, timely confirmation by laboratory tests and implementation of epidemiological surveillance are needed to mitigate the impact of a potential outbreak. In this study, we adjusted the RT-qPCR using primers and probes for the specific detection of YFV described previously by Wu et al 2018. LOD RT-qPCR was determined by standard curves using serial 10-fold dilutions of RNA from YFV 17D (vaccine from Fiocruz) Vero-2 2007 that was validated as internal positive control. The standard curve was determined by the ABI7500 FAST software and a coefficient of determination R2 = 0.998, Eff% = 98.044 and slope -3.37 were obtained. Furthermore, the cross-reactivity panel demonstrated absence of signal to YFV and did not show cross-reactivity to viruses such as Mayaro, Oropouche, Alphavirus, Influenza, Chikungunya, SARS-CoV-2, West Nile, Ilheus, Rocio, Zika and Dengue. In addition, spiked YFV samples (n=20) and negative human samples (n=20) were used to validate the assay and were compared to a standard conventional PCR. As a result, the conventional PCR assay had a 75% (15/20) sensitivity and 100% (20/20) specificity and the RT-qPCR assay had 100% (20/20) sensitivity and specificity. This demonstrated successful identification and discrimination, avoiding a longer detection using conventional PCR format that requires electrophoresis of RNA onto agarose gels. Finally, it can be successfully applied for surveillance and for monitoring of cases in Peru. This tool will aid in the detection and monitoring of YFV in endemic regions to be prepared for future outbreaks and strengthen surveillance efforts.

6702

ENDEMIC VENEZUELAN EQUINE ENCEPHALITIS VIRUS ACTIVITY IN RURAL AND URBAN SETTINGS OF PANAMA

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Venezuelan equine encephalitic (VEEV) viruses (Alphavirus genus, Togaviridae family) are arthropod-borne zoonotic RNA viruses associated with human and equine disease throughout Central and south America. Panama, like many other countries, reports annually humans VEEV infections, which indicates its active circulation in rural enzootic areas. Symptoms of VEEV infection in humans can range from mild symptoms similar to those caused by other arboviruses to severe encephalitis, approximately 1% of cases are fatal. Using a population cross-sectional survey undertaken in urban areas of Panama and Panama Oeste during the COVID-19 outbreak, we aimed to detect evidence of VEEV circulation in urban areas. A total of 2198 participants were enrolled from November 30 to December 4, 2020, in 10 townships of Panama and Panama Oeste provinces. Serum samples from participants were used to detect antibodies against VEEV using a plaque reduction neutralization test. The association between VEEV seroprevalence and the exposure variables was evaluated at the univariate and multivariate level using a logistic regression model and a likelihood-ratio test as a variable selection method. A total 60.3% of the population were women, while 25.5% were adults over 60 years old, 63.7% of the population had mixed background, 48.4% had elementary studies. A total of 1951 participants reports living for years in the investigate area. The VEEV seroprevalence was 2.9 %. Adults with more than 60 years old were at higher risk of VEEV infections compared to the other age groups. Antibodies against VEEV were found in Juan Demostenes Arosemena, Vista Alegre, Ernesto Cordoba Campos and Chilibre townships. The risk of living in Juan Demostenes Arosemena township in Panama Oeste province was 4.14 times compared to the other townships. Higher education was a protective factor for VEEV infection when compared with having at least primary or elementary studies. Our results suggest an endemic circulation of VEEV in urban settings of Panama and Panama Oeste provinces.

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TWO-DOSE VACCINE EFFECTIVENESS FOLLOWING THE FIRST REACTIVE MASS VACCINATION CAMPAIGN AGAINST HEPATITIS E IN BENTIU, SOUTH SUDAN

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A 3 dose recombinant vaccine against hepatitis E, Hecolin, was licensed in 2011. While not recommended for routine use due to lack of burden data in the general population, in 2015 WHO recommended consideration of the vaccine in outbreaks. As of early 2022, the vaccine had not been used in an outbreak. A reduced-dose vaccination schedule, if effective, could make the vaccine an important outbreak response tool. In response to an increase in hepatitis E cases in a camp for internally displaced people in Bentiu, South Sudan in late 2021, the first ever mass reactive vaccination campaign against hepatitis E virus (HEV) was conducted. Three vaccination rounds took place in March, April, and October 2022, targeting 26848 individuals 16-40 years, including pregnant women. We set up enhanced surveillance and conducted a case-control study to estimate two-dose vaccine effectiveness (VE).All suspected cases presenting to the MSF hospital who were eligible for vaccination and provided consent were enrolled in the study, comprising a questionnaire, laboratory tests and a follow-up visit after 2-4 weeks. Vaccine-eligible suspect cases were matched to community controls. We estimated VE against probable (anti-HEV IgM+ & elevated ALT, or &gt4-fold IgG rise) and confirmed (HEV RNA+) hepatitis E using conditional logistic regression.From 11 May to 30 December 2022, we enrolled 287 vaccine-eligible suspect cases, including 1 probable and 16 confirmed. Among these, 2 (11.8%) were vaccinated with &gt2 doses compared to 40 (40%) of 100 matched controls. We estimate a VE of 86.5% (95%CI 36.3-97.1) for 1-2 doses and 83.9% (95%CI, -33.1-98.1%) for 2 doses. In addition to this direct protection, we observed a 5.5-fold decrease in the incidence rate of probable/confirmed cases after the second dose campaign. Lab confirmation is ongoing, and we will revise VE estimates and incidence based on these results. Following the first mass reactive vaccination campaign against hepatitis E, incidence declined. Preliminary VE estimates suggest that the short-term protection provided by this reduced dose-regimen may be high and potentially sufficient for outbreak response.

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DIAGNOSTIC ACCURACY OF THE ZIKV DETECT™ 2.0 IGM CAPTURE ELISA AND THE ZIKA IGM RAPID TEST PROTOTYPE FROM INBIOS INTERNATIONAL INC

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Serological ZIKV diagnosis is challenging due to cross-reactivity with other flaviviruses. We evaluated the accuracy of two IgM-based serological tests from Inbios International Inc: the ZIKV Detect™ 2.0 IgM Capture ELISA and a Zika IgM Rapid Diagnostic Test (RDT) prototype, using a panel of sera from Brazil. Sensitivity was evaluated in 48 acute (≤7 days post-fever onset, DPFO) and 26 convalescent (10-60 DPFO) paired samples from RT-PCR-positive Zika cases. Specificity was evaluated in paired acute and convalescent samples from 39 RT-PCR-positive dengue cases, 25 RT-PCR-positive chikungunya cases, 50 acute febrile illness (AFI) cases with negative RT-PCR for ZIKV, DENV and CHIKV, and 23 blood donor samples; these samples were collected outside ZIKV epidemic year, except for samples from 6 dengue cases. We also evaluated the tests on paired samples from 47 AFI cases with negative RT-PCR for ZIKV, DENV and CHIKV from ZIKV epidemic year, aiming to verify whether the tests could detect ZIKV infections despite a negative ZIKV RT-PCR. The RDT results were blindly assessed. Sensitivity increased from <10% in the acute phase for both tests to 96% and 73% during the convalescent phase for ELISA and RDT, respectively, and was highest after 15 DPFO (100% and 73.7%, respectively). Specificities among the dengue samples were 87.2% and 92.3%, respectively; excluding the samples from the epidemic year, they were 96.6% and 94.4%, respectively. Specificities were 84% for both tests among the chikungunya samples; 96% and 92% in the non-epidemic AFI samples, respectively; and 91.3% and 100% among the blood donor samples, respectively. Among RT-PCR-negative AFI cases from the ZIKV epidemic, the tests' positivity increased from the acute to convalescent samples (from 40.4% to 70.2% and 17% to 44.7%, respectively), suggesting that the RT-PCR missed some Zika cases. This was more evident for the subgroup with DENV IgM seroconversion (from 38.5% to 84.6% and 7.7% to 53.8%, respectively). The ELISA had excellent sensitivity during convalescence and high specificities during years non-epidemic for ZIKV. The RDT prototype had high specificity and moderate sensitivity.

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EPIDEMIC TRANSMISSION OF CHIKUNGUNYA VIRUS DURING COVID-19 PANDEMIC LOCKDOWN MEASURES: A COHORT STUDY IN AN URBAN INFORMAL SETTLEMENT IN BRAZIL

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The observed decrease in CHIKV incidence globally during the pandemic has been speculated to be due to COVID-19-related disruption of human movement or alternatively, disruption of national arboviral surveillance. We evaluated the incidence of CHIKV infection in community-based cohort from Salvador, Brazil was followed prior to and during the initial phase of the COVID-19 pandemic when lockdown measures were implemented and identified risk factors associated with transmission. We prospectively investigated a cohort of residents from an informal urban settlement by conducting three serosurveys from Sep 21 to Dec 16, 2018, Sep 09 to Nov 11, 2019 and Nov 18 to Feb 26, 2021. We performed interviews during surveys to obtain information on demographics, self-reported symptoms, and environmental risk factors. CHIKV seroconversion was ascertained by evaluated paired samples in the anti-CHIKV ELISA IgG. Among 1,038 participants of the 1st survey, 608 (59%) were followed in the 2nd and 3rd surveys. Among the 608 participants, the incidence of CHIV seroconversion was of 6.1% (37/608) between Survey 1 and 2 (pre-pandemic) and 31.1% (178/571) between Survey 2 and 3 (post-pandemic period). Residents whose households are located more than 50 meters away from an open refuse deposit are at a lower risk of CHIKV seroconversion (OR= 0.44, 95% CI= 0.2 - 0.7). However, reporting mosquitoes at home in the past 7 days is a risk factor for CHIKV seroconversion during the post-pandemic period (OR= 1.60, 95% CI= 1.1 - 2.3). Self-reported Chikungunya-associated symptoms were significantly higher (47.2% vs 30.9%, p<0.001) in participants who seroconverted compared to those who did not. Our findings indicate that epidemic CHIKV transmission can occur and impart high (30%) attack rates despite pandemic-associated interventions that restricted human movement and that low incidence of reported Chikungunya cases in similar settings was likely due to disruption of surveillance systems. The findings, although limited by recall bias, suggest that the symptomatic illness-to-infection ratio attributable to CHIKV exposure may be lower than traditionally believed.

6706

ANTIBODY DYNAMICS TO MPOX INFECTION AND MVA-BN VACCINATION

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Since May 2022 there has been an outbreak of Mpox in non-endemic regions. A vaccinia-derived vaccine, MVA-BN (JYNNEOS), is approved for use against Mpox due to assumed cross-protection with other poxviruses. However, it is unclear what level of protection MVA-BN provides against Mpox. To begin to address this gap, we quantified and compared the magnitude and kinetics of the early human antibody response in MVA-BN vaccinees (n=32) and in individuals with PCR-confirmed Mpox (n=30) out to 4-6 months. We measured IgG, IgA and IgM antibody levels by ELISA to inactivated MPX viral lysate and several recombinant antigens, most known to play a role in viral neutralization (e.g. A29L, A30L, A35, E8L, H3L and I1L). Individuals with Mpox developed antibody responses to all antigens tested, except H3L; and were most robust to A35L, E8L, and inactivated viral lysate. We found no significant difference in antibody responses between individuals living with and without HIV/AIDS with Mpox. Antibody responses in vaccinees peaked after the second vaccine dose and were lower in magnitude, decayed more rapidly, and targeted fewer antigens than cases. These data suggest that individuals with Mpox have more robust and broader immune responses to Mpox proteins than MVA-BN vaccinees, however further work is needed to determine the level of protective immunity offered by MVA-BN.

6707

SARS-COV-2 SEROPREVALENCE AND PREECLAMPSIA MARKERS AMONG UNVACCINATED MOZAMBICAN PREGNANT WOMEN WITH FETAL LOSS

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SARS-CoV-2 infection in pregnancy has been associated with increased risk of poor pregnancy outcomes, including preeclampsia and perinatal deaths. However, there is limited information on the burden of SARS-CoV-2 infection among pregnant women and their offspring in most African countries. We estimated SARS-CoV-2 seroprevalence among unvaccinated Mozambican pregnant women with fetal losses. This is a descriptive cross-sectional study including pregnant women delivering a stillborn or an infant dying in first hours of birth (early neonatal death) at Maputo Central Hospital (MCH), Mozambique. SARS-CoV-2 immunoglobulins (Ig) were determined in maternal and fetal blood. Biomarkers of preeclampsia (sFlt-1/PlGF) were also assessed in maternal blood. A total of 100 women were enrolled in the study between March 2021 to April 2022. All were COVID-19 unvaccinated women and had a mean age of 29 years (SD ±6.74). Overall, SARS-CoV-2 Ig were detected in 68 [68%; 95% CI (0.58 - 0.76)] women and 55 [55%; 95% CI (0.54 - 0.74)] fetuses. 60 women had SARS-CoV-2 IgM [95% CI (0.81 - 0.96)] and 53 had SARS-CoV-2 IgG [95% CI (0.69 - 0.88)]. Levels of sFlt-1/PlGF were significantly increased in women with SARS-CoV-2 Ig. In conclusion, SARS-CoV-2 seropositivity among Mozambican unvaccinated pregnant women with fetal loss was high and it was associated with increased preeclampsia markers.

6708

MORTALITY FROM CHRONIC HEPATITIS C IN BRAZIL ANALYSIS OF THE MULTIPLE CAUSES OF DEATH IN THE PERIOD 2000 TO 2019

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Chronic hepatitis C is the leading cause of death among viral hepatitis in Brazil. The relevance of working with multiple causes of death (basic cause and associated causes) constitutes a breakthrough in the analysis of mortality statistics. To describe deaths from chronic hepatitis C, as the underlying cause and multiple causes of death, and to analyze the temporal and spatial distribution of these deaths in Brazil, from 2000 to 2019. This is an ecological study, with data from the Mortality Information System (SIM). All analyzes will be performed comparing mortality rates for chronic hepatitis C as the underlying cause of death and as multiple causes of death. Descriptive analysis of deaths from chronic hepatitis C will be performed, according to sociodemographic aspects. For the time series analysis, chronic hepatitis C mortality rates will be calculated by macro-region, and the temporal trend will be analyzed by Prais-Winsten regression. The spatial distribution by states of Brazil of mortality rates by chronic hepatitis C will be carried out, in the five-year period 2000 - 2004; 2005 - 2009; 2010 - 2014; 2015 - 2019. Work is still in progress, so as preliminary results the database consisted of 33.115 deaths from chronic hepatitis C in any line of the death

certificate, 25,390 (76.7%) deaths with chronic hepatitis C as the underlying cause of death and 7,725 (23.3%) from chronic hepatitis C as associated causes of death, so that the sum of the underlying cause and associated causes results in multiple causes of death. It is expected that this study of the analysis of mortality rates due to hepatitis C considering the multiple causes of death demonstrates that there is a probable underestimation of the mortality of this condition in Brazil, a factor that has not been evaluated to date.

6709

KNOWLEDGE, ATTITUDE AND PRACTICE OF THE POPULATION REGARDING THE COVID 19 PANDEMIC IN THE LARGEST MARKET OF THE DISTRICT OF BAMAKO IN 2021

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COVID-19 is an acute respiratory syndrome caused by the new coronavirus, SARS-CoV-2, the origin of which is still debated, which emerged in December 2019 in the city of Wuhan, Hubei Province, China. The spread of SARS-CoV-2 in China led to a pandemic, declared on 11 March 2020 by the WHO.From 25 March 2020, Mali recorded its first two outbreaks with two (2) confirmed cases. We conducted a prospective study from 1 April to 31 August 2021 to assess the level of knowledge, attitude and practice of the population in relation to the Coronavirus disease in the largest market of Bamako. We surveyed 400 people.The average age was 25.96± 8.95 with extremes of 18 and 72 years; the male sex was the most represented with 67.3%.The modes of transmission were well known in our sample, 57.8% spoke of greeting with the hands. The majority of the participants had claimed to practice hand washing with soap and chlorinated water with 86.3%. To improve prevention, participants recommended information, education and communication to the population.More than half of our surveys (64.5%) had poor knowledge of covid-19 followed by 33.3% who had average knowledge and only 2.3% had good knowledge of covid-19. More than half of our surveys (54%) had poor practice of barrier measures against covid-19 followed by 43% who had acceptable practice and only 3% who had good practice We found a statistically significant relationship between the participant's level of education and the level of knowledge (P=0.000)We found a statistically significant relationship between the participant's level of education and the practice of covid-19 barrier measures (P=0.005)

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WORLD HEPATITIS DAY, 2023 - COMMUNITY ENGAGEMENT ACTIVITIES

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We commemorated World Hepatitis Day 2022 with awareness activities, medical screening, and free vaccination against Hepatitis B Virus (HBV) aiming to draw public attention to hepatitis, garner stakeholder support and identify cases for management. Screening activities took place at the Maamobi General Hospital (MGH) and the Noguchi Memorial Institute for Medical Research (NMIMR), in Ghana. Participants went through pre-counselling encompassing hepatitis causes, transmission, prevention, and management. After consenting, blood samples were collected and screened for HCV antibodies and HBV markers (surface antigen/antibody-HBsAg/HBsAb, envelope antigen/antibody-HBeAg/HBeAb, and core antibody-HBcAb). In total, 351 were screened- 281 from the Maamobi community and 170 from the NMIMR. From the NMIMR participants, 4 (3.7%) were positive for HbsAg indicating HBV infection whilst 20 (18.7%) had HBsAb indicating immunity from either previous infection or vaccination. All four infected people also tested positive for HbeAb and HBcAb indicating non-replicative viral phase. A total of 21 (7.5%) and 28 (10.0%) HbsAg and HBsAb positives respectively were recorded at Maamobi. All those positive for HbsAg were also HBcAb and HbeAb positive except one, who was rather HBeAg positive. This individual could be highly infectious compared to the rest. HbsAg positive individuals were referred for clinical management at the MGH. In all 315 participants were eligible and received first dose of HBV vaccines. However, only 204/315 (64.8%) returned for all 3 doses within the 6-month span, 146/204 (71.6%) from Maamobi and 58/204 (28.4%) from NMIMR. A total of 111/315 (35.2%) were lost to follow-up. Only one person was positive for HCV antibodies. Our findings show a high HBV prevalence within the Maamobi community. This calls active surveillance within communities to find cases that may serve as transmission reservoirs for management. Furthermore, house-to-house vaccination approaches may reduce losses to follow up.

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WHO ZIKV INDIVIDUAL PARTICIPANT DATA META-ANALYSIS: PRELIMINARY FINDINGS FROM A CONSORTIUM-WIDE INITIATIVE

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Zika virus (ZIKV) infection during pregnancy is a known cause of microcephaly and other congenital and developmental anomalies. To better understand the relationship between ZIKV infection during pregnancy and adverse fetal, infant, or child outcomes, international leaders in ZIKV research established the ZIKV Individual Participant Data (IPD) Consortium in 2017. Datasets from 33 of 64 participating studies (21 cohorts and 12 surveillance-based) of contributors from Brazil, Colombia, French Guiana, Grenada, Guatemala, Honduras, Kenya, Puerto Rico, Spain, Trinidad and Tobago, and the USA were included in this preliminary analysis. Selection bias was assessed using metadata and a four-question survey; data from 24 retained studies were pooled to estimate absolute (AR) and relative risk (RR) using a meta-analytic approach to account for heterogeneity. According to the study definition, 6,655 mothers (59.6%) had evidence of ZIKV infection, 3,597 (32.2%) were ZIKV-negative, and this information was missing in the remaining 8.1%. 41.2% of participants had arbovirus-related symptoms. The median age of participants was 27 years, the median gestational age at birth was 39 weeks, and the median gestational age at ZIKV infection was 18 weeks. The preliminary estimates with a 95% confidence interval showed the AR of microcephaly, miscarriage, and fetal loss in ZIKV-positive women was 3.43 (0.95-11.65), 0.15 (0.01-2.08), and 0.41 (0.05-3.26), respectively. In ZIKV-negative women, the AR was 0.06 (0.00-1.36), 0.02 (0.00-1.29), and 0.17 (0.01-2.69). Congenital zika syndrome (CZS) using the study definition was 4.43 (1.96-9.68) and 0.29 (0.01-7.24) for ZIKV-negative women. When comparing ZIKV -positive and -negative women, the RR of microcephaly, miscarriage, fetal loss, and CZS was 1.36 (0.70-2.65), 1.24 (0.54-2.87), 1.81 (0.78-4.19) and 0.84 (0.11-6.39), respectively. The consortium's goal is to identify, collect and synthesize IPD from longitudinal studies to inform the development of recommendations for pregnant women, couples planning a pregnancy, and public health practitioners.

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SEROEPIDEMIOLOGY OF DENGUE AND CHIKUNGUNYA INFECTIONS IN GHANA: A SECONDARY DATA ANALYSIS, 2021.

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World Health Organization estimates that a third to half of the world's population is at risk of getting infected with Chikungunya. This infection

is common in the tropics. Located in a tropical region, Ghana is prone to these vector-borne diseases, but there is limited data on Dengue and Chikungunya infection. Therefore, this analysis aims to determine the seroprevalence, factors associated with these infections and their seasonality patterns. This study was a secondary data analysis of Dengue and Chikungunya infections in Ghana. Data was obtained electronically from the Virology Department of Noguchi Memorial Institute for Medical Research. The institute processed samples collected from the sentinel sites located in seven different regions in Ghana. The period of analysis was from 2016 to mid-2018. To estimate seroprevalence, the proportion of participants that were reactive to IgM/IgG for Dengue and Chikungunya was determined. Bivariate analysis was conducted to determine factors associated with these infections, and trend analysis was performed to determine the seasonality of infections.A total of 1,105 participants' entries were analysed. The mean age in years recorded was 33±16, and 64% (693/1105) of female participants were recruited. The seroprevalence of 62% (681/1105) for Dengue and 41% (424/1053) for Chikungunya were recorded. The odds of being infected with Dengue were higher among residents of Greater Accra (OR=1.87, 95%CI [1.43-2.46]) and Northern regions (OR=4.62, 95%CI [2.00-10.63]) than in the Ashanti Region. There was no distinct seasonal pattern, as infections occurred all year round.The seroprevalence of Dengue and Chikungunya was estimated to be high. Residents of Greater Accra and the Northern Region are more likely to have increased odds of being infected with Dengue and Chikungunya viruses. No seasonal pattern was observed, and can be partially attributed to insufficient data and the duration of study considered. These two diseases are recommended to be incorporated into the malaria program for differential diagnosis, as higher seropositivity is recorded for Dengue and Chikungunya.

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DENGUE VIRUS SEROEPIDEMIOLOGY IN KINSHASA, DEMOCRATIC REPUBLIC OF CONGO

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Dengue virus (DENV) presents a major public health threat across tropical climates, yet little is known about its epidemiology within sub-Saharan Africa. In highly malaria-endemic countries such as the Democratic Republic of Congo (DRC), underreporting and misdiagnosis of DENV cases are thought to be common in the absence of readily available diagnostic tests, limiting prevalence estimation. We screened a convenience sample of dried blood spots (DBS) from a 2021 cross-sectional survey of children and adults ≥6 months old in Kinshasa Province to estimate the seroprevalence of DENV. This household survey was the final follow-up visit of a 4-year longitudinal study that collected demographic, behavioral, and clinical data, malaria diagnostic test results, and DBS samples from all participants. We used a high throughput, semi-automated antigen capture ELISA assay to detect samples positive for DENV IgG, and conducted bivariate analyses to identify crude associations of individual and household characteristics with prior DENV infection. Plasma was eluted from 258 DBS, comprising a convenience sample of the 1,138 individuals enrolled in the survey. Overall, 47.7% (n=123/258) of samples were DENV IgG-positive. Evidence of past infection was detected in each of the three health areas surveyed and in all age groups, although peri-urban sites and adults ≥25 years experienced the highest frequencies of infection (44.7% and 49.6%, respectively). Children <5 had the lowest frequency of infection (0.8%; n=1), and approximately equal IgG-positivity was observed among individuals from rural (26.8%) and urban (28.5%) settings. No associations were observed between sex, concomitant P. falciparum infection by PCR, or fever in the prior week, and prior DENV infection in this selected sample. Additional analyses assessing household ecology and environmental factors are ongoing. In this preliminary assessment of DENV in the DRC, >45% of individuals had evidence of at least one DENV infection. The high DENV prevalence detected indicates a need for additional studies to determine the burden of infection in the DRC and sub-Saharan Africa.

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CLINICAL FEATURES OF RESURGENT DENGUE 2 AS A MAJOR CAUSE OF ACUTE FEBRILE ILLNESS IN NICARAGUA FOLLOWING THE ZIKA EPIDEMIC

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Dengue virus has been endemic to Nicaragua for decades with periodic re-emergence of 1 or >1 dengue virus serotypes (DENV-1-4). Symptomatic dengue ranges from undifferentiated fever to dengue shock syndrome. We collected epidemiological and clinical data and acute and convalescent-phase sera to identify and characterize dengue as a cause of acute febrile illness (AFI) in post-Zika (2018) Western Nicaragua. We assessed clinical features of acute primary (1°) and secondary (2°) dengue vs other AFI in children (age <18) and adults. Among 820 subjects enrolled (80% with convalescent follow-up), 193 (29%) had acute dengue (all DENV-2) confirmed by paired serology and/or reverse transcriptase (RT)-PCR. Most (170, 88%) was 2° dengue. Dengue accounted for a greater proportion of AFI (31.7% vs 26.0%) in children vs. adults. Those with acute dengue were less likely than others to have rhinorrhea (5.2% vs 11.3%, p=0.02), dry cough (19.7% vs 27.0%, p=0.04), productive cough (7.8% vs 18.3%, p<0.001), chest crackles (0.5% vs 4.0%, p=0.02), and diarrhea (12.4% vs 24.5%, p<0.001) but more likely to have lower WBC and platelet counts (p<0.001). Features associated with 2°rather than 1°dengue were chills (80.0% vs 50.0%, p=0.004) and headache (90.6% vs 68.2%, p=0.002), whereas rash was more frequent in 1° dengue (63.6% vs 14.1%, p<0.001). Absence of rhinorrhea, cough, and sore throat and presence of headache and rash were associated with acute dengue in children but absence of diarrhea in adults. Lower WBC and platelet counts were associated with acute dengue vs other AFI. Headache was more frequent in 2°dengue and rash in 1° dengue in all age groups. Twenty-nine patients with acute dengue were treated with antibiotics; one died. We identified acute DENV-2 as a major cause of AFI in Western Nicaragua post-Zika. Compared with our pre-Zika AFI study at the same hospital, we observed exclusively DENV-2 vs >1 serotype and a higher proportion of AFI attributable to dengue (29% vs 5%).

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PERSISTENT, CONSISTENT, AND NEGLECTED: INVESTIGATING THE GEOGRAPHIC CLUSTERING AND PREDICTORS OF LA CROSSE VIRUS DISEASE IN APPALACHIA

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Mosquito-borne La Crosse virus (LACV) is the leading cause of arboviral encephalitis among children in the United States. Most infections are reported from socioeconomically disadvantaged communities in the Appalachian region, but despite decades of focal endemicity in the area, LACV disease remains neglected with minimal public health infrastructure to prevent, detect, or respond to cases. We recently conducted a national study of geographic LACV disease clustering where we found that eastern Tennessee and western North Carolina form a persistent hotspot for LACV disease. Here, we increase the spatial resolution of our previous research by incorporating the sites of all reported LACV disease in Tennessee and North Carolina from 1997-2020. Our objectives were to investigate fine-scale spatial clustering of LACV disease clusters and to identify environmental predictors of disease risk. The results of our study show that LACV disease is heterogeneously distributed; most cases are consistently reported from a subset of geographic clusters with elevated risk relative to the study area overall. We also found that a key set of environmental, demographic, and economic predictor variables were associated with disease risk in the region. Timely and targeted public health response to reported infections may have prevented additional transmission within the clusters, but a lack of vector control infrastructure allowed LACV disease to persist in these communities for the entire period. To prevent the continued persistence of LACV disease in resource-deprived areas, the risk predictors we identified should be used to guide targeted public health interventions. In our presentation, we will contextualize our findings within the epidemiology of LACV disease and suggest approaches to reduce the disease burden in Appalachia.

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MULTIPLEX SAMPLE-SPARING IMMUNOASSAY TO MEASURE SEROPREVALENCE OF CHIKUNGUNYA, DENGUE, AND ZIKA VIRUSES

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Chikungunya, dengue, and Zika viruses (CHIKV, DENV, ZIKV) co-circulate and cause similar clinical symptoms. We previously developed a multiplex assay to detect past DENV and ZIKV infections. However, due to antibody cross-reactivity, current serological assays for CHIKV using an inactivated virus or the E1/E2 envelope protein are unsuitable to distinguish between alphaviruses. To address this, we created a multiplex immunoassay utilizing the antigenically distinct regions of the E1 protein for six medically relevant alphaviruses, including CHIKV, ONNV, RRV, MAYV, VEEV, and EEEV. We tested the assay's ability for specific and sensitive detection of past CHIKV infection using 69 reference samples (24 CHIKV-infected and 45 CHIKV-uninfected). The multiplex assay's CHIKV antigen was 100% sensitive to CHIKV-positive sera and 100% specific to CHIKV-negative, flavivirus-positive sera. There was no cross-reactivity between the MAYV, RRV, and EEEV antigens to CHIKV-positive sera, but the closely related ONNV antigen showed low cross-reactivity that could be resolved at higher sample dilution. In comparison, CHIKV-immune sera reacted strongly in CHIKV and MAYV E2 ELISA assays. However, MAYV E2 binding was not supported by MAYV neutralization. Next, we combined the CHIKV antigen coupled bead into the multiplex bead set configured with DENV and ZIKV EDIII antigens to assess the seroprevalence of these viruses among 172 febrile illness patients in 2015 (n=83) and 2018 (n=89) in Leon, Nicaragua. In 2015, 62.7% of patients reported fever had CHIKV, 83.1% had DENV, and 3.6% had ZIKV. The 2018 seroprevalence for CHIKV (56.2%) and DENV (73.3%) in age-matched patients with fever was comparable to 2015. The proportion of primary and secondary DENV prevalence in 2015 (50.7% vs. 49.2%) and 2018 (47.7% vs. 52.3%) were similar. However, ZIKV seroprevalence in these patients increased sharply from 3.6% in 2015 to 42.7% in 2018 due to the 2016 ZIKV outbreak in Nicaragua. This multiplex immunoassay provides a significant advantage over traditional assays to accurately measure seroprevalence of CHIKV, ZIKV, and the four DENV serotypes using a small blood sample

6717

EPIDEMIOLOGICAL CHARACTERISTICS OF MEASLES CASES IN LIBERIA IN LIBERIA, 2018-2021

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Measles remains a disease of public health concern in Liberia, with annual outbreaks since 2017. It is an immediately reportable vaccine-preventable disease. We described measles' epidemiological characteristics and associated factors in Liberia from 2018 to 2021. We reviewed Measles case-based surveillance data from 2018 to 2021 obtained from the National Public Health Institute of Liberia (NPHIL). All cases that met Measles case definition for the period as clinically compatible, lab confirmed, and epi-linked were included. The data was extracted from the weekly surveillance reports, cleaned and analysed using Epi Info version 7.2. We calculated frequency, proportion, and rates. The median age of the 5905 measles cases reviewed was 7 (IQR:3-13) years. Majority of the cases, 72% (4238) were clinically compatible, while epi-linked, 15% (884) and lab confirmed 13% (783) were the least. The majority of the cases were females, 51% (2991). About 34% (1996) of the cases were vaccinated, while 50% (2972) had unknown vaccination status. Montserrado County accounted for the highest, 20% (1184) followed by Nimba, 12% (715). Pleebo District (Maryland) accounted for the highest, 9% (537) followed by Bushrod District, 6% (358) in Montserrado. Vaccination status (vaccinated) (OR=0.22, 95%CI: 0.05-0.99, p=0.031) was associated with measles outcome. Those vaccinated were less likely to die from Measles compared to others. Measles burden remained generally high in Liberia with low vaccination rates observed among cases. This decrease in vaccination coverage needs to be further investigated. The need to increase measles vaccination coverage to improve measles outcome is recommended. Measles, vaccination, Liberia, clinically compatible, lab confirmed, epi-linked

6718

SARS-COV-2 INFECTION IN BROWN-HEADED SPIDER MONKEYS (ATELES FUSCICEPS) AT A WILDLIFE RESCUE CENTER ON THE COAST OF ECUADOR SOUTH AMERICA

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Human populations can be affected in unpredictable ways by the emergence and spread of zoonotic diseases. The COVID-19 pandemic was a reminder of how devastating these events can be if left unchecked. However, once they have spread globally, the impact of these diseases when entering non-exposed wildlife populations are unknown. The current study reports the infection of brown-headed spider monkeys (Ateles fusciceps) at a wildlife rescue center in Ecuador. Four monkeys were hospitalized and all tested positive for SARS-CoV-2 by RT-qPCR. Fecal samples (n=12) from monkeys at the rescue center tested positive as well;

three zookeepers responsible for feeding and deworming the monkeys were also positive, suggesting human-animal transmission. Whole genome sequencing using Oxford Nanopore Technologies identified the omicron clade 22B BA.5 lineage in most samples. These findings highlight the threat posed by an emerging zoonotic disease in wildlife species and the importance of preventing spillover and spillback events during epidemic or pandemic events.

6719

MEASLES SURVEILLANCE SYSTEM EVALUATION IN THE FATICK REGION IN 2022

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Measles surveillance is done on a case-by-case basis and aims at elimination. The Fatick region recorded an outbreak measles in 2021 and performances of its surveillance system is unknown. The study objective was to evaluate the measles surveillance system in the Fatick region. We conducted a descriptive cross-sectional study based on the CDC's guideline for evaluating surveillance systems. The health facilities to be visited were selected on a purposive basis. Data were collected using questionnaire administration and literature review. Usefulness, simplicity, acceptability and data quality attributes were assessed. Data were entered and analyzed using Epi Info 7.2.1.0 software. The score for each attribute was calculated based on the averages of the scores for each level. A score below 50% was classified as poor, a score between 50% and 80% was considered fair and a score of 80% or higher was good. A total of 24 (89%) providers were surveyed out. The scores were 96%, 88% and 82% respectively for usefulness, simplicity and acceptability. Promptness of weekly reports was 59% (n=27). The proportion of archived notification forms was 100% (n=27) at the level of the health posts and centers. The compliance rate between the registers and the data entered in the DHIS2 was 100% (n=27). The proportion of missing data was 12.2% (n=156) and 15.4% (n=26) respectively at the health center and health post levels. In conclusion, the measles surveillance system in the Fatick region was useful, simple and acceptable. The quality of the data was affected by missing data in the filling of the notification forms. It is necessary to train health hut actors and make the IDSR guide available to improve the measles surveillance system.

6720

THE EFFECT OF PRIOR ZIKA VIRUS INFECTION ON MARKERS OF MALE FERTILITY

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Zika virus (ZIKV) swept through the Americas in 2015 and 2016. Previously considered a mild illness of little clinical importance, unusual features of ZIKV were identified during the American epidemic - prolonged shedding in semen, sexual transmissibility, and congenital anomalies. In mouse models, ZIKV caused profound decreases in testicle size and sperm count, causing significantly impaired fertility. It is unknown if ZIKV has this effect in humans. One case series of 15 men showed decline in sperm count and testosterone after acute ZIKV that recovered after several weeks. To investigate the long-term effect of ZIKV infection on human male fertility, we recruited a cohort in two sites that experienced intense ZIKV transmission 1-2 years before the study. Healthy men aged 18-40 years were enrolled July 2018-March 2019. We recorded demographic, clinical, and epidemiological data. Men provided semen and blood samples quarterly for 12 months. Blood was tested for ZIKV EDIII IgG, dengue IgG and IgM, testosterone, and follicle stimulating hormone (FSH). Fresh semen analysis was performed on-site. Markers of fertility were compared between ZIKV-seropositive and seronegative men. Data were analyzed with Student's t-test and Wilcoxon rank-sum test for continuous data and Chi-squared test for categorical data. We enrolled 110 men (50 in Peru, 60 in Nicaragua). Median age was 23 years (IQR 19-27) and 55% were students. 35/97 (38%) reported vaccination to yellow fever. More than 90% were seropositive for dengue IgG. 39% were seropositive for ZIKV infection at enrollment (42% in Peru, 37% in Nicaragua, not significantly different). There was no association between age and odds of ZIKV positivity. 26% of men reported having impregnated a partner, with no difference by ZIKV status. There were no differences at enrollment by ZIKV exposure in semen pH, total sperm count, percent abnormal sperm, total motile sperm count, vitality, or round cell count. Further analyses are in progress, but these preliminary data reassuringly suggest that any effect of Zika virus infection on male fertility is likely short-lived.

6721

CLINICAL AND EPIDEMIOLOGICAL DIFFERENCES BETWEEN THE FIRST AND SECOND COVID-19 WAVES IN PATIENTS OF A HOSPITAL IN NORTHERN PERU

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Peru reported the second highest number of COVID-19 cases in Latin America, after Brazil. The first COVID-19 wave occurred during March December in 2020, and the second wave occurred during January September in 2021. The differences between these waves remain largely unknown, and there is yet no comparison between them in Peru. We evaluated the differences in the clinical and epidemiological characteristics of COVID-19-affected patients during the two waves in northern Peru. We conducted a retrospective study using the clinical follow-up database of Lambayeque and the epidemiological notification form database of NotiWeb. The COVID-19-associated factors during the two waves were determined using a simple and multiple regression analysis, and the prevalence ratio (PR) was estimated. During the second wave of COVID-19 there was an increase in the symptoms of cough in 12.1%, odynophagia in 5.0%, chills in 16.0% compared with the first wave. The frequency of nasal congestion in the second wave was 2.17 times of that in the first wave (PR: 2.17). The second wave was marked by a higher proportion of affected children and adolescents and a greater percentage of respiratory symptoms than the first wave.

6722

CLINICAL SYMPTOMS OF CONFIRMED CASES OF CRIMEAN CONGO HEMORRHAGIC FEVER IN SENEGAL

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Emerging infectious diseases are considered major challenges for human survival. Among them, diseases caused by arboviruses such as Rift Valley fever virus (RVFV) and Crimean Congo hemorrhagic fever virus (CCHFV) have great economic, medical and veterinary impact. However, their epidemiology still need to be better understand in Africa. Indeed, despite significant efforts in capacity building, many countries are still not well prepared to detect these viruses, probably due to the lack of apropriate surveillance systems. In Senegal, a new surveillance system named 4S for Syndromic Sentinel Surveillance in Senegal, has been implemented in 2015. In the sentinel sites, blood sample is collected for any arbovirus and VHF suspected case and shipped to Institut Pasteur de Dakar for laboratory diagnosis. Next Generation Sequencing is also conducted on PCR positive

samples for genetic characterization. From 2015 to now, about 10,000 samples have been tested and several RVF and CCHF cases have been detected in 9 different regions while only few human cases were detected in 4 regions before 2015. Indeed, an RVF outbreak in 2020 and 3 CCHF fatal cases in 2022 and 2023 in Northern Senegal and Dakar have been detected. Our results also showed that apart from these fatal CCHF cases, clinical symptoms of the confirmed cases are usually mild with no death and large outbreaks are still not been detected in Senegal. Viral genome sequence analyses highlighted virus introductions in Senegal from other countries including Mauritania and high viral genetic diversity for CCHF with probable reassortment events. The implementation of this syndromic sentinel surveillance in Senegal has improved CCHF and RVF detection in humans in Senegal. However, for a better understanding of their epidemiological profile in Senegal, implementation of sentinel surveillance in animals and arthropods as well as seroprevalence studies in humans and animals are needed. Our results, also showing virus introductions from other countries, called for collaborative interventions between African countries for a better disease surveillance and control.

6723

EVALUATION OF THE SURVEILLANCE SYSTEM FOR ACUTE FLACCID PARALYSIS BEFORE AND DURING COVID-19 IN PALESTINE, 2014-2021

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A nationwide Acute Flaccid Paralysis (AFP) surveillance system is the gold standard for detecting cases of Poliomyelitis and a main component of the WHO's Global Polio Eradication Initiative (GPEI). Since the COVID-19 pandemic could potentially have a negative impact on surveillance systems, we compared the performance of the Palestinian national AFP surveillance during 2020-2021 with earlier years by making a descriptive retrospective study from the surveillance dataset provided by Palestinian ministry of health and we evaluated the attributes of the AFP surveillance in Palestine from 2014 to 2021 for completeness, timeliness and sensitivity by comparing it to the WHO AFP-surveillance standards for certification. Timeliness was measured as samples reaching the laboratory within three days of sample collection; completeness was measured as having no missing data on the investigation form, collecting "adequate samples" and performing a follow up investigation after 60 days; sensitivity was measured as having two or more AFP samples per 100,000 population per annum. the Results were a total of 286 AFP cases (57% Male) reported in 2014-2021 in the West Bank (65%) and Gaza (35%). (54%) were 0-5 years old. Completeness was >98%. Of all samples, (70%, SD=13) reached the laboratory in three days or less of being taken. Sensitivity of the system met the WHO criteria before the COVID-19 pandemic in 2014-2019 (2.4 per 100,000) but dropped in 2020-2021 during the pandemic to (0.9 per 100,000). We concluded that sensitivity was affected by the pandemic and made recommendations to the ministry of health to bolster it to reach the WHO-set criteria, such as training new public health staff and enforcing the reporting mandate more vigorously

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INNOVATIONS FOR ENCOURAGING MEMBERS OF THE LOCAL COMMUNITY TO LIVE SAFELY WITH BATS IN THE MOUNTAIN ELGON AREA, EASTERN UGANDA

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Bats are an important element of our environment. Currently, there is increased Bat-Human interaction as humans move closer to bat habitats like caves and forests. Bats have been linked to numerous Emerging Infectious Disease (EID) events (Ebola and Murburg) and have been recognized as important reservoir hosts for viruses that cross to humans and domestic animals. In this regard, bats are seen as harmful by most of the people in various communities and therefore usually killed at sight. One objective in our bio-surveillance project in the Mt Elgon area is to create awareness among local communities especially where people are living in close proximity to bat habitats about the benefits as well as the risks of associating with bats. One of our approaches has targeted the primary school going age group at Kapteka Primary school as it is a few metres from one of our cave sites for activities that include information exchange in a classroom setting, quizzes and knowledge acquisition assessment using fine art and puzzles. We anticipate that the knowledge transfer to this age group would be impactful in changing the misconceptions & myths associated to bats and educating them on how to safely live with bats. In this presentation we shall present our tentative results that have so far; Engaged 55 pupils who all indicated awareness about the existence of bats around them. About 70% of them indicated they had ever visited a bat cave. 50% of them were aware that bats are said to cause them diseases like Ebola & Murburg. From this engagement, we also established that 10% of them had ever eaten a bat. Close to 80 % of them were interested in being part of a "Bat protection program" if initiated to them.

6725

OPTIMIZING TRAP PLACEMENT TO PREDICT WEST NILE VIRUS

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Since its emergence in the New York Metropolitan area in the fall of 1999, the West Nile Virus (WNV), which is the leading cause of mosquito-borne disease in the continental United States, has been spreading rapidly. With over 52,000 cases nationwide to date, among which around 2,700 are from Illinois, taking adequate measures for the control of WNV has become vital. The lack of vaccines or medications to treat WNV makes prevention through mosquito control the only solution for controlling the spread of the infection. Mosquito traps that are used to test for the presence of the virus in mosquito populations play a crucial role in monitoring WNV and informing response. But how do you decide where to place a mosquito trap for WNV surveillance? And what makes a good trap, anyway? We present a statistical approach to determine the value of a mosquito trap in predicting human WNV cases in the next two weeks within a 1500m radius of the trap. We then use that value to understand what landscape, demographic and socioeconomic factors cause a mosquito trap to have the ability to predict correctly when human cases will occur, and when they will not, in the Chicago metropolitan area and its suburbs. This approach enables resource-limited mosquito control programs to identify better locations for their trap-based surveillance to increase trap efficiency while reducing the number of traps needed.

6726

GENETIC AND PHYLOGENETIC ANALYSIS OF INFLUENZA A VIRUSES & EVIDENCE OF AVIAN INFLUENZA INFECTION IN PIGS IN SENEGAL

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The threat of an influenza pandemic is looming, with new cases of sporadic avian influenza infections in human frequently reported. Pigs are considered important intermediate hosts and possible 'mixing vessels' for genetic reassortment of influenza viruses. However, epidemiological information on influenza infection of pigs in tropical and resource-limited countries remains sparse. So here, we investigated the epidemiology and genetic characteristics of IAVs as well as serological evidence of avian influenza virus infections in pigs at interfaces with human populations in Senegal. This study was carried out from September 2018 to December 2019 in the single pig slaughterhouse in Dakar, which receives animals from different regions of Senegal. Influenza A viruses were diagnosed by qRT-PCR and a subset of positive samples were selected for NGS sequencing. Serum samples were tested by HI assay using four reference viruses including H9N2, H5N1, H7N7 and H5N2. Influenza A Virus was detected in 30.7% of 1691 samples tested and H1N1pdm09 virus (38.07%) was the most commonly identified subtype followed by H1N2 (16.3%) and H3N2 (5.2%). Year-round influenza activity was noted in pigs, with the highest incidence between June and September. Phylogenetic analyses of all eight gene segments revealed that the isolated IAVs were closely related to human IAV strains belonging to H1N1pdm09 and seasonal H3N2 lineages. Genetic analysis revealed that Senegalese strains possessed several key amino acid changes, including D204 and N241D in the receptor binding site, S31N in the M2 gene which contained the key amino acid target of amantadine drugs and P560S in the PA protein. Serological analyses revealed that 83.5% of the 1636 sera collected were positive for the presence of antibodies against either H9N2, H5N1, H7N7 or H5N2. Influenza H7N7 (54.3%) and H9N2 (53.6%) were the dominant avian subtypes detected in Senegalese pigs. Results of this study show the co-circulation of multiple subtypes of influenza viruses among Senegalese pigs. Therefore, regular monitoring and frequent surveillance of influenza viruses with one health approach are essential.

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SOCIOECONOMIC VALUES ATTACHED TO CAVES AND BATS IN ELGON REGION OF UGANDA: IMPLICATIONS FOR BAT-BORNE PATHOGEN SPILLOVER

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Understanding of the nature of the human-wildlife interactions provides an opportunity for designing the dynamic nature of the host-pathogen interfaces and determining the risk of zoonotic disease occurrence. Considering bat reproductive and roosting strategies, caves are critical to shaping people's potential exposure to zoonotic pathogens, but this key factor of spillover has been insufficiently studied in Uganda. We present preliminary data on some of the records about socioeconomic values associated with caves as well as bats within Mount Elgon areas of Uganda. We made records of the anthropogenic activities in seven caves (Tutum, Mise, Kaptum, Wui, Chekwoputoi, Ngwat and Kupngweny) that had bat roosts around Mt. Elgon region. These caves spread across different altitudinal zones including the national park (Elgon) and where human settlements dominate. Data from observations around the cave was also complimented with a record of statements from human communities within each cave. Anthropogenic activities were classified according to the approaches for human welfare economics. All the caves experienced anthropogenic activities. These activities were majorly pursued to access material and immaterial assets including food, guano, rock salt and tourism. Security and safety related values included shelter for humans and livestock. Security and safety values were more pronounced in lower altitude areas where civil conflicts were common. Bat hunting was more pronounced in high altitude areas evidenced by fire events and tree branches with hooks. Although these are preliminary records, this data ought to be included in designing the human-bat interface to explicitly understand points of potential pathogen spillover.

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WEST NILE VIRUS SEROPREVALENCE IN HUMANS LIVING IN THE TAMPA BAY REGION OF FLORIDA

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West Nile Virus (WNV) is an arbovirus spread primarily by Culex mosquitos with humans being an accidental dead-end host. The virus is endemic to the continental United States, having arrived in1999. WNV was introduced to Florida in 2001, with 460 confirmed cases and resulted in 29 deaths since.It is estimated that eighty percent of cases are asymptomatic, with mild cases presenting as a non-specific flu-like illness. The Centers for Disease Control estimate that about 1 in 150 people infected withWNV develop a neuroinvasive form of the disease with 10% leading to death. Recent reports have shown that WNV can persist in the kidney for years following infection and has been linked with the development of chronic kidney disease. Other reports have shown that patients who've had WNV commonly experience depression and mood disorders years following infection leading to significantly reduced quality of life. Currently, detection of WNV in humans occurs primarily in healthcare via PCR when patients present with severe manifestations of disease. This strategy is problematic given thes hort window of detectable viremia meaning that most WNV infections never receive an official diagnosis. While there are a few chicken-based and mosquito-based WNV surveillance programs in theUnited States, there is no human surveillance for WNV. Thus, the true burden of WNV in humans residing in the United States is unknown and could be a contributing factor into the rise in mental health problems and kidney disease in the United States during the last 20 years. This study utilized enzyme linked immunosorbent assay (ELISA) for IgG antibodies to test serum and plasma samples collected atTampa General Hospital during 2020 and 2021. Plaque reduction neutralization tests were performed to confirm positive results. We found that nearly half of samples were positive for WNV antibodies, indicating a gross underestimation of WNV infection in humans. There was no statistically significant relationship between the presence of WNV antibodies and COVID-19 status.

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IDENTIFYING THE VERTEBRATE HOSTS WITH POSSIBLE ASSOCIATION TO JAPANESE ENCEPHALITIS VIRUS DISPERSAL IN NATURE BY BLOOD MEAL SOURCE IDENTIFICATION AND RNA VIROME DETERMINATION IN JAPANESE ENCEPHALITIS VIRUS VECTORS

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In Asia, Culex mosquitoes are of particular interest because of their role in maintaining endemic mosquito-borne viral diseases, including the Japanese encephalitis virus (JEV). Nonetheless, host-feeding preferences, along with naturally infecting RNA viruses in certain Culex species, remain understudied. In this study, selected blood-fed mosquitoes were processed

for avian and mammalian blood meal source identification. Concurrently, cell culture propagation and high-throughput sequencing (HTS) approaches were used to determine the RNA virome of Culex mosquitoes collected in Ishikawa Prefecture, Japan. The identification of blood meal sources from wild-caught Culex spp. revealed that Cx. tritaeniorhynchus, which is the JEV primary vector, has a robust preference toward wild boar (62%, 26/42), followed by heron (21%, 9/42). The other two species, Cx. bitaeniorhynchus and Cx. orientalis, which were recently incriminated as the vector for JEV genotype V showed a distinct preference for avian species, including migratory birds. Interestingly, they did not share the same host preference; rather, Cx. orientalis and Cx. bitaeniorhynchus each shared one avian host with Cx. tritaeniorhynchus thus indicated a broader blood meal preference. From the HTS results, 34 virus sequences were detected, four of which were newly identified virus sequences of unclassified Aspiviridae, Qinviridae, Iflaviridae, and Picornaviridae. The absence of observable cytopathic effects in mammalian cells and phylogenetic analysis suggested that all identified virus sequences were insect-specific. Further investigations involving other mosquito populations collected in different areas are warranted to explore previously unknown vertebrate hosts that may be linked to JEV dispersal in nature.

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DENGUE SEROTYPE DYNAMICS AT THE KENYAN COAST

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Dengue fever (DF), caused by four distinct serotypes of dengue virus (DENV-1-4) is transmitted by the mosquito vector Aedes Aegypti and Aedes albopictus. DF is responsible for more than 390 million infections globally. In Kenya, DENV is an emerging public health concern, especially at the Kenyan coast where DF is a common occurrence. In this study, we determined the heterotypic infections of DENV serotypes from November 2019 to September 2022 from study subjects presenting with febrile illness at Mtongwe Naval Base hospital in south coast and Lamu County Hospital in the north coast. DENV serotypes were identified by qPCR. Our data shows cyclical transmission of three dengue serotypes. DENV1 was the most dominant serotype accounting for 85% (350/413) of all DENV infections. DENV1 cases were detected across the entire period with peaks in January-April 2020 (lowest=13 cases, highest=41cases) and September 2021 to May 2022 (lowest=10 cases, highest=70cases). DENV2 was reported between December 2019 to April 2020 (lowest=4 cases, highest=12 cases). For DENV3, few cases were reported in December 2019 to March 2020(highest=2 cases). From July 2022 to December 2022, cases of DENV3 increased gradually (lowest=2 cases, highest=7 cases). The burden of infection was highest in males (68%) between 19-39 years (55%) and the most common clinical symptoms included headache 84.5% (349/413), chills 74.6% (308/413), joint ache 74.5% (313/413), muscle pain 73.6% (304/413) and eye pain 56.4% (233/413). Of the 251 DENV1 positive samples, (Mtongwe Naval Base=122 and Lamu County Hospital=129) that were sequenced, we obtained complete sequences for 135 samples. Phylogenetic analysis showed that the genomes belonged to DENV-1, genotype V and all clustered with genotype V isolates from China. Our findings provide data on the transmission dynamics of DENV serotypes observed over a 3-year study period. Such data is useful in bridging the science gaps necessary for development of more effective vaccines, and also reinforces the importance of surveillance in the management of the infection to mitigate public health disruptions associated with outbreaks of dengue.

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SEROLOGICAL EVIDENCE OF ZIKA VIRUS CIRCULATION WITH DENGUE AND CHIKUNGUNYA INFECTIONS IN SRI LANKA

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Arbovirus diseases remain a public health threat, while dengue is endemic in the South Asian region, two outbreaks of chikungunya infections have been reported in Sri Lanka. There is very limited data on zika virus (ZIKV) infections in Sri Lanka, and this could be due to a lack of ZIKV surveillance in Sri Lanka. Our aim was to determine the presence of antibodies to dengue, chikungunya and zika infections in an adult population from a suburban population in Sri Lanka in 2017. A total of 149 healthy adult volunteers over 18 years of age (mean age 43+/-14 years, males 43%), with no prior diagnosed history of dengue, chikungunya or zika infections, and no history of overseas travel participated in the study. Using serological assays, a total of 94.6% (141/149) of the participants' demonstrated dengue IgG antibodies, 37.5% (56/149) were positive for chikungunya IgG and 5.3 % (8/149) were positive for anti-zika virus IgG antibodies. Anti-ZIKV IgG antibodies was confirmed by testing 40 samples including the 8 zika IgG positive samples for ZIKV specific antibodies by neutralization assay. This clearly demonstrated neutralizing antibody activity against ZIKV at 6.7% (10/149) of the study population, strongly suggesting the presence of ZIKV in this population. While DENV seroprevalence remains high in the region, the overall low ZIKV seroprevalence indicate limited Zika spread within the population. There is no recorded history of the presence of ZIKV in Sri Lanka and to the best of our knowledge this is the first report. In addition, this study indicates that >90% of individuals had asymptomatic dengue but no serious symptoms. These results provide a cross-sectional view on the DENV, ZIKV and CHIKV epidemic status in this area. It further demonstrates a need for implementation of enhanced surveillance to detect circulating viruses and more effective measures against the spread of these arbovirus diseases in the region.

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DENGUE VIRUS SURVEILLANCE IN AEDES AEGYPTI

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Arboviral diseases are increasingly important contributors to global human mortality and morbidity. This is exemplified by unprecedented emergence and re-emergence of epidemic arboviral diseases in the recent past such as dengue, chikungunya, Rift Valley fever and yellow fever. In many African countries, the impact of arboviral diseases is undetermined due to paucity of active surveillance, poor disease reporting systems, and lack of appropriate diagnosis. As a result, the possibility of the causative viruses circulating unnoticed, causing unresolved disease and/or outbreaks in humans, cannot be underestimated. Surveillance targeting vectors is essential to provide an early warning of the presence of viruses to reduce the potential for human disease. In this presentation, I will describe the use of cost-effective monitoring tools to assess the population dynamics of Aedes aegypti mosquito, and application of molecular (PCR, RT-PCR, sequencing) and virological (cell-culture) approaches to depict its vertebrate hosts and viral associations in an urban setting in Kenya. The study findings will inform predictive risk assessment in support of preparedness plans and disease control operations.

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ZIKA EPIDEMIC IN COLOMBIA: STUDYING THE SPATIO-TEMPORAL EMERGENCE OF AN AEDES-BORNE DISEASE AND ASSOCIATED FACTORS AT ECOLOGICAL LEVEL

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Zika, a viral disease transmitted to humans by the bite of infected Aedes mosquitoes, emerged in the Americas in 2015 and caused large epidemics. In Colombia alone there were 72,031 Zika cases recorded in the national surveillance system (SIVIGILA) between epidemiological weeks (EWs) 22/2015 and 39/2016. Using these data, we aimed at identifying socioeconomic and environmental factors associated with the emergence and persistence of Zika across the 1,121 Colombian municipalities and 70 EWs. We fitted a zero-state Markov-switching space-time model under the Bayesian framework assuming that Zika switches between periods of presence and absence in each municipality according to spatially and temporally varying probabilities of emergence and persistence. These probabilities are assumed to follow a series of mixed multivariate logistic regressions. We present the mean odds ratio (OR) and the 95% credible interval (CI). Our results suggest that Zika emerged sooner in more densely populated areas (1.27, 1.18-1.37) and/or with higher weekly maximum temperatures (1.08, 1.04-1.12, lagged one week). On average, the odds of Zika emergence decreased by 6% with a 10 mm3 increase in the weekly accumulated precipitation lagged four weeks (0.94, 0.91-0.96), by 11% with a 0.1 increase in the Normalized Difference Vegetation Index (0.89, 0.80-0.99), and by 3% with 100 meters increase in the elevation (0.97, 0.95-0.99). More densely populated areas also presented higher odds of Zika persistence (1.32, 1.20-1.46). Zika was more likely to persist in a municipality where/when more cases were registered in the previous week (2.81, 2.21-3.66). The estimated probability of Zika presence increased weeks before cases started being registered. This is an important result because an emerging disease may circulate unnoticed for some time. The environmental factors found to be associated with the emergence of Zika may be proxies of the presence of the vector. The population density was the main driver of the first Zika epidemic in Colombia, indicating that more densely populated areas should be prioritized for the prevention of emerging Aedes-borne diseases.

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VIRSCAN SEROLOGICAL PROFILING OF THE PENAN TRIBE, AN INDIGENOUS GROUP IN SARAWAK, MALAYSIA

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Understanding the serological and exposure profile of a population, especially those residing in the animal-human interface, is of importance in understanding disease spillover and emergence risks. However, serological surveillance is often limited by the requirement of having a hypothesis. One needs to know what to test for to be able to identify antibodies to that pathogen. Here, we report our experience applying a highly multiplexable, high throughput assay, Phage ImmunoPrecipitation Sequencing (PhIP-Seq), to determine the serological profile of members of the Penan Tribe, an indigenous community in Sarawak, Malaysia. These communities are largely rural and live in very remote areas of Borneo. VirScan, developed by the Elledge group at Harvard University (and was kindly provided to us by Prof Steve Elledge), is a PhIP-Seq assay that allows for the testing of antibodies to approx. 200 human viruses using a small sample volume. Peptide tiles, derived from virus sequences, are presented on the phage surface and antibodies from samples bind these phages, which will be subsequently immunoprecipitated and sequenced to determine their identity. Using VirScan, we examined 130 plasma samples from 5 different Penan villages, and 20 samples from urban Sarawak as a comparator. We sought to determine whether members of the Community would have roughly a similar antibody exposure profile to that of their urban counterparts. Our preliminary analysis - subject to secondary verification - shows that human endemic viruses, such as the human herpesviruses and others, are common in the Penan population. Incidentally, we also note some individuals with antibodies to blood-borne pathogens such as Hepatitis C, where we are following up with serological verification. We are optimistic that this technology has a potential in the field of sero-epidemiology as it allows relatively hypothesis-free and high throughput testing of samples. We believe the PhIP-Seq assay will have value in helping identify specific viruses for surveillance or study.

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SEROPREVALENCE OF ARBOVIRUSES IN SLOTHS FROM A RURAL ZONE WITH FAST URBANIZATION CLOSE TO PANAMA CITY

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Panama, due to its geographical position and great biodiversity, has played an important role in the discovery and control of emerging zoonotic diseases with impact on public health. These pathological agents with potential to cause human disease and even outbreaks, have been described in different reservoirs, principally birds and mammals, such as the two sloths species common in Panama, Choloepus hoffmanni and Bradypus variegatus. They have been involved in the transmission of parasitic agents Trypanosoma cruzi, Trypanosoma rangeli, Leishmania panamensis and arboviruses such as Oropouche, Punta Toro group virus PTV, Utive virus, and some uncharacterized Orbiviruses called PanSloth 149 and D50, were isolated from them in the 1980s. However, the current status of these mammals and their role as a possible reservoir in Panama is unknown. This descriptive study aims to determine the current seroprevalence against arboviruses with epizootic potential in 60 sloths captured in rural areas of the province of West Panama, endemic for Dengue. To detect neutralizing antibodies against arboviruses: PTV, Madariaga MADV, Mayaro MAYV, Venezuelan Equine Encephalitis VEEV, Una UNAV, Chikungunya CHIKV, Yellow Fever YFV, Dengue serotype 2 DENV-2 and Pan Sloth 149 and D50 viruses, plaque neutralization assay was used. The highest seroprevalence found were 53.3% for PanSloth D50 and 23.3% for 149, whereas 6.7% of the sloth sera had neutralizing antibodies for VEEV and 6.7% for MADV, even if human cases in that region have not been detected recently. While all tested sloths were negative for UNAV, MAYV, CHIKV, PTV and DENV-2. We aim to provide data on the presence of zoonotic viruses with emerging potential in sloths in the province of West Panama that is under increasing deforestation and urbanization, a risk factor for emergence. Future studies are needed to have a seroprevalence study of these viruses in sylvatic and domestic animals from this region and to determine if sloths play a role in the transmission cycle of these viruses and their spill over to humans.

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WHEN CASE REPORTING BECOMES UNTENABLE: CAN SEWER NETWORKS TELL US WHERE COVID-19 TRANSMISSION OCCURS?

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Monitoring SARS-CoV-2 in wastewater is a valuable approach to track COVID-19 transmission. Designing wastewater surveillance (WWS) with representative sampling sites and quantifiable results requires knowledge of the sewerage system and virus fate and transport. We developed a multi-level WWS system to track COVID-19 in Atlanta using an adaptive nested sampling strategy. From March 2021 to April 2022, 868 wastewater samples were collected from influent lines to wastewater treatment facilities and upstream community manholes. Variations in SARS-CoV-2 concentrations in influent line samples preceded similar variations in numbers of reported COVID-19 cases in the corresponding catchment areas. Community sites under nested sampling represented mutually-exclusive catchment areas. Community sites with high SARS-CoV-2 detection rates in wastewater covered high COVID-19 incidence areas, and adaptive sampling enabled identification and tracing of COVID-19 hotspots. This study demonstrates how a well-designed WWS provides actionable information including early warning of surges in cases and identification of disease hotspots.

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T-CELL RESPONSES AS CORRELATES OF DIFFERENT DISEASE OUTCOMES OF DENGUE VIRUS INFECTION

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Dengue virus (DENV) circulates in the tropics worldwide, causing an estimated 400 infections, 100 million clinical cases, and at least 22,000 deaths from dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). Dengue is a growing public health problem worldwide, and climate change is increasing the transmission intensity of dengue and allowing Aedes aegypti to spread to more regions. Currently, there is no comprehensive understanding of the role of adaptive immunity in the context of multiple DENV infections. In our study, we analyzed samples from children with a history of natural DENV infection from an ongoing prospective cohort study of dengue in Managua, Nicaragua, established in August 2004. After a first natural infection, children have different amounts of DENV-specific T cells; analyzing samples collected prior to a subsequent DENV infection allows us to determine if the T cell response has an influence on the clinical outcome of the next DENV infection. We measured DENV antigen-specific T cells in healthy children having experienced a DENV infection 4 ± 2 years before a subsequent infection using an Activation Induces Markers (AIMs) assay. We found that pre-existing DENV-specific CD8+ T cell profiles significantly predicted the outcome of the subsequent infection. Deciphering mechanisms of DENV-specific T cell responses is important to understand immunopathology and to define correlates of protection against clinical disease and is an important contribution towards dengue vaccine development and evaluation.

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METABOLIC SYNDROME CONTRIBUTES TO ENHANCED DISEASE SEVERITY FOLLOWING EMERGING VIRAL INFECTIONS

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The SARS-CoV2 pandemic highlights how the metabolic state impacts immune responses to viruses and viral disease severity. Individuals with metabolic syndrome (MetS) are more likely to develop serve disease, require hospitalization and succumb to emerging viral infections as compared to individuals who do not have MetS. The exact mechanisms surrounding immune dysfunction and enhanced disease severity in MetS patients are unknown. However, many studies point to the presence of chronic cytokines as playing a key role in immune-mediated dysfunction. This study uses a murine MetS model to study the immune dysfunction and chronic inflammatory cytokines associated with MetS during viral infection The objective of this study is to understand the mechanisms underlying the increased disease severity seen in individuals with metabolic syndrome following viral infection. We have shown that chronic inflammation predisposes mice to more severe disease following West Nile (WNV) dengue and SARS-CoV-2 infection. Additionally, in our murine model, we have shown that vaccination against SARS-CoV-2 or WNV is significantly impaired with MetS. Finally, we have shown that by limiting inflammation at the time of infection or vaccination improves outcomes and partially restores the protective efficacy of vaccines. Our current lack of understanding of how chronic inflammation leads to MetS-associated immune dysfunction creates large gaps in our knowledge and prevents the development of targeted therapies to reduce the disease severity associated with MetS. We have developed a murine model of MetS which mimics the disease phenotypes seen in humans with elevated disease severity following WNV, dengue or SARS-Cov-2 infection and poor responses to vaccination. With this model, we are able to identify both the mechanisms causing immune dysfunction and test targeted therapeutics to improve disease and vaccine outcomes.

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ACUTE IMMUNOLOGICAL PROFILE AND PROGNOSTIC BIOMARKERS OF PERSISTENT JOINT PAIN IN THE CHIKUNGUNYA FEVER: A SYSTEMATIC REVIEW

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Chikungunya virus infection (CHIKV) increases the risk of persistent arthralgia; however, there is no consistent evidence regarding prognostic biomarkers of progression to chronic arthropathy. This systematic review, following the PRISMA guidelines, provides an overview of currently available literature about the potential role of the acute immunologic response for predicting long-term join pain in patients with a diagnosis of CHIKV. We searched for observational studies using the terms “chikungunya”, “cytokines”, “biomarkers”, and “joint pain” in PubMed/MEDLINE, LILACS, Cochrane Library Plus, and SCOPUS databases, restricting to articles published in English and up to January 2023. We excluded reviews and studies in which biomarkers were measured after an in vitro stimulation of human cells. The risk of bias was evaluated using the Newcastle-Ottawa Scale. The PROSPERO registration number for this review is CRD42021279400. Thirty-seven studies were selected for qualitative synthesis with a maximum duration from diagnosis to clinical evaluation of 60 months. The sample sizes ranged from 8 to 346 participants (age’s range: 0-90 years). Most of the studies (73.0%) were rated as at high risk of bias. We identified an immunologic profile during the acute phase of CHIKV

that includes increased levels of proinflammatory cytokines (IFN-α, IFN-γ, IL-2R, IL-6, IL-7, and IL-8), anti-inflammatory cytokines (IL-1Ra, and IL-4), chemokines (MCP-1, MIG, and IP-10) and growth factors (VEGF, G-CSF, and GM-CSF). Only one out of two studies reported differences in the cytokine levels during the acute phase which predicted persistent joint pain at 20 months of follow-up. Also, persistence of anti-CHIKV IgG seemed to be a potential prognostic marker. The evidence suggests the existence of an inflammatory response in the acute phase of CHIKV that persists during its chronic phase; however, there is no unequivocal candidate set of biomarkers of progression toward long-term articular sequelae. This may be due to the heterogeneity of the studied populations, the definition of outcomes, and the timing for quantification of biomarkers during disease.

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EBOLAVIRUS -SPECIFIC NEUTRALIZING ANTIBODY PERSISTS AT HIGH LEVELS IN EBOLAVIRUS DISEASE SURVIVORS TWO YEARS AFTER RESOLUTION OF DISEASE IN A SIERRA LEONEAN COHORT

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Ebolavirus (EBOV) infection results in Ebola Virus Disease (EVD), an often-severe acute viral disease with a non-specific presentation, hemorrhagic manifestations, and death. Since its recognition, periodic outbreaks of EVD continue to occur in Sub-Saharan Africa. The 2013-2016 West African EVD outbreak was the largest recorded, resulting in a substantial cohort of EVD survivors with persistent health complaints and variable immune responses. Ebolavirus spp. continue to emerge in often surprising ways including geographically (SUDV in Uganda), and rarely from reinfection or recrudescence in EVD survivors. In this study, we characterize humoral immune responses in EVD survivors and their contacts in Eastern Sierra Leone with the aim of understanding the natural course of humoral immunity and transmission in the context of EVD. We found high levels of EBOV IgG in EVD survivors and lower, yet substantial, antibody levels in household contacts indicating subclinical transmission (85.2% and 59.4% seropositivity, respectively). Neutralizing antibody function was prevalent but variable in EVD survivors—greater than 80% of GP-IgG positive survivors had neutralizing antibody but of those individuals over 20% had weakly neutralizing antibody responses—bringing questions about the durability of immune responses from natural infection with EBOV. Indeed, this finding may also have implications for the long-term durability of EBOV vaccination. These data are particularly interesting in the context of rare cases of re-emergent EBOV from EVD survivors and requires further investigation, specifically into the non-neutralizing Fc-mediated antibody functional responses to natural EBOV infection. Additionally, we found that certain discrete symptoms—ophthalmologic and auditory—are associated with EBOV IgG seropositivity while a wide array of symptoms are associated with presence of neutralizing antibody.

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PREVALENCE OF DENGUE AND CHIKUNGUNYA ANTIBODIES AMONG CHILDREN IN GRENADA, WEST INDIES

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The country of Grenada, West Indies, has experienced several arborvirus outbreaks in the last decade: chikungunya virus (CHIKV) in 2014 and Zika virus (ZIKV) in 2016. Additionally, dengue virus (DENV) is endemic to Grenada, circulating at low levels, particularly during the rainy season. Given the persistence of the mosquito vectors on the island, Grenada is at risk of future outbreaks, highlighting the importance of sero-surveillance in the population. In this study, we performed CHIKV and DENV immunoglobulin G (IgG) antibody testing on a cohort of children who were born during the ZIKV epidemic and have been followed for 5 years to assess neurodevelopmental outcomes. Children underwent approximately yearly neurologic assessments, at which time a blood sample was drawn. Using an in-house IgG enzyme-linked immunoassay (ELISA), we tested samples collected from children greater than 12 months of age, by which time we would expect maternal passive antibodies to have waned. We tested 295 samples from 237 children ranging from 12-29 months of age (median 21.0 [IQR 17.3-24.5]). Among 18/237 (7.6%) children with a positive ELISA (median 21.3 months [IQR 17.2-24.3]), 14 had both DENV and CHIKV antibodies detected, 3 had DENV antibodies, and 1 had CHIKV antibodies. Using maternal surveys, we found no significant differences in race, income, housing and floor composition, latrine type, presence of window screens, rainwater collection and storage, and history of maternal CHIKV and DENV exposure between children with and without detected antibodies. In this cohort of children, there were significantly higher than expected rates of CHIKV and DENV antibodies detected (prevalence of 7.6%), suggesting that arboviruses likely circulate at higher than both predicted and diagnosed levels, but no clear risk factors for childhood infection were identified. ELISA testing on years 4 and 5 from this cohort of children will be completed shortly, providing additional confirmation that antibody detection represents primary infection rather than maternal antibodies, and allowing for additional risk factor analysis.

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ANTIBODY INDUCED RESPONSE AGAINST SARS-COV-2 OMICRON SUBLINEAGES IN A COHORT VACCINATED WITH CORONAVAC FOLLOWED BY A TWO BOOSTER DOSES PROTOCOL WITH BNT162B2 AND AD26.COV2.S

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The development of vaccines against SARS-CoV-2 has enabled a gradual return to normalcy across the world. However, the production and distribution of vaccines was not fast enough and allowed the emergence of variants with high transmissibility and capacity to evade immune response

induced by prior infections and vaccination. Thus, our study evaluated the antibody response of a Brazilian cohort vaccinated with a primary protocol of two doses of CoronaVac, followed by two booster doses with BNT162b2 or Ad26.COV2.S, against Omicron sublineages BA.1, BA.5 and BQ.1.1. A total of 160 individuals were included and divided into 3 time points: 9, 12 and 18 months after the primary protocol. At each time point, individuals were divided equally into 3 subgroups: No booster, 1 booster and 2 boosters (except for the 9 months group, where second booster was not available yet). Samples were subjected to a viral microneutralization assay, against Omicron sublineages, to evaluate the neutralization titers and the seroconvertion rate. For the BA.1, 9 months after primary protocol, the first booster significantly increased the VNT50 mean (133.1 to 575.8) and the seroconvertion rate (33.3% to 76.6%) when compared to the no booster subgroup. In contrast, in the 12 months group, a reduction in the VNT50 mean was observed as the first and second booster doses were administered (1292.3, 1048.1 and 949.1 for no booster, 1 booster and 2 boosters groups, respectively). However, the seroconvertion rate increased as the booster doses were distributed (85%, 90% and 100%, respectively). For the 18 months group, the VNT50 mean decreased between no booster and 1 booster groups, but the neutralization mean after second booster increased significantly (1881.4, 1402.5 and 2361.5, respectively). The seroconvertion rate, at this time point, was maintained at 100% for all the subgroups. Our data shows the positive impact, over time, of the booster doses in the serological response against BA.1. The same process will be performed with sublineages BA.5 and BQ.1.1 to evaluate the antibody neutralization against sublineages that already showed capacity to evade immune response.

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ENGINEERING THE SURFACE OF DENGUE VIRUS 2 ENVELOPE PROTEIN TO SELECTIVELY ELICIT DIMER-SPECIFIC ANTIBODIES

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Dengue viruses (DVs) cause millions of infections globally each year and yet there is not a vaccine that provides complete protection for all individuals. DVs are antigenically distinct but can evoke cross-reactive immunity to other DVs. Among this cross-reactive response, weakly neutralizing antibodies can exacerbate secondary infections through antibody-dependent endocytosis of the new viruses, which proves to be a challenge for vaccine development. A major target of neutralizing antibodies against DV is the envelope (E) glycoprotein that exists as head-to-tail homodimers on the surface of the virus. Within the E-specific antibodies, a subset bind across the dimer interface, including type-specific antibody 2D22 and cross-reactive E-dimer Epitope antibodies, and are strongly neutralizing. However, these antibodies are challenging to elicit as this dimer epitope is not immunodominant. Here, we engineer a resurfaced DV2 E dimer (RS1) to only display the dimer region. Starting with a stabilized version of the soluble E dimer, we used molecular modeling to identify mutations on the surface of the protein which do not affect thermostability or secretion and are not within the epitope of interest. Through biochemical and biophysical characterizations, we determined that RS1 expresses 50 times better than wildtype E, is thermostable, and remains dimeric at low nanomolar concentration. Additionally, RS1 binds to antibodies targeting the dimer epitope, but not to antibodies that interact with other regions of the E protein. To test if immunization with RS1 focuses the antibody response to the cross-dimer region, we primed and boosted mice with WT stable E dimer alone, RS1 alone, or sequential administration of WT E dimer and RS1. Overall, we observed that RS1 elicits fewer anti-DV2 antibodies than WT E dimer, and we are currently testing if sequential administration of WT E and RS1 elicits a greater fraction of antibodies targeting the dimer epitope. Our study highlights a structure-guided protein design approach to generate better dengue vaccine antigens that can focus the immune response to epitopes of importance on the envelope protein.

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CHARACTERIZING THE IMMUNE RESPONSE TO ZIKA VIRUS USING EPITOPE MAPPING, REPORTER VIRUS PARTICLES, AND ANTI-ZIKV ANTIBODIES

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To characterize the immune response to ZIKV infection and vaccines we have epitope mapped over 100 anti-ZIKV MAbs at amino acid-resolution, using a comprehensive ZIKV prM/E library of 672 single alanine mutants expressed in human cells. We identified epitopes of patient MAbs, including highly neutralizing MAbs protective in animal models of ZIKV fetal disease. Epitope locations suggest that some MAbs act by binding across adjacent E proteins, preventing rearrangements necessary for ZIKV infectivity. Mapping also reveals epitopes specific for ZIKV or common to DENV, information that can help create better vaccines and therapeutics. We have also identified mutations that increased ZIKV RVP budding, which may aid the design and production of anti-ZIKV vaccines, by screening each individual ZIKV library prM/E variant for ZIKV particle budding and infectivity. To provide critical reagents, we developed ZIKV reporter virus particles (RVPs) capable of one round of infectivity, with luminescent or fluorescent readout, and demonstrated reproducible neutralization titer data (NT50 values) across different RVP production lots, volumes, time frames, and laboratories. We also isolated anti-ZIKV MAbs for ZIKV-specific immunodetection, diagnostic applications, and ZIKV neutralization studies. After immunization with DNA and sub-viral particles, and phage library panning with RVPs, we isolated 48 ZIKV-specific conformational MAbs against prM/E, including one that potently neutralized ZIKV RVPs (IC50 45 ng/ml) with a quaternary epitope spanning adjacent E proteins.

6745

COMPREHENSIVE MUTAGENESIS OF DENGUE VIRUS ENVELOPE PROTEINS TO MAP ANTIBODY EPITOPES AND IDENTIFY RESIDES ESSENTIAL FOR FUNCTION

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To characterize the immune response to dengue virus (DENV) infection, we have epitope mapped over 200 anti-DENV monoclonal antibodies (MAbs), using high-throughput, rapid screens of MAb binding to DENV prM/E comprehensive mutation libraries for all four DENV serotypes, 3,380 mutations in total. Each library of individual mutant expression plasmids was transfected into human cells to achieve native protein expression and folding, and immunoreactivity of MAbs to each individual prM/E variant was quantified by high-throughput flow cytometry. The epitopes obtained were both conformational (including quaternary) and non-conformational, were spread across prM and E domains I-III, and many have been correlated with their abilities to protect against DENV infection. A number of anti-DENV MAbs cross-reacted with ZIKV prM/E, predominantly within the fusion loop but also within Domain II of the E protein, identifying critical immunogenic residues shared by DENV and ZIKV. We have also produced DENV virions from all four DENV mutation libraries using a previously developed DENV reporter virus particle (RVP) system, allowing us to screen each individual DENV Env variant protein for DENV particle budding and infectivity. For DENV3, we identified residues whose mutation eliminated virus infectivity but did not impact E protein expression, antigenicity, virion assembly, or particle budding. We identified variants that showed increased DENV virion budding, up to 5-fold above wild-type, indicating the ability to engineer highly expressed, non-infectious DENV variants for use in vaccine design.

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IMMUNOLOGICAL INSIGHTS FROM EPITOPE MAPPING ON THE CHIKUNGUNYA VIRUS ENVELOPE

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To characterize the immune response to Chikungunya virus (CHIKV), we have epitope mapped over 70 monoclonal antibodies (MAbs) against the CHIKV envelope glycoprotein E2/E1, using a shotgun mutagenesis library of 910 E2/E1 alanine-scan mutants. Published studies used epitope maps to characterize broadly cross-reactive and ultrapotent neutralizing MAbs that blocked post-attachment steps, and whose binding mapped to functionally-important E2 domains A or B, suggesting that MAbs inhibit virus-host membrane fusion by preventing exposure of the E1 fusion loop. Additional studies characterized MAbs that induce structural changes on E2 domains A and B. Other mapped MAbs included human E1-specific MAbs cross-reactive across the alphaviruses, isolated from survivors of equine encephalitis virus infection. MAb binding patterns and epitope mapping identified differences in E1 reactivity based on exposure of epitope on E1 through pH-dependent mechanisms or presentation on the cell surface prior to virus egress. We also used CHIKV E2/E1 mutants to map the binding site on E2 A and B domains of cell adhesion molecule Mxra8, identified as enhancing attachment and internalization into cells of CHIKV and other alphaviruses, by infectivity screens of cells targeted by CRISPR/Cas9 gene knockouts. We also isolated human MAbs against CHIKV E2/E1. Our most potent MAb, IM-CKV063, was highly neutralizing (50% inhibitory concentration, 7.4 ng/ml), showed high-affinity binding (320 pM), and gave therapeutic and prophylactic protection in animal models up to 24 h post-exposure. Epitope mapping identified an inter-subunit conformational epitope on E2 domain A. Subsequent studies demonstrated that IM-CKV063 blocks both virus entry and virus release. To provide critical reagents for analyses of MAb or serum immune responses to CHIKV infection, we developed a pseudotyped lentiviral reporter virus system for CHIKV, using reporter virus particles (RVPs) displaying E2/E1. These replication-incompetent RVPs perform one round of infectivity and enable safe (BSL-2) and reproducible virus neutralization assays with luminescent or fluorescent readout.

6747

COMPARISON OF TRADITIONAL PLAQUE ASSAY TO IMMUNOFOCUS ASSAY FOR QUANTIFICATION OF CLINICAL (WILD-TYPE) YELLOW FEVER VIRUSES

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Clinical isolates (wild-type) of yellow fever virus produce variable cytopathic effects (CPE) in tissue culture and are often reported to form faint or undetectable plaques using traditional in vitro plaque assays. While flow cytometry-based in vitro neutralization assays have also been developed, they are equipment intensive and less amenable to higher throughput approaches. He we compare traditional 6 well vero-cell based plaque assay quantification of wild-type YFV isolates to a 96 well immunofocus assay for quantification of representative strains of wild-type YFV, including West Africa I, East Africa, South America I and South America II genotypes. The immunofocus method was optimized to quantitate wild-type yellow fever virus using the commercially available pan-flavivirus monoclonal antibody 4G2, a mouse-monoclonal antibody which binds a conserved epitope on the fusion loop of flavivirus structural E protein. We evaluate the sensitivity of detection of wild-type YFV by plaque assay compared immunofocus-forming assay and the performance of serum plaque reduction neutralization test (PRNT) to serum focus reduction neutralization test (FRNT) against select wild-type YFVs. Our results demonstrate that yellow fever virus isolates, when compared to traditional plaque assay, can be reliably quantified by 96-well immunofocus-forming assay in vitro assay using commercially available reagents.

6748

A PANEL OF WILD-TYPE YELLOW FEVER VIRUSES REVEAL NEW INSIGHTS INTO THE POTENCY AND BREADTH OF 17D-ELICITED NEUTRALIZING ANTIBODIES IN A VACCINATED COHORT

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Yellow fever (YF) is a severe disease caused by the prototypic flavivirus, yellow fever virus (YFV), transmitted by mosquitoes. Significant control of YFV has been achieved through vaccination with the 17D vaccine. In 2016 the historical vaccination regime of prime, followed by boost every 10-yrs was changed to single vaccination by the CDC and WHO based in part on data that show long-term persistence of YFV neutralizing antibodies (NAbs). Yet, analyses of NAb titers (NTs) following single-dose vaccination estimate approximately 20% of vaccinees have NTs that fall below assay limits of detection (LoD) by 10-yrs post-vaccination. Furthermore, assays used to establish NTs typically only assess neutralization against the attenuated 17D vaccine strain virus, and serum neutralizing potency against clinically relevant wild-type (WT) YFVs remains largely unknown. Using a panel of 17D-immune sera from a non-endemic human cohort <10-years post vaccination (n = 50), we investigated breadth and potency of NAbs using focus reduction neutralization assays. Breadth and potency were assessed using a panel of WT YFVs representative of the 7 YFV genotypes found globally, including contemporary isolates of clinical significance. We found significantly reduced potency of NAbs against WT viruses compared to 17D, particularly to strains belonging to the South American I genotype responsible for the recent outbreak in Brazil. Pairwise amino acid distances and antigenic cartography were used to characterize antigenic relatedness of WT YFV to one another. To further understand variables that may play a role in directing Ab responses <10-years post-vaccination, we employed multiple variable regression evaluating the effects of time since- and age at vaccination, and Zika and dengue virus infection history on 17D-immune sera potency and breadth. Importantly, for subject serum samples with NTs against 17D at or just above the LoD, we define potency against WT YFVs, a more authentic and stringent test of potential neutralization. These data suggest potentially elevated risk of vaccine breakthrough, which may better inform future vaccination recommendations.

6749

CHARACTERIZATION OF MBC-DERIVED MABS FROM AN INDIVIDUAL WITH SEQUENTIAL DENGUE AND ZIKA VIRUS INFECTIONS

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Zika virus (ZIKV) is a mosquito-borne flavivirus first isolated in 1947 in Uganda that has caused large outbreaks in the Americas in 2015 and 2016. ZIKV is transmitted by the same Aedes species mosquitoes that transmit dengue viruses (DENV). With tropical climates rising further north above the equator, there is an increased risk of ZIKV and DENV co-transmission in the southern United States as Aedes aegypti mosquitos travel to these warmer climates. Therefore, with increased populations at risk of infection, there is a need to better understand how concurrent or prior flavivirus exposures can impact protective immunity to ZIKV in order to develop candidate vaccines. In this study, we aim to understand the human serum and memory B-cell (MBC) response in individuals exposed to ZIKV as their first known flavivirus exposure and in those who were exposed to ZIKV secondary to a prior DENV infection to understand whether DENV infection affects MBC responses to secondary ZIKV infection. Here, we assess the breadth

and depth of binding of strongly neutralizing ZIKV monoclonal antibodies (mAbs) isolated from MBCs of three individuals - two with primary and one with secondary ZIKV infections. Furthermore, we have isolated a panel of seven mAbs from the MBCs of a secondary ZIKV infected individual; mAbs 2E9, 1D2, and 1C6 show type-specific binding and neutralizing response to ZIKV, while mAbs 2G7 and 3C9 show a DENV/ZIKV cross-reactive response but a highly specific DENV2 neutralizing response. These latter mAbs represent a previously unrecognized class of DENV-neutralizing mAbs, exhibiting broadly reactive binding capacity but serotype-specific functional activity.

6750

TARGETS OF DENGUE CROSS-NEUTRALIZING POLYCLONAL SERA

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The four dengue (DENV) serotypes infect 100-400 million individuals yearly, causing a half a million cases of life-threatening hemorrhagic fever and shock syndrome. Each DENV serotype has unique (type-specific) as well as shared (cross-reactive) antibody epitopes on the viral envelope (E) protein. Typical primary DENV infections are mild yet stimulate durable protective immunity to the serotype of infection; importantly, primary DENV infections also generate antibodies that cross-react with other DENV serotypes as well as with Zika virus and other related flaviviruses. In contrast, secondary infection with a different DENV serotype leads to the development of a new population of polyclonal serum antibodies that cross-neutralize and protect against DENV 1-4 but surprisingly do not cross-neutralize or protect individuals from Zika virus and other flaviviruses. A major difference in the E proteins of DENV and Zika viruses is the presence of two as opposed to one glycosylation site on the DENV E protein, which may significantly affect antibody responses elicited to these two closely related flaviviruses. Furthermore, we currently do not understand the specific molecular properties of Zika virus neutralizing or DENV broadly cross-neutralizing antibodies secreted into plasma by long-lived plasma cells. Using specific engineered DENV antigens, viral chimeras, and novel imaging techniques, we are able to isolate serum antibodies from individuals exposed to multiple DENV serotypes and to identify protective E protein targets of dengue cross-neutralizing polyclonal serum.

6751

DETERMINANTS OF IMMUNIZATION IN POLIO SUPER HIGH-RISK UNION COUNCILS OF PAKISTAN

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The current polio epidemiology in Pakistan poses a unique challenge for global eradication as the country is affected by ongoing endemic poliovirus transmission. Across the country, union councils (UCs) that serve as core reservoirs for poliovirus with continuous incidences of polio cases are categorized as super-high-risk union councils (SHRUCs). A cross-sectional survey was conducted in 39 SHRUCs using a two-stage stratified cluster sampling technique. 6,976 children aged 12-23 months were covered. A structured questionnaire was used for data collection. Data were analyzed using STATA version 17. Based on both vaccination records and recall, 48.3% of children were fully-, 35.4 % were partially-, and 16.3% were non-vaccinated in the SHRUC districts. Three-quarters or more of the children in SHRUC districts of Sindh and Khyber Pakhtunkhwa (KP) received a vaccination card, whereas only one to two-thirds of the children in the Balochistan SHRUCs did so. The dropout rate between vaccine visits was higher than the WHO-recommended cutoff point of 10% for all vaccine doses in the SHRUC districts. The of being fully vaccinated was higher among the children of educated parents. Full vaccination was found significant among the children of any SHRUC districts compared to district Killa Abdullah. In conclusion, context-specific strategies with more focus on community engagement and targeted mobilization, along with robust monitoring mechanisms, would help address the underlying challenges of under-immunization in the SHRUCs.

6752

IDENTIFYING SOURCES OF HEPATITIS E VIRUS TRANSMISSION DURING OUTBREAKS THROUGH MODEL-DRIVEN ESTIMATION

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During a waterborne infectious disease outbreak, such as an outbreak of hepatitis E virus in a refugee camp, understanding the relative contribution of environmental sources of infection (e.g., contaminated water) versus person-to-person transmission is key to informing an effective public health and vaccine response. Given the long and variable incubation period for hepatitis E virus (2-9 weeks), distinguishing between epidemic curves driven by environmental sources and person-to-person transmission is challenging. Here, we used person-level case data (with household structure) from simulated outbreaks to develop a statistical method that identifies modes of infection. We simulated epidemic curves for hepatitis E outbreaks using individual-based dynamic mechanistic models under different assumptions on the mode of infection: (i) environmental source (independent of human infection); (ii) person-to-person transmission; and (iii) hybrid modes including both sources. To determine the contribution of person-to-person transmission in different outbreak scenarios, we generated most-likely infection networks and estimated the instantaneous reproduction number (Rt), accounting for temporal clustering of cases within households. We found the average Rt in the population in scenarios with an environmental source alone (100% environmental), 25% person-to-person transmission (75% environmental), and 75% person-to-person transmission (25% environmental) was similar (Rt=2.2); however, the contribution to Rt from within households (a representative proportion of person-to-person transmission) was estimated to be 0.4%, 6.4%, and 30%, respectively. Accounting for household structure in Rt provided a reliable measure for both the predominant mode of infection and the contribution of person-to-

person transmission even when the epidemic curves appeared similar. This method may be applied in waterborne infectious disease outbreaks to guide public health response and reactive vaccine interventions.

6753

ALTERNATIVE MODALITIES AMPLIFYING TRANSMISSION OF EASTERN EQUINE ENCEPHALITIS VIRUS IN AVIAN HOSTS, THE FACTS ARE IN THE FECES

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Eastern Equine Encephalitis virus (EEEV) is considered the most pathogenic arbovirus in the United States with approximately 35% mortality in severe infections and long-term neurological sequelae among survivors. EEEV is transmitted through the bite of an infected mosquito. However, recent data suggests non-vector modalities could affect EEEV transmission. Experimental animal models using House Sparrows and Zebra Finches (Passerines) has shown that fecal-oral transmission potential exists that may amplify EEEV in its natural host environment, providing an alternative explanation for increased transmission in Florida during winter months when mosquito populations are low. Upon experimental infection of passerines with 105 PFU of virus (IV), EEEV was detectable in avian feces for a minimum of five days following infection. Further research revealed that birds exposed to infective feces through fecal-oral route displayed no symptoms of illness, yet demonstrated RT-PCR results indicative of EEEV infection in feces and various organs including the liver, heart, and brain (Ct between 24.04 to 34.90 in feces, 24.06 to 32.50 in liver, 29.41 to 33.03 in heart and 26.84 to 33.92 in the brain). Continued research could determine whether such transmission is possible among avian hosts in their natural environment, which would impact EEEV risk potential. Passerine birds are an important enzootic host for EEEV transmission and confirmation of EEEV transmission through fecal-oral route in the avian host adds an alternative modality to the transmission cycle and the ecology of this virus. Furthermore, these findings can direct future research and public health efforts for EEEV surveillance and control with an alternative method of transmission confirmed.

6754

MUTATIONS OF THE FLAVIVIRUS CONSERVED RESIDUES IN THE ENVELOPE PROTEIN DOMAIN I-DOMAIN III LINKER ATTENUATE THE MOUSE NEUROINVASIVE PHENOTYPE OF WEST NILE VIRUS

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West Nile virus (WNV) is an emerging flavivirus that has caused over 25,000 cases of neurological disease and 2,300 deaths in the United States since 1999. Develop of WN vaccines is a public health priority, especially live-attenuated vaccines (LAVs) that can elicit protective immunity with one single immunization. In the 21st century, candidate WN LAVs are expected to be rationally designed and have a defined molecular basis of attenuation. The envelope (E) protein is a class II fusion protein that facilitates the cell entry of WNV, making it a major component for the rational design of candidate LAVs. Rearrangement of the three domains encoded by the discontiguous sequence of the E gene (EDI, EDII, EDIII) triggers the conformational change of the E protein from dimer in the virion to trimer in the host cell to induce the membrane fusion process during viral entry. Specifically, the relative movement between EDI and EDIII stabilizes the E protein trimer that exhibits the membrane fusion activity. Therefore, the EDI-EDIII linker has been postulated to be a target for the engineering of attenuating mutations. In this project, we undertook site-directed mutagenesis analysis of eight flavivirus conserved residues in the EDI-EDIII linker region, using the cDNA infectious clone of WNV NY99 strain. The E-L295 residue was shown to be suited for the rational design of candidate LAVs. Alternative amino acid substitutions of the E-L295 residue exhibit a varying level of attenuating effect on the mouse neuroinvasive phenotype of WNV in outbred Swiss mice, including the fully attenuated E-A295S mutant that remains capable of multiplying to high infectivity in Vero cells, the acceptable substrate for the manufacturing of flavivirus LAVs. Significantly, the WNV E-L295 residue is conserved between different flaviviruses, warranting the investigation of the equivalent E residue as the target for the engineering of broadly effective attenuating mutations.

6755

INFLUENCE OF BREEDING SITES MICROBIOTA AND NUTRIMENT CONTENT ON AEDES AEGYPTI MICROBIOTA AND VECTOR COMPETENCE FOR ARBOVIRUSES

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Since several decades, arboviruses represent major public health problems in tropical and subtropical regions. Their transmission is complex and influenced by several factors associated to mosquito, virus, host and environment. Among these factors, nutrition and microbiota appeared to be crucial for the mosquito development. However, little is known about the influence of the nutriments and field breeding site bacterial communities on the mosquito's ability to transmit arboviruses. Here, we aimed to i) evaluate the influence of breeding site microbiota on Aedes aegypti microbiota as well as on the transmission of dengue (DENV) and Zika (ZIKV) viruses, and ii) study if the addition of commercial diet in the breeding site water could influence Ae. aegypti fitness, lifespan, microbiota, and ability to transmit arboviruses. All these investigations were performed in both field and laboratory waters. In field vs laboratory condition, metagenomics data revealed a modification of Ae. aegypti microbiota at the larval and adult stages depending on the breeding site water microbial composition. Furthermore, even if DENV transmission efficiencies were homogenous, ZIKV transmission seemed to be modulated indirectly by the breeding site. The evaluation of the influence of diet on Ae. aegypti demonstrated that the nutriments contained on the diet could significantly modulate mosquito's pupation, emergence and survival rates, body size and microbiota in both laboratory and field waters. Interestingly, the diet seemed to also modify the ability of Ae. aegypti to be infected by DENV. These results highlight the importance of the breeding site water and nutriments on microbiota establishment in Ae. aegypti, as well as on its fitness and ability to transmit arboviruses. Furthermore, they emphasize the need of standardization of vector competence evaluations at regional or international scales to obtain an accurate risk estimation and for an enhanced preparedness in view of arbovirus spread.

6756

THE EFFECT OF ENVIRONMENTAL TEMPERATURE ON TRANSMISSION DYNAMICS AND VIRAL GENETICS AMONG CULEX TARSALIS MOSQUITOES INFECTED WITH RIFT VALLEY FEVER VIRUS (RVFV)

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Rift Valley Fever Virus (RVFV) is an emerging, zoonotic arbovirus endemic to sub-Saharan Africa with a potential to invade new geographic areas, including the United States. Common mosquito species in the US, including Culex tarsalis, have been shown to be efficient vectors of RVFV. However, the ability of insect vectors to become infected and transmit arboviruses is mediated by environmental temperature, which is increasingly important to understand in the context of a rapidly changing climate. Therefore, the objective of our study is to evaluate the impact of temperature on the transmission efficiency of RVFV as well as population genetics of the virus in different tissue compartments of the mosquito over the course of infection. Culex tarsalis mosquitoes were infected with RVFV through an artificial,

infectious blood meal and held at 18°C, 28°C and 32°C. Mosquitoes were dissected to obtain legs and wings, midguts, carcasses, and saliva at 7- and 14-days post infection to determine how temperature influences transmission in this competent vector species. RNA extracted from the samples will be used study genetic interactions between the mosquito and virus by performing transcriptomic sequencing and gene expression analyses. Data collection and analysis are ongoing, but preliminary results on dissemination and transmission rates at each temperature will be presented. These experiments will fill critical gaps in our knowledge on RVFV infection dynamics and maintenance in a competent mosquito vector to inform the development of effective control strategies.

6757

VECTOR COMPETENCE OF AEDES AEGYPTI TO DENGUE SEROTYPES TWO AND THREE IN AYAWASO WEST DISTRICT IN GHANA

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Dengue fever is an emerging arboviral disease which is found in tropics and sub-tropical climates. This fast-growing infectious disease records about 100 to 400 million infections per year. In Africa, the prevalence of dengue disease is 14%. Aedes aegypti, the transmitting vector has become abundant in Africa due to urbanization and trans-Atlantic trade. This poses a risk to a potential outbreak of some arboviral diseases including dengue. Some studies have shown that Ae. aegypti aegypti is more efficient than Ae. aegypti formosus which is thought to be predominant in Africa. Recent studies have however shown that the domestic forms of Aedes species have taken over from the forest types. In Ghana, limited information is known of the subspecies of Aedes mosquitoes and the efficiency of them transmitting dengue virus. This study therefore investigates the vector competency of Ae. aegypti in an urban location in the country. Larvae and pupae were collected and reared in the insectary until they emerged. Adult female aedes mosquitoes were infected with dengue 2 and 3 serotypes and then midgut infection and virus dissemination were established by RT-PCR. It was realized that the infectivity rate of both dengue serotypes was high with DENV-2 and DENV-3 having of 71.4 % and 60.7%, respectively. The dissemination rate was significantly higher in dengue 2 compared to dengue 3 in infected mosquitoes with DENV-2 having a 100% dissemination rate in the colony while DENV-3 had a 50% dissemination rate. These findings indicate that the high susceptibility to dengue virus in the study site in the Ayawaso west district in Accra poses a potential risk for future outbreak of the disease. The country therefore should enhance vector control tools and strategies to prevent dengue fever in the absence of an effective treatment or vaccine

6758

CELLULAR MECHANISMS INVOLVED IN THE VIRAL INTERFERENCE OF INFECTION BETWEEN DENGUE AND YELLOW FEVER VIRUSES IN AEDES MOSQUITO CELLS

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Yellow Fever (YFV) and dengue viruses (DENV) are arthropod-borne viruses transmitted by Aedes mosquitoes and, in Brazil, the main transmission vector is Aedes aegypti. DENV is prevalent throughout Brazil, causing outbreaks every year, but since 1942 Ae. aegypti-transmitted YFV has not been responsible for outbreaks of urban origin. Due to the absence of urban Yellow Fever outbreaks, we hypothesized that mosquito infection by one virus would interfere with each other infection, a process known as viral interference of infection. Then, we showed that C6/36 (Ae. albopictus) mosquito cells initially infected with the DENV would not allow infection with the YFV (wild-type and 17DD strain). In short, experiments were performed in C6/36 cells, initially infected with DENV-2 for 7 days and subsequently infected with YFV (DENV-2/YFV). After YFV infection, DENV-2-infected cells died more quickly than when they were infected only with the DENV-2 and, under light microscopy, the DENV-2/YFV-infected mosquito cells showed morphological changes, such as, increased cell volume. Considering apoptosis as a possible mechanism for cell death, RT-qPCR-based experiments showed that DENV-2/YFV sequential infections of C6/36 cells resulted in activation of the apoptosis pathway, with upregulation of the DREDD gene (CASP8), an initiator of the cell death cascade on the apoptosis pathway. Additionally, upregulation of the Michelob_x gene, a positive regulatory gene for cell death, and downregulation of the IAP-2, a cell death regulator gene, were observed in DENV-2/YFV infections compared with DENV-2 alone. Furthermore, the IMP gene expression, a gene responsible for maintaining the integrity of cell membrane, was strongly downregulated in the context of the same experiment (DENV-2/17DD infections). Our data indicate that DENV-2/17DD infections of C6/36 cells reduced cell viability due to a lack of control of programmed cell death. In the nature, this impairment of mosquito cell membrane maintenance may reduce the Ae. aegypti vectorial capacity in the transmission of the YFV in the urban environment, when sequentially infected with DENV and YFV.

6759

AEDES AEGYPTI MOSQUITO BITES ENHANCE INFECTION OF MYELOID CELLS WITH DENGUE VIRUS IN HUMAN SKIN

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Biting of humans by infected Aedes aegypti mosquitoes is the primary mode of transmission for several arboviruses of public health importance, including the dengue virus (DENV1-4). However, little is known about the immune response at the site of infection. We inoculated Aedes aegypti adult females with DENV-2 by intrathoracic injection before exposing full-thickness human skin explants to infected mosquitoes. Skin explants inoculated with 4 logs of DENV-2 by a bifurcated needle were used as a control to assess the effects of mosquito probing on cutaneous immunity. Skin explants were analyzed by confocal microscopy using antibodies to cell-specific markers and NS3 protein, and RNA sequencing of whole skin biopsies. NS3 expression was detected in keratinocytes in the epidermis and the extent of infection was similar between Aedes-probing or needle skin inoculation. In contrast, DENV inoculation by Aedes-infected mosquitoes resulted in earlier and increased replication of DENV in the dermis, reaching a 2-fold boost in infected cells at 24h when compared to needle inoculation. Within the dermis, increased replication of DENV by Aedes-infected mosquitoes was mediated by earlier and increased recruitment and infection of macrophages. Increased infection of Langerhans cells but not dermal dendritic cells also contributed to increased DENV replication observed in mosquito-bitten skin. In the absence of DENV, Aedes bites boosted the recruitment of macrophages to the bite site, but not other myeloid cells. Transcriptomic comparisons between mock or infected (needle or Aedes) groups were performed across

three-time points (2, 8, and 24h post-infection). Pathway Analysis identified canonical pathways relevant to experimental conditions at different time points and revealed evolving transcriptomic signatures tied to virus delivery method. Our findings reveal that DENV delivery by Aedes-mosquitoes bites induces a cutaneous immune response that favors virus infection and dissemination in human skin.

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VECTOR COMPETENCE OF US BORDER AEDES AEGYPTI MOSQUITOES FOR DENGUE VIRUS SEROTYPE 1 ISOLATED FROM A MEXICO BORDER COMMUNITY

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Dengue is the most important mosquito-borne viral human disease in the tropical and subtropical regions of the world. In the last decades, dengue outbreaks have been reported in urban communities located in northern Mexico and in the Southeast Texas of the United States (US). Aedes aegypti, the main vector of dengue viruses (DENV), is distributed along the US-Mexico border region. Several dengue cases have been reported from Ciudad Juarez, a Mexican border city neighboring El Paso-Texas during the past few years, including the isolation of DENV-1 from a febrile patient with no travel history outside Ciudad Juarez. In this study, our aim was to determine if strains of Ae. aegypti mosquitoes from El Paso and Rio Grande Valley were competent vectors of the DENV-1 Ciudad Juarez isolate. Ae. aegypti mosquitoes from both US border communities were orally exposed to two different DENV-1 doses (6 log 10 PFU/mL or 4 log 10 PFU/mL) and maintained from 7 to 21 days at 28 °C. Individual mosquito body, legs/wings, and saliva were tested by plaque assays and identified by an immunofluorescence assay. Infectivity rates ranged from 76% to 93% in both Ae. aegypti strains after the mosquitoes ingested 6 log PFU/ml of DENV-1 and significantly decreased to 16% to 63% after ingesting 4 log PFU/mL of the virus. Dissemination rates significantly increased ($p<0.05$) through time (7 to 14 days) in both Ae. aegypti strains, with no associations between dissemination rates and the viral dose. DENV-1 transmission rates in Rio Grande and El Paso Ae. aegypti mosquitoes were 3.23% and 5.71%, respectively. These results showed that the DENV-1 efficiently infected and disseminated in both US border Ae. aegypti strains, but the very low transmission rate suggested the presence of a salivary gland barrier in these U.S. border Ae. aegypti strains. This study highlights the epidemiological importance of evaluating the risk of DENV-1 introduction and transmission in the U.S. border communities. While further studies are needed, these preliminary findings could explain the very low prevalence of dengue cases in the Rio Grande Valley and the absence of cases in the El Paso community.

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EXPLORING POSSIBILITIES FOR BUNYAMWERA VIRUS MAINTENANCE CYCLE TRANSMISSION

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Bunyamwera virus (BUNV), an Orthobunyavirus found cocirculating with Rift Valley Fever Virus (RVFV) during an outbreak in Rwanda (2018), was genomically identified as an alternative etiology for clinically ill cattle who were RVFV negative. Given the propensity of other related Bunyaviruses for vertically transmission from infected mothers to progeny and the importance of said transovarial transmission to the maintenance of RVFV during interepidemic periods, we investigated whether BUNV shared a similar maintenance cycle. RVFV in Africa is maintained in interepidemic periods in Aedes mosquitoes via transovarial and transstadial transmission, including after larva consumed infectious organic material in their rearing water. We hypothesized that BUNV may share this characteristic cycle via Ae. aegypti. We first tested Ae. aegypti (Rock) for vector competence to BUNV and found that in our colony, no mosquitoes became infected following an infectious bloodmeal. Further, a second bloodmeal - which has been shown to increase infectivity of other arboviruses - did not result in any infected mosquitoes, either. We also tested environmentally mediated transmission by exposing 4th instar larvae to BUNV by offering a sole food source of infected Vero cells scraped from flasks 24 hours post inoculation with BUNV. 5/19 pools (10 larva each) were positive for BUNV by quantitative RT-PCR, at 5 days post exposure, with an average detected titer of 1.17*10^1. Similarly exposed larvae were allowed to emerge as adults and no pools tested positive for BUNV. When testing for transovarial transmission sixty adult females partook of an infectious BUNV bloodmeal (1.7*10^6 PFU/mL), but none developed a midgut infection at after 18-26 dpe, indicating no BUNV infection reached the ovaries. Our data suggests that Ae. aegypti are unlikely to contribute to the maintenance of BUNV in a RVFV-like transmission cycle, including transovarial, transstadial, or environmentally mediated transmission.

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EFFICACY AND SAFETY OF AN INACTIVATED WHOLE-VIRION SARS-COV-2 VACCINE (CORONAVAC) IN BRAZILIAN HEALTHCARE PROFESSIONALS: THE PROFISCOV STUDY

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The inactivated SARS-CoV-2 vaccine, CoronaVac (Sinovac, China), offers several advantages. Frontline healthcare professionals (HCP) in Brazil were highly impacted early in the pandemic, putting them at high risk of infection from COVID-19. This study reports the final analysis of vaccine efficacy (VE) and safety in HCP. In this phase 3, randomized, placebo-controlled trial conducted at 16 Brazilian sites, we assigned adults (≥18 years) in a 1:1 ratio to receive two intramuscular doses of CoronaVac or placebo 14 days apart. The primary efficacy was symptomatic COVID-19 cases confirmed >14 days post-second dose. Exploratory efficacy analyses were the VE against COVID-19 with fever≥1 day, World Health Organization (WHO) progression score ≥3 and ≥4. Safety was evaluated by the frequency of solicited and unsolicited adverse reactions (ARs) up to 7 days after vaccination (NCT04456595). Between July 2020 and February 2021, 12,688 participants underwent randomization, and 11,620 were included in the pre-protocol efficacy population. The mean age was 39.2 (±10.8), with 64% females and 57% having any comorbidity. An interim analysis conducted on December 16, 2020 (median follow-up time: 148 days) showed a VE of 50.4% (95% CI: 35.2-61.2), authorizing the vaccine for emergency use in January 2021. In the final analysis (median 371 days of follow-up), VE was 44.6% (95% CI: 34.9-52.8). The VE against COVID-19 with fever≥1 day, WHO≥3, and WHO≥4 was 64.3%, 82.1%, and 100%, respectively. The incidence of ARs was higher in the vaccine than in the placebo (78.4% vs. 65.4%), but most were grades 1 and 2. Common solicited local and systemic ARs within 7 days after any dose were injected-site pain and headache, respectively. Rhinorrhea was the most frequent unsolicited AR (80% grade 1). No difference in serious adverse events within 7 days after any dose between groups was found (0.8% vs. 1.0%). In conclusion, a two-dose regimen of CoronaVac administered to adult frontline healthcare

professionals was well-tolerated and conferred modest protection against symptomatic COVID-19; however, protection against severe disease was high.

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PRIOR VACCINATION ALTERS THE DYNAMICS OF THE EVOLVING T CELL RESPONSE IN HUMANS UNDERGOING CONTROLLED CHALLENGE WITH DENGUE VIRUS 1

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T cell correlates of protection from dengue infection are poorly defined in humans; however, memory T cell responses are implicated in both host protection and pathology. A clinical trial was performed to evaluate the efficacy of a dengue vaccine consisting of a priming dose of purified inactivated tetravalent dengue (TDEN) vaccine followed by booster vaccination with a live attenuated TDEN vaccine administered at an interval of 90 or 180 days after. Between 27 and 60 months after booster vaccination, six vaccinated volunteers (vaccinees) and four unvaccinated controls underwent live virus human challenge (LVHC) with 3.25 X 103 PFU Dengue Virus 1 (DENV-1) strain 45AZ5, administered subcutaneously. Five of six vaccinees and all four controls developed RNAemia and clinical symptoms of dengue fever, with earlier and shorter RNAemia and symptom duration observed in vaccinees compared to controls. PBMC collected prior to challenge (baseline) and post-challenge were stimulated in vitro with six peptide pools spanning the full DENV-1 proteome and analyzed by mass cytometry (30 analytes), and traditional flow cytometry. We observed distinct patterns of CD4+ and CD8+ T cell responses that differed depending on the development of RNAemia and prior vaccination status. While the majority of RNAemic vaccinees produced CD8+ T cell responses by day 90 after LVHC, the control volunteers did not produce strong CD4+ or CD8+ T cell responses relative to vaccinees after LVHC. Additional effector function and multifunctional responses, co-stimulatory molecule expression, and memory subset data will be presented to compare the maturation of T cell responses in a dengue human infection model in subjects with and without history of dengue vaccination.

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CHARACTERIZING A NOVEL DENGUE VACCINE BY LEVERAGING CLINICAL TRIAL DATA WITH A MULTI-LEVEL MODEL

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A safe and effective vaccine that can be universally administered could be key to effectively controlling dengue. Takeda's QDENGA, which recently completed phase-III clinical trials, is a potential candidate for such a vaccine. However, initial trial results suggest that QDENGA may have differential protection by outcome, infecting serotype, and baseline serostatus. To accurately account for this differential protection when projecting impact of QDENGA, it is necessary to obtain estimates of protection that accord with how impact projection models are parameterized. We did so by developing a multi-level model using a survival analysis framework that simultaneously considers trial-wide, country-level, age-specific, and serostatus-specific clinical trial data on reported cases and hospitalizations in both treatment and placebo arms to estimate vaccine and epidemiological parameters. We found that protection varied by both serotype and serostatus, with protection against disease ranging from 70.9% (95% CI: 62.0, 80.6) among seropositives infected by DENV-2 to -17.4% (95% CI: -87.4, 42.2) among seronegatives infected by DENV-4. Importantly, using a multi-level model to account for shared baseline epidemiological characteristics between arms allowed us to obtain efficacy estimates with reduced uncertainty relative to trial estimates. This is highlighted by our estimates for protection against hospitalization due to DENV-3 among seronegatives. While the trial estimated an efficacy of -87.9% (95% CI: -573.4, 47.6), indicating enhanced risk of disease, our model estimates a value closer to the null (-21.7%, 95% CI: -79.6, 33.1). We used these model-derived efficacy estimates to project public health impact, which indicates that QDENGA could avert 38% (95% CI: 36-42) of cases among baseline seropositives and 1% (95% CI: 0.4-17) of cases among baseline seronegatives, reflecting uneven protection by serostatus. These results suggest that while QDENGA may be an important tool in controlling dengue, the heterogenous protection it offers may hamper its impact.

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DURABLE B AND T CELL IMMUNITY TEN YEARS AFTER DENGUE VACCINATION OF FLAVI- NAÏVE PEOPLE

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Limited data are available on durability of immunity after dengue vaccination of flavi-naïve people living in non-endemic areas. However this data is critical as followup studies in dengue seronegatives receiving both the Sanofi and Takeda vaccines have shown different levels and serotype-specificity of protection after vaccination compared with dengue seropositives. Further, durability of immunity is a key question for any vaccine. We enrolled 13 people who had received an early version of Takeda's dengue vaccine as part of an NIH-sponsored study and 13 people who had prior natural dengue infection, and characterized durability of neutralizing antibodies and T cell responses to DV1-4. T cell responses were measured by re-expanding memory CD4+ and CD8+ T cells with live DV1-4 for 7 days in vitro. The number of re-expanded dengue-specific memory CD4+ and CD8+ T cells was determined by flow cytometry, using IFNy and Ki67 as markers of memory immunity and proliferation, compared with mock-expanded cells. B cell responses were measured by neutralization assays in Vero cells and secretion of dengue-specific antibodies from restimulated memory B cells. We found flavi-naïve recipients of an early version of the Takeda live attenuated tetravalent dengue vaccine had re-expandable memory T cells to DV2 and some people had re-expandable memory T cells to DV4 10 years post vaccination. Flavi-naïve vaccine recipients also had neutralizing antibodies to DV2 with cross-reactive antibodies to DV1, 3, and 4. As volunteers reported no travel to dengue endemic areas after vaccination and no other flavi-virus infections or vaccinations, we conclude these are persistent memory responses to vaccination. In contrast, while people who had natural infection had detectable neutralizing antibodies (predominantly to DV3), only volunteers who had 2 dengue infections had re-expandable memory T cells years after infection (to DV1 and 3). We conclude that a single dengue infection does not produce durable memory T cell immunity in previously flavi-naives living in non-endemic areas, while an early version of Takeda's live attenuated dengue vaccine does.

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CONDUCTING AN EBOLA VACCINE TRIAL IN A REMOTE AREA OF THE DEMOCRATIC REPUBLIC OF THE CONGO: CHALLENGES, MITIGATIONS, AND LESSONS LEARNED

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Conducting a vaccine trial in a low- and middle-income country (LMIC) can present unique challenges and lessons learned. This Ebola vaccine trial, enrolling 699 healthcare providers and frontliners and jointly set up by the University of Antwerp (Sponsor) and the University of Kinshasa (Principal Investigator), was conducted in Boende, a remote town in the Democratic Republic of the Congo (DRC), between December 2019 and October 2022 (ClinicalTrials.gov: NCT04186000). While being bound to strict international

regulations, this trial, exemplary for being a public-private partnership, required collaboration between several international stakeholders (i.e. two universities, a pharmaceutical company, and a clinical research organization), local communities and government agencies. Throughout its 34-month duration, the Sponsor and Principal Investigator team had to address several logistical and administrative challenges, cultural differences, language barriers and regulatory, political and ethical considerations, while tailoring and adapting the study to the specific local context. Lessons learned include the importance of community engagement and clear communication with participants in all phases of the study, but also among different stakeholders. Challenges, mitigations and lessons learned are presented in categories, ranging from safety management, trial documentation and logistics, communication, and climate conditions to financial and administrative hurdles. Ultimately, to reach the successful end of the vaccine trial in this remote Ebola endemic area of DRC, careful planning, collaboration, and great flexibility and adaptability was often required from all involved parties. As the vaccine trial presented in this paper was able to obtain high retention rates (i.e., 92% of participants completed the study) despite the encountered challenges, we hope that other international teams aspiring to conduct similar trials in remote areas of LMICS, can learn from these challenges, mitigations and lessons learned.

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THE IMMUNOGENICITY OF A TETRAVALENT LIVE DENGUE VACCINE (DENGVAXIA) ADMINISTERED TO CHILDREN IN THE PHILIPPINES WITH BASELINE IMMUNITY TO ONE DENGUE VIRUS SEROTYPE

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Antibody-dependent enhancement (ADE) of dengue virus (DENV) infection occurs when an individual with non-neutralizing dengue antibodies from prior exposure to dengue experiences a second infection with a different serotype. Due to the increased risk of ADE and subsequent severe disease in individuals with only one previous infection, vaccination against dengue will likely be most beneficial for this at-risk population. We aimed to define the properties of antibodies in a cohort of 215 primary immune children aged 9-14 from the Philippines who did (60%) or did not (40%) receive a single dose of Dengvaxia. Paired blood samples collected before vaccination (baseline) and 12-18 months after vaccination (Year 1) were tested for antibodies stimulated by the vaccine or incident natural DENV infections. To detect and distinguish vaccine responses from natural infections, we developed a multiplexed, bead-based serological assay to simultaneously quantify serum antibodies to different structural and non-structural antigens from the four DENV serotypes, Zika, and Yellow fever viruses (vaccine backbone). At Year 1, 29% of children had no detectable antibody response to the vaccine, while the remaining 71% had specific antibody responses to one or more vaccine antigen. Children with baseline immunity to DENV4 responded poorly to the vaccine (relative response 0.498, p=0.01) compared to children with prior immunity to DENV1, 2, or 3. All clinically inapparent and symptomatic DENV infections in Year 1 were detected by serology using immunodominant DENV antigens that were absent in the vaccine. In Year 1, 36% of unvaccinated and 28% of vaccinated children experienced a natural infection (relative risk = 0.79; 95% CI = 0.53 - 1.19). Studies to assess vaccine clinical efficacy and safety in years 1 through 5 post-vaccination are ongoing.

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CHARACTERISING THE IMMUNOGENICITY AND EFFICACY OF SECOND-GENERATION DENGUE VACCINE

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A second-generation vaccine (TAK-003) developed by Takeda Pharmaceutical has recently completed its phase III trial and received licensure for use in multiple countries, including Indonesia and Brazil. While overall results indicate that the vaccine is efficacious against symptomatic and hospitalised dengue, efficacy has also decayed with time and may depend on several factors such as the vaccine recipient's age and baseline serostatus, as well as the infecting serotype. Critically, efficacy estimates are subject to large uncertainty, due to the limited number of cases in subgroups. No efficacy estimates have been published by age, infecting serotype and baseline serostatus. A Bayesian survival model was developed to refine efficacy estimates of TAK-003. We calibrated the model to publicly available data on virologically confirmed dengue cases and hospitalisations, by trial arm, baseline serostatus, and either age-group or infecting serotype, up to 54-months. A second model was developed to infer the underlying neutralising antibody titres induced by TAK-003 and to link them with protection against clinical disease. Our survival model fits the observed trial attack rates well, including by baseline serostatus, infecting serotype and age-group. In agreement with published trial data, we found that vaccine efficacy is highest in baseline seropositive individuals and against DENV-2. By month 36, no statistically significant efficacy was estimated against DENV-1, DENV-3 and DENV-4 in the baseline seronegative group. Despite the limitations of fitting to aggregated publicly available data, we have developed a survival model which can reconstruct the observed attack rates and links antibody dynamics with protection. The model supports a mechanism of action whereby TAK-003 is efficacious against DENV-2 irrespective of baseline serostatus, whereas efficacy against DENV-1, -3 and -4 depends on an individual's past dengue exposure. As vaccine rollout is imminent, refined characterisation of the vaccine's complex efficacy profile can help policymakers determine the optimal use of TAK-003.

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SAFETY AND IMMUNOGENICITY OF A 40 MG ADJUVANTED DOSE OF A CHIKUNGUNYA VIRUS VIRUS-LIKE PARTICLE (CHIKV VLP) VACCINE: RESULTS FROM THREE PHASE 2 CLINICAL TRIALS

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PXVX0317 is an aluminum hydroxide adjuvanted form of the CHIKV VLP vaccine that has previously demonstrated a good safety profile and robust immunogenicity. Here, we report the safety and immunogenicity of the selected single adjuvanted 40µg dose of PXVX0317 in 145 subjects 18-64 years of age from three phase 2 trials. In dose ranging study PXVX-CV-317-001, a >4-fold rise over baseline in anti-CHIKV serum neutralizing antibody (SNA), as determined by a luciferase-based virus neutralization assay (NT80), occurred in 100% of the 40µg vaccine recipients, with a peak GMT of 1713, by 28 days after dosing. The immune response was durable, with a >4-fold rise in 90% of vaccine recipients and a GMT of 280 at day 731. In study EBSI-CV-317-002, which compared prior recipients of heterologous alphavirus vaccines with alphavirus vaccine-naïve controls, the day 22 rate of >4-fold rise in anti-CHIKV SNA was 100% in both groups and was maintained in 93% of participants for 181 days post-vaccination. A higher percentage of prior alphavirus vaccine recipients (93.3%) had a >4-fold SNA rise at day 8 than controls (66.7%, p=0.021). The GMTs peaked in both groups at day 22 and were similar at this and all subsequent

visits. In open-label study EBSI-CV-317-010, the rate of >4-fold rise in anti-CHIKV SNA at day 22 was 100%, when GMTs peaked at 2365. In each study, the 40µg dose was well tolerated and the majority of solicited adverse events (AEs) were of mild or moderate severity. The most common local solicited AE was injection site pain, while the most common systemic AEs were fatigue, headache, and myalgia. In study EBSI-CV-317-002, there were no significant differences in the incidence of solicited AEs between prior recipients of alphavirus vaccines and alphavirus vaccine-naïve control subjects. Across the 3 studies, there were no vaccine-related study discontinuations or SAEs. A single 40µg dose of the adjuvanted CHIKV VLP vaccine, PXVX0317, was well tolerated in three phase 2 clinical trials, including in prior recipients of a heterologous alphavirus vaccine, and generated a rapid SNA response which persisted for 2 years. Phase 3 studies of a 40µg dose of PXVX0317 are ongoing.

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IN VIVO EFFICACITY OF SULFADOXINE PYRIMETHAMINE IN PREGNANT WOMEN INFECTED WITH PLASMODIUM FALCIPARUM IN MALI

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Pregnant women infected with Plasmodium falciparum and her newborn are relatively a high risk to develop low birth weight, maternal anemia, prematurity, and mother death. Sulfadoxine Pyrimethamine as Intermittent Preventive Treatment is recommended from week 13 to delivery to prevent P. falciparum infection during pregnancy. In some parts of Africa, P. falciparum resistance to Sulfadoxine Pyrimethamine has reached a high threshold warranting. This study aimed to assess the level of efficacy of Intermittent Preventive Treatment with Sulfadoxine Pyrimethamine. A prospective observational study was conducted from 2018 to 2019 during routine consultation to collect data on SP delivery and malaria. Pregnant women were included during the first administration of Sulfadoxine Pyrimethamine when gestational age was between 16 and 30 weeks. In vivo efficacy was determined after 42 days of follow up, according to the 2009 World Health Organization standard protocol. A descriptive analysis was done to determine the proportion of preventive failures, Kaplan Meier curve and Log rank test were used to determine the time of failure and confounding factors. A total of 254 women were enrolled with a mean age of 22 years. Efficacity with and without molecular correction was 99.2 percent and 82.3 percent respectively. The real efficacity was not influenced by site, residence, gestate, Insecticid Traited Net use and anemia according to the survival curve, P value is lower to 0.05, Log rank. The proportion of anemia decreased significantly during follow-up from 81.4 percent to 64.5 percent, P value is lower to 0.001. Sulfadoxine Pyrimethamine remains effective to prevent P. falciparum infection and anemia during pregnancy. However, it's monitoring is essential in the framework of the surveillance of this molecule.

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TRANSCRIPTOMIC APPROACH TOWARDS UNDERSTANDING THE MOLECULAR MECHANISMS OF IMIDAZOLOPIPERAZINE (IPZ) IN THE MALARIA PARASITE PLASMODIUM FALCIPARUM

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Imidazolopiperazine (IPZ), KAF156, a close analogue of GNF179 is a promising antimalarial candidate. IPZ is effective against Plasmodium falciparum and P. vivax clinical malaria in humans with transmission blocking property in animal models and effective against liver stage parasites. Despite these excellent drug efficacy properties, in vitro parasites have shown resistance to IPZ. However, the mechanism of action and resistance of IPZ remains poorly understood. To decipher the mechanism of action and resistance of IPZ, we performed a differential transcriptome study using bulk RNA sequencing on P. falciparum Dd2 strains wild type and its mutant resistant to IPZ (pfcarl, pfact and pfugt known to confer drug resistance to IPZ in vitro) in GNF179 exposed and unexposed conditions of their schizont stages. We report in wild type parasites GNF179 treatment down regulated putative lipase enzymes disrupting thus the hydrolysis of Phosphoinositol 4,5 - bipohosphate (PIP2) and Triglyceride (TAG) which are essential for P. falciparum survival and proliferation as well as membrane permeability and protein trafficking. Furthermore, we found that in wild type parasites, GNF179 disrupted lipid metabolism, transport and synthesis by repressing expression of Acyl CoA Synthetase, export lipase 1 and esterase enzyme. Finally, our data report that genes involved lipid metabolism are associated to IPZs resistance.These transcriptomic data constitute a great advance to identify the mechanism of action and resistance of IPZs. It's essential to perform qPCR to validate level of the differentially expressed genes in this study and perform antibody experiments to target key genes which have been validated by qPCR

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INVESTIGATION OF MARKERS OF ARTEMISININ RESISTANCE AT SELECTED INTERVALS DURING THE 72-HOUR PERIOD AFTER ARTEMISININ BASED COMBINATION THERAPY DOSING IN KISUMU WESTERN KENYA

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Post-treatment parasitemia occurs in at least 25% infections in sub-Saharan Africa despite continued efficacy of artemisinin-combination therapy (ACT) across Africa. Plasmodium falciparum mutation in chloroquine resistance transporter gene (pfcrt76), multi-drug resistance gene1 (pfmdr1), deubiquinating enzyme gene (pfcubp-1) as well as clathrin vesicle-associated adaptor 2, µ subunit encoding gene (pcap2mu) and multi-drug resistant protein 1 gene (pfmrp1) have been associated with recurrent parasitemia. As new markers of ACT resistance in Africa continue to be unveiled across different regions, surveillance of changes in these polymorphisms during the course of treatment is useful in establishing their role in ACT treatment outcome. Each of the 118 P. falciparum samples obtained from individuals enrolled in an ACTs clinical efficacy study comparing outcomes of artemisinin-lumefantrine versus either dihydroartemisinin-pipearaquine or artemether-mefloquine between 2013 and 2015 were screened at three or four-time points; day zero before start of treatment then days 2 and 3 after initiation of treatment plus the day of subsequent parasitemia by microscopy. Sequence analysis was done to evaluate genotyped frequency of drug resistance polymorphisms, Pfmdr1, gene copy number and genetic diversity typing of the 12 microsatellite loci. The results indicated that the most polymorphic loci of pfap2mu and pfcubp-1 genes were S145C at 18% and E1528D at 19%. Pfmdr1 86, 184 and 1246 had significant increase in wild type alleles at time-points 3 and 4 ($p < 0.05$). Multiple copies of the pfmdr1 gene were observed in 4.55% of the samples analyzed. Microsatellite profile analysis showed that the mean number of alleles in all the loci across the 8 populations ranged from 9.250 to 1.000. The mean parasite clearance half-life was 2.63 hours (IQR). Low clearance rates attained in this study suggests that ACTs are still effective treatment in Kenya. However, increased wild-type pfmdr1 86,184 and 1246 as well as polymorphisms in pfap2mu and pfcubp-1 in post day zero suggest that these genes could be responding to ACT dosing and therefore require continued monitoring.

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INSIGHTS INTO THE EMERGENCE OF THE 431V RESISTANCE MUTATION IN PLASMODIUM FALCIPARUM: LINKAGE WITH A NOVEL INTRON MUTATION

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Sulfadoxine-pyrimethamine (SP) plays a critical role in malaria chemoprevention across Africa. However, the increasing P. falciparum resistance to SP has impeded its protective efficacy. The genetic mechanism of SP resistance is well-established and is caused by mutations in the dihydrofolate reductase (dhfr) and dihydropteroate synthase (dhps) genes. Recently, the 431V mutation in the dhps gene has emerged in West Africa, and studies suggest that it may decrease the effectiveness of SP. The principle objective of this study is to investigate the possibility that there is a selective sweep associated with the upstream intron of the dhps variants carrying the 431V mutation. Preliminary evidence suggests that a linked intron mutation located in a microsatellite region upstream of dhps is associated with the 431V haplotypes VAGKGS and VAGKAA. We utilize high-throughput Illumina sequencing of the intron variant and associated dhps polymorphism to explore two alternative explanations for the observed association in clinical samples. The first explanation is that the mutation has phenotypic significance for the SP resistance haplotype. The intron mutation may act as a splice element and have a role in the transcription of the 431V variant, ultimately conferring resistance towards antifolate. The second hypothesis is that the intron variant may have spread by genetic hitchhiking to linked dhps variants with the 431V mutation as they emerged and spread under positive selective drug pressure arising through the continuing use of SP. Linked polymorphisms are a useful tool for investigating the dispersal of resistant haplotype lineages across the African continent.

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MALARIA PREVALENCE, TRANSMISSION POTENTIAL AND EFFICACY OF ARTEMISININ COMBINATION THERAPY IN THE KENYAN CENTRAL HIGHLANDS: AN EMERGING ZONE PREVIOUSLY CHARACTERIZED AS MALARIA FREE

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Emerging infectious diseases are those that have recently appeared within a population or whose incidence or geo-range is rapidly increasing or threatens to increase in the near future. The current study sought to re-evaluate malaria prevalence and transmission patterns in the Kikuyu area of the Kenyan Central highlands, a non-traditional/ low risk malaria transmission zone where there have been anecdotal reports of malaria cases and presence of vectors of malaria and to evaluate susceptibility to ACTs. The potential role of climate factors was also evaluated. Sampling of adult mosquitoes was carried indoors while mosquito larvae were sampled outdoors and reared to adults in the laboratory. The malaria clinical study was an open label non randomized trial where the efficacy of one artemisinin-based antimalarial combination drug, Artemether Lumefantrine (AL) was evaluated. Microscopy was used at the health facility while molecular analysis targeting various markers used in the lab. Climate data for the study area was also obtained. A rich repertoire of mosquito vector species was identified, with the Anopheles funestus group being the predominant vector species at 76.35% of all. Only two adult mosquitoes which were non-blood fed and negative for malaria parasites were collected. Of the 838 patients screened, 471, with a slide positivity rate of 2.1%. Parasitological outcome of the 41 cases revealed 100% (95% CI 1.96) as ACPR. There was delayed parasite clearance (parasites present on Day 3) in 3(7.3%) of the cases. Analysis of the Pfk13 gene in the positive P. falciparum cases from the study sites revealed no mutations associated with artemisinin resistance. The pfmdr1 86Y mutation was found in 0% (0/41) of the isolates. Analysis of long term climate data showed an increase of about 1.3ºC in both the mean minimum and maximum temperatures consistent with forecasts from other sources. The positivity rate observed in the study site was very low but the fact that 61% of participants who tested positive did not report recent history of travel from the area and the finding of highly competent known vectors of malaria suggest a changing

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THERE IS NO TIME TO WASTE: WE NEED TO UNDERSTAND THE PROPHYLACTIC ACTION OF SULFADOXINE-PYRIMETHAMINE AGAINST MALARIA

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Sulfadoxine-pyrimethamine (SP) is the chemoprevention drug combination of choice for preventing Plasmodium falciparum malaria in infants, children, and pregnant women. However, the antimalarial effectiveness of this drug combination is potentially threatened by the spread of SP-resistant parasites. This has led to significant investments in developing alternative chemoprevention drugs and novel malaria prevention tools to supplement chemoprevention, such as malaria vaccines and monoclonal antibodies. Yet, these investments are at risk as a result of significant knowledge gaps regarding SP's antimalarial action against liver and blood stage parasites, impact on immunity development, and SP's non-parasitic activity. We review published evidence of SP's mechanism of action and highlight these knowledge gaps. We then demonstrate why new evidence is needed to inform investments in chemoprevention drug development, such as to accurately compare SP (the standard of care) to alternative chemoprevention tools, from early-stage development through to later phase clinical trials. We strongly urge chemoprevention funders, researchers, clinical investigators, regulatory agencies and policymakers to define what level of evidence for SP's malarial and non-malarial activity is necessary to support regulatory approvals of new chemoprevention and other tools where SP is the current standard of care. This includes defining the preclinical and clinical evidence to support timely and accurate candidate selection for new chemoprevention tools. We also call for new clinical, observational, and modelling studies to provide much needed evidence for SP's non-parasitic killing action and impact on immunity acquisition. Should our call for this evidence remain unanswered, the global malaria community risks wasting precious investments in malaria prevention for the simple reason that we do not adequately understand our standard of care for chemoprevention.

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PHENOTYPIC VALIDATION OF MOLECULAR MARKERS ASSOCIATED WITH SEASONAL MALARIA CHEMOPREVENTION AND ONGOING SELECTIVE SWEEPS IN SENEGAL

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Drug resistance in Plasmodium falciparum is a major threat to malaria control efforts. Senegal is a malaria-endemic country that has implemented successive antimalarial drug-based strategies for two decades. Previously, we profiled several known drug resistance markers (pfcrt, pfmdr1, pfdhr, pfdhps, and pfkelch13) and their surrounding haplotypes from 3,284 samples (collected 2000 – 2020) collected from febrile patients with malaria at health facilities spread throughout low (no Seasonal Malaria Chemoprevention (SMC)), moderate (SMC started in 2019), and high transmission zones (SMC started in 2014) in Senegal. We observed rapid changes at Pfcrt K76T and Pfdhps A437G that coincide with the implementation of SMC in 2014, which we hypothesize reflects SMC-induced changes in resistance or parasite fitness. We also found evidence of a selective sweep at chromosome 7, 8, 9, and 11 based on identifying regions of the genome with excess identity-by-descent in genetically related parasites. To test this hypothesis and determine whether drug resistance was responsible for the selective sweeps, we grouped parasites into categories based on whether parasites were mutant at Pfcrt K76T, Pfdhfr triple mutant (N51C, C59R, and S108N), Pfdhps A437G, and part of the identified selective sweeps. Representative parasites from each grouping were then culture-adapted and phenotyped for drug susceptibility to several antimalarials (chloroquine, amodiaquine, lumefantrine, mefloquine, piperaquine, sulfadoxine, and pyrimethamine) and phenotyped for in vitro parasite fitness. This strategy allowed us to assess the individual contribution of each mutation to the assayed drug resistance and fitness phenotypes and test for potential epistatic interactions between markers. Phenotypic assessment and genetic validation of each of these mutations in a Senegalese background is necessary to assess the impact of SMC and determine if it is causing changes in drug resistance in the population. Ongoing molecular surveillance and genetic validation of these markers will be used to continue to monitor and guide drug interventions.

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DEVELOPMENT AND EVALUATION OF A NOVEL PROTOCOL TO ASSESS THE EFFICACY OF SEASONAL MALARIA CHEMOPREVENTION (SMC) USING SULFADOXINE, PYRIMETHAMINE AND AMODIAQUINE IN AN AREA OF HIGH ANTIMALARIAL DRUG RESISTANCE IN NAMPULA, MOZAMBIQUE.

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Seasonal Malaria Chemoprevention (SMC) requires that a 3 day course of sulfadoxine, pyrimethamine and amodiaquine (SPAQ) provide 28 days protection from malaria infection among children 3-59 months living in areas with highly seasonal malaria. Chemoprevention efficacy is a function of a chemopreventive drug's ability to clear existing sub-patent malaria infections and to prevent new infections over the four week period of protection. A novel and simply implemented protocol aims to determine if sub-optimal protection occurs with complete adherence to a 3 day regimen of SPAQ and, if it occurs, whether it results from drug resistance or low drug exposure. Directly observed therapy (DOT) of SPAQ was given to children of 3-59 months on days 0, 1 and 2 as the first round of SMC. Large volume dry blood spot (DBS) and thick smear microscopy slides were collected on days 0, 7 and day 28. Pharmacometric analysis was done on DBS samples on days 7 and day 28. Parasitemia, detection, quantification and genotypying was conducted for identified antimalarial drug resistance genes; Pfdhfr, Pfdhps, Pfcrt, and Pfmdr1. Small volume dry blood spots were taken one month prior to the implementation of the first cycle of SMC and over 28 days after the final cycle and genotyped for the drug resistance genes. Preliminary results indicate a high rate of day 28 slide positivity and low level parasitemia in Mozambique. Large volume dry blood spots indicate significant survival of low level drug resistant parasites in the presence of therapeutic drug levels. Genotyping of breakthrough parasitemias indicates the same genotypes are those causing disease taken from symptomatic children during the same period. Full results and interpretation will be presented. Preliminary results suggest that although SMC is impacting disease, SPAQ is not clearing existing sub patent infection despite the presence of therapeutic drug levels. This indicates that the effectiveness using this SMC drug regimen Mozambique may be short lived in this province. Full results will be presented. This serves as a novel evidence-based method to measure chemoprevention efficacy of SMC.

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EVIDENCE OF CHLOROQUINE SUSCEPTIBLE PLASMODIUM FALCIPARUM MALARIA IN AN URBAN MEDIUM TRANSMISSION ZONE IN ZAMBIA

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Plasmodium falciparum resistance to anti-malarial drugs remains a major hindrance to malaria control and elimination. The P. falciparum parasite has developed resistance to most antimalarial drugs introduced in countries endemic to malaria. Many countries have observed decreases in the prevalence of chloroquine resistance with the discontinuation of chloroquine use. In Zambia, chloroquine was used as the first-line treatment for uncomplicated malaria until treatment failures led the Ministry of Health to replace it with artemether-lumefantrine in 2003. There are limited treatment alternatives and with the threat of the emergence of resistance to the available anti-malarial drugs, a reintroduction of chloroquine could be a viable option. This study was conducted to determine the prevalence of the chloroquine resistance-associated Pfcrt-76T and Pfmdr-86Y mutations in blood samples collected from patients in Ndola, a medium malaria transmission zone, an urban setting in Zambia. A cross-sectional study was conducted at Chipulukusu clinic in Ndola district between January and March 2020. Samples were collected from all malaria-positive individuals attending the clinic. Rapid Diagnostic Tests were used to screen for malaria-positive individuals. Parasite DNA was extracted from Dried Blood Spots and blood slides were collected by finger-prick from all malaria-positive individuals. Polymerase Chain Reaction-Restriction

Fragment Length Polymorphism was used to genotype the P. falciparum chloroquine resistance transporter (PfcrtK76T) and the P. falciparum multi-drug resistance (Pfmdr1N86Y) genes that are associated with Chloroquine resistance. Three-hundred and ninety-eight specimens were successfully analyzed. No chloroquine-resistant genotypes were detected for both genes. This study reveals the return of chloroquine-sensitive malaria in Ndola District, Copperbelt province, following the cessation of CQ from routine use in the treatment of uncomplicated malaria. Chloroquine may have a role in malaria prevention or treatment in Zambia and throughout the region in the future.

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INSIGHTS INTO THE MODE OF ACTION AND A NOVEL MUTANT PFCRT-MEDIATED MECHANISM OF RESISTANCE TO THE ANTIMALARIAL CLINICAL CANDIDATE ZY-19489

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There is an urgent need for new antimalarial candidate drugs. One such molecule is ZY-19489, a fast-killing triaminopyrimidine currently in Phase II trial in combination with ferroquine (FQ). The ZY-19489 + FQ combination can replace artemisinin-based combination therapies (ACTs) as a non-ACT treatment option in case of global emergence of artemisinin resistance hence insights into its mode of action and mechanism of resistance are imperative. This study aimed to leverage in vitro selection and whole genome analysis (IVSWGA), quantitative trait loci (QTL) analysis, stage-specificity experiments and transport studies using P. falciparum lines expressing wildtype (Dd2Dd2) or mutant P. falciparum chloroquine resistance transporter (pfcrt) alleles to characterize the mechanisms of resistance to ZY-19489. IVSWGA identified parasites with a PfCRT N246H mutation that conferred a 9-fold shift in IC50 in Dd2Dd2-N246H lines compared to Dd2Dd2. QTL analysis of recombinant progeny of an NF54xRF7 cross mapped the activity of ZY-19489 to a chromosome 7 region harboring pfcrt, thus validating the influence of this locus on ZY-19489 activity. Data from purified PfCRT reconstituted in liposomes also showed that ZY-19489 blocks PfCRT-mediated efflux of CQ from the digestive vacuole (DV), implying competition of ZY-19489 with CQ for the PfCRT binding cavity. Curiously, Dd2Dd2-N246H parasites were highly sensitized to known DV-acting drugs including CQ. No change in susceptibility was observed for lumefantrine or atovaquone. These mutants also had distended DVs reminiscent of PfCRT variants earlier shown to have hemoglobin (Hb) processing defects. Heme fractionation assays provided evidence of ZY-19489 inhibiting early steps of Hb degradation and confirmed by metaprint analysis, which revealed signatures of a possible effect on Hb catabolism in ZY-19489-treated lines. Stage-specificity tests showed that ZY-19489 is most potent against schizonts and rings, the latter recently shown to be the initial assembly stage of the parasite's Hb processing machinery. These data implicate PfCRT N246H mutation in mediating ZY-19489 resistance.

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MOLECULAR SURVEILLANCE OF PLASMODIUM FALCIPARUM DRUG RESISTANCE REVEALS PRESENCE OF I431V DHPS MUTATION IN PARASITES HARBORING QUINTUPLE AND QUADRUPLE DHPS MUTATIONS IN SENEGAL

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In Senegal, therapeutic artemisinin combination therapies (ACTs), intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP), and seasonal malaria chemoprevention (SMC) with SP and amodiaquine (AQ) are used to treat or to prevent malaria. Using molecular surveillance to detect signs of emerging drug resistance is essential for helping national malaria control programs to assess drug resistance risk. Molecular surveillance of mutations associated with artemisinin resistance is particularly important, as it may likely be too late to prevent its spread by the time it is detected through therapeutic efficacy studies. Therefore, we used target amplicon deep sequencing (TADS) to sequence the entire pfdhps, pfdhfr, pfcrt, pfmdr1, and pfk13 genes. In this study, eighty-eight (88) samples collected between 2020 and 2021 in Kedougou, Kaolack and Kolda, Senegal-regions of malaria incidence ≥ 15 cases per 1000 inhabitants were sequenced with TADS at pfcrt, pfmdr1, pfdhfr, pfdhps and pfk13 using iSeq100 and analyzed using Geneious Prime. Using this approach, we determined the frequencies of known and previously uncharacterized mutations at each of these genes. K13 mutations previously associated with artemisinin resistance were not observed, but several nonsynonymous mutations (K189T, R255K, D547Y, V566L, V589I, E596D, and V637I) whose contribution to artemisinin resistance is unknown were observed. The K189T was particularly striking and was detected in 28.7% of samples. For pfdhps, we detected a new mutation, I431V, that was present in multiple samples with the S436A, A437G, K540E, A581G, & A613S quintuple mutation pfdhps haplotype and the triple pfdhfr mutant haplotype (N51I, C59R & S108N). While it is unclear whether I431V contributes to SP resistance, its association with the quintuple pfdhps and triple pfdhfr mutant haplotypes may be a cause for concern. These findings highlight the utility of amplicon sequencing in profiling drug resistance genes mutations and serve as an early warning and detection system for drug resistance.

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EVOLUTION OF GENOMIC MARKERS OF PLASMODIUM FALCIPARUM RESISTANCE TO ANTIFOLATES AND AMINOQUINOLINES IN UGANDA

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Antimalarial drug resistance threatens global malaria control efforts. Resistance-mediating mutations of concern include those in the target proteins for sulfadoxine-pyrimethamine, an important drug for chemoprevention, and in transporters for aminoquinolines, including the artemisinin-based combination therapy partner drugs amodiaquine

and piperaquine. To gain insight into antimalarial drug resistance trends, we surveyed for key P. falciparum polymorphisms from 10-16 health facilities across Uganda from 2016-22. We further assessed for evidence of evolutionary selection of resistant isolates by evaluating diversity in genomic regions flanking resistance loci. Five mutations in the targets of sulfadoxine (PfDHPS 437G, 540E) and pyrimethamine (PfDHFR 51I, 59R, 108N) were very common (80-100%). The prevalence of PfDHFR 164L and PfDHPS 581G mutations, which mediate higher level antifolate resistance, varied between sites and over time. The PfDHFR 164L mutation was most common at 4 sites in southwestern and central Uganda (>20-75%), with prevalences increasing from 2016-17 (14%) to 2022 (30%), and increases were also seen in other parts of the country. The PfDHPS 581G mutation was also most common in the four sites in southwestern and central Uganda, although significant temporal changes in prevalence were not detected. Mutations in PfCRT and PfMDR1, associated with aminoquinoline resistance, were increasingly uncommon. The PfCRT 76T allele was detected in 5/16 sites in 2021 and 4/16 sites in 2022, and was consistently seen only in western Uganda bordering Democratic Republic of Congo. The PfMDR1 86Y mutation, which was previously very common, was absent at all sites from 2018-2022. The 1246D mutation decreased, with 0% prevalence at 12 sites in 2022. In regard to evolutionary selection, isolates with antifolate and aminoquinoline resistance-associated alleles showed similar diversity, compared to wild type isolates, in genomic regions flanking the resistance loci. These results suggest limited evidence of recent selection, consistent with stable transmission of resistant isolates.

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RISK FACTORS OF CHEMOPROPHYLAXIS FAILURE MALARIA AMONG BANGLADESHI UN PEACEKEEPERS IN AFRICA

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Mefloquine has been recognized as a highly effective malaria chemoprophylaxis for nonimmune travelers in endemic areas. Bangladesh arms forces participating in United Nation Peace Keeping Mission for a long, mainly for the African region. In spite of prophylaxis intake, the number of malaria cases among deployed troops is alarming. This study identified the risk factors associated with chemoprophylaxis failure in malaria. A longitudinal case-control study was conducted among 859 Bangladeshi UN Peacekeepers deployed in DR Congo from Feb 2018 to Jan 2019. Troops used mefloquine (5mg/kg body weight) as weekly malaria chemoprophylaxis. Persons who suffered from Malaria during UN mission tenure were considered as case and location-matched (camps) 1:3 control has been taken. Face-to-face interviews were done using a semi-structured, questionnaire to gather information related to lifestyle, compliance with prophylaxis intake, and other malaria preventive measure. An unobtrusive observational assessment was also carried out and noted a document on preventive practices. Logistic regression analysis was performed to determine the best predictors. Among 859 troops, 88(10.2%) suffered from malaria during the last 12 months of study time, considered as a case where 288 respondents had been taken as control. Respondents having body weight index below normal (AOR: 0.18, CI: 0.04-0.79), doing lighter duty (AOR: 4.37, CI: 1.09 -17.24), no or rarely physical exercise (AOR: 0.08, CI: 0.01-0.36), having sleep disturbance (AOR: 0.43, CI: 0.19-0.97), history of Malaria (AOR: 0.2.14, CI: 1.04-4.40), experienced side effects of mefloquine (AOR: 0.23, CI: 0.06-0.88), irregular intake of mefloquine (AOR: 0.17, CI: 0.04-0.67), chemoprophylaxis took at own arrangement (AOR: 5.15, CI: 2.14-12.39), not properly use mosquito repellent during night duty (AOR: 0.30, CI: 0.10-0.53), mosquito net were not properly hanged (AOR: 0.14, CI: 0.02-0.81) found significantly associated. Adopting a healthy lifestyle, strict compliance of chemoprophylaxis intake and malaria prevention drills with close monitoring can reduce the disease burden.

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SUSCEPTIBILITY OF PLASMODIUM FALCIPARUM ISOLATES FROM EASTERN UGANDA TO GANAPLACIDE AND PHOSPHATIDYLINOSITOL 4-KINASE INHIBITORS

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Novel antimalarials are urgently needed to combat rising resistance to available drugs. During drug discovery and development, compounds need to be tested for activity against parasites now circulating in the field. We assessed ex vivo drug susceptibilities to the imidazolopiperazine ganaplacide and inhibitors of phosphatidylinositol 4-kinase (PfPI4K) of Ugandan Plasmodium falciparum isolates collected from 2016 to 2022. For ganaplacide, decreased susceptibility of laboratory strains has been linked to polymorphisms in P. falciparum cyclic amine resistance locus (PfCARL), acetyl-CoA transporter (PfACT), and UDP-galactose transporter (PfUGT). For PfPI4K inhibitors belonging to the 2-aminopyridine and 2-aminopyrazine series, mutations in PfPI4K have been linked to resistance. We also tested related PAN-kinase inhibitors. Drug susceptibilities were assessed using the 72-hour SYBR Green growth inhibition assay. The median IC50 for ganaplacide was 13 nM, but individual isolates had up to 5-fold increased IC50s. Compounds targeting PfPI4K showed a wide range of activity (median IC50s 1-200 nM), with varied susceptibilities for individual isolates. Median IC50s for two lead PfPI4K inhibitors, MMV048 and UCT943, were 65 and 11 nM, respectively. To determine phenotype-genotype associations, we sequenced a large number of the studied isolates using molecular inversion probe and standard dideoxy sequencing. Both PfCARL and PfPI4K were highly polymorphic, with 9 mutations in PfCARL and 23 in PfPI4K present in >5% isolates. None of these mutations had previously been selected by in vitro drug pressure or was associated with altered ex vivo susceptibility of Ugandan strains to the compounds. No mutations were observed in PfACT or PfUGT. Overall, Ugandan P. falciparum isolates were highly susceptible to these compounds under development as next-generation antimalarials, consistent with a lack of pre-existing or novel resistance-conferring mutations in circulating Ugandan parasites.

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QPCR ANALYSIS OF RING STAGE SURVIVAL ASSAYS FOR SURVEILLANCE OF ARTEMISININ PARTIAL RESISTANCE IN PLASMODIUM FALCIPARUM

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Recent reports from Africa of emergence and spread of kelch13 mutations and artemisinin-partial resistance (ART-R) highlight the urgent need for improved malaria surveillance methods. Current approaches to detect ART-R include the ex vivo ring stage survival assay (RSA). The original RSA (% survival, relative to controls, 66 h after a 6 h 700 nM pulse of DHA) is a technically burdensome assay, requiring extensive microscopy time to count parasites. We recently developed an extended recovery RSA (eRRSA) that relies on longer culturing time after DHA exposure followed by qPCR

detection to quantify surviving parasites, eliminating the need for counting parasites by microscopy or flow cytometry. To determine whether this assay developed for in vitro assays of parasite cultures was valid for studies of fresh isolates, we applied eRRSA to dried blood spots preserved on filter paper, collected from symptomatic Plasmodium falciparum malaria patients in 2022 from northern and eastern Uganda, an area of emerging ART-R and kelch13 mutations. Fresh parasite samples were exposed to a pulse of 700 nM DHA, and analyzed by standard RSA microscopy at 72 h, and collected on filter paper at 120 h for qPCR analysis. 72 h RSA survival ranged from 0-50% (median 3.1%); fold change in qPCR Ct values (a measurement of parasite survival) ranged from 1.5 - 500 (median 43). Results with the two assays demonstrated a strong inverse correlation (Spearman, r = -0.8; N = 88). Kelch13 mutations (C469Y and A675V) associated with ART-R in other studies were detected in 24% of samples and were moderately associated with higher RSA /eRRSA survival values (Fisher's exact test p=0.033). Some samples classified as ART-R (greater than 10% survival) by both microscopy and qPCR had wild type kelch13 genotypes, indicating the importance of a phenotypic surveillance approach. Our results show that collecting filter paper samples for subsequent RSAs by qPCR is an attractive option for surveillance of ART-R in samples from remote field locations with limited resources.

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DECIPHERING PLASMODIUM FALCIPARUM ARTEMISININ RESISTANCE IN BANGLADESH: A GENOTYPIC-PHENOTYPIC EVALUATION OF KELCH13-DEPENDENT AND INDEPENDENT DETERMINANTS

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Bangladesh successfully eliminated 93% of its malaria. However, the rise of kelch13 (k13)-mediated artemisinin resistance (ART-R) to the ART derivatives, and subsequently ART combination therapy (ACT) failures of Plasmodium falciparum malaria in the neighboring Greater Mekong Subregion (GMS) raises the specter of ART-R as a major threat to the goal of malaria elimination in Bangladesh. 90% of the country's endemic malaria resides in the Chittagong Hill Tract's (CHT) geopolitical region that borders k13-ART-R prevalent Myanmar. We report low-moderate ART-R from culture-adapted patient isolates (20% isolates demonstrating 2-6% survival by Ring Stage Survival Assays, RSAs) even though the ACT remained an effective treatment in these recent CHT patients. However, these infections harbored no WHO validated/candidate k13 SNPs. These samples are currently being whole-genome sequenced to identify potential k13-independent ART-R-associated SNPs. Although resistance-causing k13 SNPs have not yet been observed in this region, their spread from neighboring countries with similar ACT use and transmission patterns as well as possible de novo origins in the CHTs is a major concern. To preemptively define the potential for k13 SNPs to arise and spread on both CHT k13-independent ART-R and ART-S backgrounds, we used CRISPR-Cas9 to edit these SNPs into both. We measured k13-induced ART-R in edited clones. In a CHT ART-S background; F446I, the most prevalent Myanmar SNP did not exhibit resistance (1-1.52% RSA survival); C580Y, dominant in eastern GMS and R561H, a prevalent Thailand and Rwanda SNP induced ART-R of 4.24-5.25% and 10.65-12.33% survival respectively. Ongoing RSA and competitive growth assays will uncover the precise impact on resistance and fitness of each of these k13 SNPs in both backgrounds and will also reveal if non-k13 resistance factors in ART-R isolates contribute to the resistance potential and/or sustainability of a given k13 SNP. Together these findings will provide a comprehensive evaluation of k13 and non-k13 factors in ART-R in the CHTs and may have implications for Africa where both k13-dependent and independent ART-R are emerging.

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TRENDS OF PLASMODIUM FALCIPARUM MOLECULAR MARKERS OF ASSOCIATED WITH RESISTANCE ARTEMISININS AND REDUCED SUSCEPTIBILITY TO LUMEFANTRINE IN MAINLAND TANZANIA FROM 2016 TO 2021

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Recent reports of artemisinin partial resistance in Africa suggest that complete resistance to artemisinin-based combination therapies (ACTs) might emerge soon. This study utilized samples collected during therapeutic efficacy studies to assess the trends of molecular markers associated with resistance or reduced susceptibility to the current drugs. Samples (n=2,015) were collected at eight sites in Tanzania, in Kigoma, Mbeya Mtwara, Mwanza, Morogoro, Pwani, Tanga, Mbeya, Mtwara, Mwanza and Tabora: at five-time points between 2016 and 2021. Capillary sequencing was used to detect drug resistance markers in pfmdr1 gene, encoding for multi-drug resistance protein and kelch 13 gene (k-13) associated with artemisinin resistances. Sequencing success was ≥80.0% across all the years and 1,733/1,778 (97.5%) samples had k-13 wild-type parasites, while 24 (2.1%) had synonymous mutations (at codons P417P, C469C, R471R, V487V, F505F, G538G, R539R, and S624S). Only eight samples (0.4%) had non-synonymous where seven mutations are not validated by WHO (I416V, E433D, R471S, P475S, A578S with one sample except Q613E which had two samples) and one sample from Morogoro region in 2020 with R622I (validated by WHO). For pfmdr1; N86 (wildtype) was 100% while Y184F mutant samples increased from 30% in 2016 to about 60% in 2021. D1246Y mutations occurred in four samples (0.23%); two from Morogoro and Tanga in 2016 and other two from Kigoma and Morogoro in 2020. pfmdr1 haplotypes (N86Y, Y184F and D1246Y) were constructed with 1,708 samples and 985(57.66%) had NYD while 719 (42.09%) had NFD. Minor haplotypes included NYY (in three samples, 0.17%), YFD (two samples 0.12%) and (NFY (one sample, 0.05%). NYD haplotype decreased from 60% in 2018 to 45% in 2021 while NFD increased from 38% in 2016 to 55% in 2021. These findings show that validated k-13 mutations were only detected in one sample (with R622I) from Morogoro in 2020. Remarkable changes were observed in pfmdr1 markers with an increase in Y184F mutations and NFD haplotype. Intensified surveillance is urgently needed to monitor the trends of these mutations and their potential impact on the performance of ACTs.

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DEVELOPMENT OF SELECTIVE PLASMODIUM FALCIPARUM PROLYL-TRNA SYNTHETASE INHIBITORS THAT ARE INSENSITIVE TO HALOFUGINONE RESISTANCE

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The emergence and spread of resistance to all first-line antimalarials threatens our ability to treat and contain malaria. Therefore, new antimalarial therapies that exploit novel targets and pathways essential for multiple life-cycle stages are highly sought after for primary prophylaxis and transmission blocking, in addition to acute treatment. We have previously identified the molecular target of halofuginone (HFG), one of the most potent known antimalarials and a synthetic derivative of the natural product febrifugine, as the cytosolic prolyl-tRNA synthetase (PfcProRS). ProRS a member of the aminoacyl-tRNA synthetase (aaRS) family, whose canonical function is to charge tRNA with cognate amino acids for downstream use by the ribosome for protein biosynthesis. Although HFG is highly effective against malaria, parasites quickly develop resistance (~5 generations) through increased intracellular proline, which competes with HFG in the ProRS active site. Furthermore, HFG inhibits human ProRS with comparable potency, limiting the therapeutic window of this inhibitor class. To identify and optimize novel ProRS inhibitors that are insensitive to elevated proline levels and selective for PfcProRS over the human homolog, we have developed a novel time-resolved Förster resonance energy transfer (TR-FRET) assay for human and Plasmodium ProRS ligand characterization. The single-step assay is HTS-compatible and enables the sensitive and quantitative profiling of small molecule inhibitors in substrate-dependent (proline, ATP) fashion. Supported by this platform we have developed a new series of proline-uncompetitive PfcProRS inhibitors that are insensitive to HFG-resistance mechanisms. To enable the development of selective PfcProRS inhibitors, we have established a high-throughput synthetic strategy to rapidly access focused libraries for SAR exploration. Preliminary studies have yielded mid-nanomolar inhibitors with ~3-fold selectivity for the parasite enzyme. In parallel, we have successfully screened over 60,000 compounds to identify novel chemotypes for ProRS inhibitor development.

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UNDERSTANDING THE DEVELOPMENT OF DRUG RESISTANCE IN LIVER STAGES OF PLASMODIUM FALCIPARUM

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Despite remarkable gains in reducing the global burden of malaria, there remains an urgent need for novel anti-malarial drug treatments. Chemoprophylaxis remains the mainstay for malaria prevention, but its efficacy is compromised by non-adherence to medication and the threat of drug resistance. A safe and effective long-acting intramuscular (LAI) drug-dosing preparation would provide a promising approach to deliver a new medicine vision for malaria control and eradication. However, understanding the emergence and spread of antimalarial drug resistance in the context of LAI will be critical for the development of this new approach. A powerful tool to study drug resistance is experimental selection of resistance in vitro followed by whole-genome sequencing. Due to the limitations in the in vitro culture of malaria liver stages, we made use of the Plasmodium berghei mouse model to explore the probability of resistance emerging in hepatic merozoite stages and the impact of pre-existing resistance from blood stage development on the efficacy of prophylactic treatment. Here we present a pilot study using the cytochrome bc1 inhibitor, atovaquone. We treated mice with subtherapeutic doses of atovaquone and sequenced the recrudescent parasites to identify mutations in the cytochrome b locus. In a series of independent selections, we isolated parasites with an M133I, Y268N, or Y284F mutation in cytochrome b. We then evaluated the effect of these mutations on parasite transmission stage development and liver stage efficacy. Only the M133I mutant was able to complete development in the mosquito and generate sporozoites that could be tested in liver stage efficacy studies. Both the Y268N and Y284F mutants failed to progress beyond oocyst stage, consistent with published reports. Phenotypic profiling of the mutant parasites is ongoing. The overall goals of these studies are to understand the emergence and spread of antimalarial resistance in the context of LAI-C drugs and inform dose selection for chemoprevention in the context of pre-existing resistance. These learnings will also be applicable to other chemoprophylaxis approaches targeting liver stages.

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LEVERAGING ON ROUTINE REVIEW MEETINGS IN ANTIMICROBIAL STEWARDSHIP

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The WHO recommends rational antimalarial medicines use to avert antimicrobial resistance (AMR). In Kenya, malaria treatment guidelines recommend the right dose of Artemether Lumefantrine (AL) as the first-line treatment for test-positive uncomplicated malaria. Cases are recorded in registers, summarized monthly, then uploaded to Kenya Health Information System (KHIS). The KHIS data indicate a mismatch between patients tested positive and AL doses dispensed. We assessed the impact of biannual malaria commodities review meetings on commodity stewardship. A standard template was shared with the 47 counties to collect aggregated data on the number of patients tested, confirmed positive, and treated, as well as commodities used per county. Key information was downloaded from KHIS for the County Referral Hospitals (CRHs), for April and October 2022 in an excel spreadsheet. This included number of patients tested positive, number of patients by weight categories and doses of AL dispensed per CRH. Comparison of total patients tested positive to total number of patients treated was done. Conversion of doses dispensed into tablets was done to compare with number of tablets that should have been dispensed based on the reported patient numbers by weight category. We compared the performance in April and October 2022. The median months of stock (MOS) for AL in the counties was 13 (IQR 6.2 – 26.3) while for mRDTs was 3.4 (IQR 2.3 - 7.3). Generally, for AL, mRDT, Artesunate injection, Sulfadoxine-Pyrimethamine, and Insecticide-Treated Nets (ITNs), under-stocked counties increased from 21% to 24.3%, adequately stocked increased from 32% to 36%, overstocked reduced from 48% to 40%. The ITNs were best stocked (61%) while AL 12s was worst (6%). Treatment for only patients who tested positive improved from 28% to 57%. For CRHs, concordance between number of positive patients and treated improved from (26% to 57%). Number of facilities having concordance improved from 16% to 38%. The review meetings helped improve malaria commodity stocking and rational use in 2022. The Ministry should improve inclusivity in meetings to strengthen antimicrobial stewardship.

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INVESTIGATING THE ACCURACY OF MALARIA DIAGNOSTIC TESTS: A BAYESIAN META-ANALYSIS COMPARING CONVENTIONAL AND ULTRASENSITIVE RAPID DIAGNOSTIC TOOLS

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Malaria remains a significant public health challenge, affecting millions of people worldwide. Rapid, accurate, and sensitive diagnosis of malaria is crucial for effective disease management and control. Conventional rapid diagnostic tests (cRDTs) have been widely utilized for malaria diagnosis; however, recent advancements in diagnostic technology have led to the development of ultrasensitive rapid diagnostic tests (uRDTs).This study aims

to evaluate and compare the diagnostic performance of cRDTs and uRDTs for malaria diagnosis through a Bayesian meta-analysis of diagnostic test accuracy in the available literature.A comprehensive search of electronic databases, including PubMed, Embase, and Web of Science, was conducted to identify relevant studies published up to September 2022. Studies comparing the diagnostic performance of cRDTs and uRDTs for malaria diagnosis were included. The primary outcomes were sensitivity, specificity, and false positive rate. A Bayesian random-effects model was employed to pool the results and calculate summary statistics.In this meta-analysis, 15 studies comprising 18,602 samples were included. The pooled sensitivity of uRDTs was substantially higher than that of cRDTs (62.6% (95% Confidence Interval (CI) 47.4% to 75.6%) vs. 51.5% (CI 35.1% to 67.6%)). The specificity demonstrated a slight difference between uRDTs and cRDTs (97.8% (CI 94.7% to 99.1%) vs. 98.4% (CI 95.6% to 99.3%)). The false positive rate (1 - specificity) of uRDTs was 2.2% (CI 0.9% to 5.3%) compared to 1.6% (CI 0.7% to 4.4%) for cRDTs. Subgroup analyses revealed consistent performance across diverse transmission settings and asymptomatic populations. This study highlights the superior diagnostic performance of ultrasensitive rapid diagnostic tests (uRDTs) over conventional rapid diagnostic tests (cRDTs) for malaria diagnosis. Implementing uRDTs in endemic regions could significantly enhance case detection and improve disease management, warranting further research on cost-effectiveness and feasibility across diverse settings.

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PRECLINICAL PERFORMANCE AND USABILITY EVALUATION OF A NEW POINT-OF-CARE TEST FOR GLUCOSE-6- PHOSPHATE DEHYDROGENASE DEFICIENCY

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Current treatment guidelines for radical cure of Plasmodium vivax malaria recommend the use of 8-aminoquinolines, which can result in potentially life-threatening complications if administered to people deficient in the glucose-6-phosphate dehydrogenase (G6PD) enzyme. Accordingly, treatment guidelines recommend testing for G6PD deficiency (G6PDd) prior to administration of such drugs. The Wondfo G6PD/Hb Test is a new point-of-care (POC) G6PD test that can help decentralize testing and expand access to safe treatment methods. A retrospective diagnostic accuracy study was performed on 264 frozen blood specimens (34 deficient, 23 intermediate, 207 normal) previously collected in Mae Sot, Thailand. Index testing was performed in duplicate under typical lab and field conditions (22.8°C -27.9°C, 28%-52% humidity; 28.8°C -31.5°C, 58%-71% humidity, respectively). Reference testing by spectrophotometer (G6PD) and HemoCue 301+ (hemoglobin) were performed on site. The Wondfo G6PD/Hb Test demonstrated sensitivity of 1 (95%CI: 0.9-1) and specificity of 0.94 (95%CI: 0.9-0.97) among G6PDd males and females in lab conditions with similar performance in field conditions (sensitivity 1, 95%CI: 0.89-1; specificity 0.94, 95%CI: 0.9-0.96). Among intermediate females (G6PD activity <70%), the test demonstrated sensitivity of 1 (95%CI: 0.85-1) and specificity of 0.37 (95%CI: 0.3-0.45) in lab conditions and similar performance in field conditions (sensitivity 1, 95%CI: 0.85-1; specificity 0.34, 95%CI: 0.26-0.42). Optimization of thresholds on the Wondfo Test achieved sensitivity of 1 (95%CI: 0.85-1) and specificity of 0.94 (95%CI: 0.89-0.79) for intermediate females. A usability evaluation was performed, and data will be presented. A prospective matrix equivalency study is underway in Memphis, TN, US, to evaluate test performance on fresh venous and capillary specimens (planned completion May 2023). Performance will be reported. These data provide key insights into product performance for a promising new POC G6PD test to inform further product development efforts and evidence generation for regulatory approval.

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PRACTICAL FACILITY-LEVEL APPROACHES TO REDUCE MALARIA TEST POSITIVITY RATES IN OYO STATE, NIGERIA

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Malaria Test Positivity Rate (TPR) is used to assess the effectiveness of malaria interventions. However, over the years, this rate has remained high in routine data across Nigeria, including Oyo state. The high TPR has been inconsistent with other data triangulated from therapeutic efficacy studies and fever monitoring exercises reporting national TPR average of 49-52%; suggesting that the high TPR may reflect poor quality data and conduct of malaria diagnosis. This study reports on the effect of the two measures introduced to improve the accuracy of TPR data using secondary quantitative data from the National District Health Information System (DHIS) for both primary healthcare centers (PHCs) and secondary health facilities (SHFs). The two measures were facility-level audits of archived used RDT cassettes at 733 PHCs introduced in September 2021, and a 12-day basic malaria microscopy training (BMMT) at 17 SHFs which was completed in June, 2021. There was a sustained decline in state malaria RDT test positivity rate from 69% in October 2021 to 53% in October 2022 at PHCs. Furthermore, a period review from Jan - Sept. 2022 showed TPR decline from 61% - 54% when compared to January to September 2021 with TPR range from 72% - 76%. An independent T-test was done to compare the mean TPR for each year with a statistically significant decline (t= 14.857, $p<0.01$). At SHF, following the BMMT in June 2021, the microscopy based TPR declined from 60% in July 2021 to 37% in July 2022. Period review done from July 2020 - June 2021 shows TPR of 62% -52% respectively compared to TPR 60%-39% in July 2021 - June 2022 respectively. An independent T-test was done to compare the mean TPR for each year in the SHFs with a statistically significant decline (t= 3.622, p 0.02). This study concludes that supervised archiving and auditing of cassettes is a model that can be considered for future scale-up to continue the positive trend at PHCs, while BMMT should be further encouraged for accurate microscopy-based diagnosis. The findings reinforce the critical role of capacity building of human resources and the influence of audits on increasing the accuracy of malaria diagnosis and data reporting.

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THE ROLE OF PSYCHOSOCIAL FACTORS IN PROMPT AND APPROPRIATE CARE SEEKING FOR FEVER IN CHILDREN UNDER 5: FINDINGS FROM THE KENYA MALARIA BEHAVIOR SURVEY

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Psychosocial factors can influence caregivers' care-seeking for fever for children under 5 (U5), yet there remains a paucity of evidence examining these factors in Kenya. To assess correlates of care-seeking for fever among children, Kenya's Division of National Malaria Program (DNMP) and Breakthrough ACTION Kenya conducted the Malaria Behavior Survey in 2022 in 8 malaria- endemic counties in Western Kenya. The study population included 920 female caregivers of U5 from 1,456 households. 33% reported that a child they cared for had a fever in the last 2 weeks, and 80% of those caregivers reported seeking care for fever. Bivariate and multivariable logistic regression models examined the socio-demographic and psychosocial factors associated with prompt and appropriate care-seeking, defined as care sought same or next day from a health facility or community health volunteer (CHV) by caregivers of U5 with a fever in the 2 weeks before the study. 61%of caregivers sought care same or next day, and 64% sought care from a health facility or CHV. Only 50% sought prompt and appropriate care. In the final model, respondents discussing malaria with their partner in the past 6 months had 2 times increased odds (95% CI: 1.15-3.64) of seeking prompt and appropriate care compared to those who had not. Those who perceived that CHVs always had malaria rapid diagnostic tests had 1.9 higher odds of seeking prompt and appropriate care (95% CI: 1.1-3.4). While perceiving that CHVs always had treatment for malaria trended in the same direction, associations were not statistically significant. Household wealth and perceived distance to a facility were also not significantly associated with prompt and appropriate care-seeking. Less than half of respondents (46%) reported that they spoke with their partner about malaria in the last six months, and only 50% reported that CHVs always have rapid diagnostic tests. These results suggest that programs should encourage partner communication about malaria and improve caregivers' perceptions of CHVs. There is also a need to explore the influence of other health system and structural factors on care-seeking.

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THE EXPERIENCE OF TESTING AND TREATMENT FOR MALARIA IN THE RETAIL SECTOR: COMPARING THE PROVIDER AND ATTENDANT REPORTED OUTCOMES

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Improving access and adherence to parasitological diagnosis is critical for malarial control. Over 70% of ACTs consumed in Kenya are sold in the private retail sector, yet they rarely offer malaria diagnostics. We conducted a cluster-randomized trial in 39 registered medicine retail outlets in Western Kenya designed to improve uptake of testing and adherence to results. Outlet attendants of study outlets were trained to perform mRDTs, capture photos of cassettes and enter information about clients on a mobile App. Simultaneously, outlet clients with or history of fever in the last 48 hours were randomly selected for exit interviews. In this study, we compare the experiences of testing and treatment as reported by the outlet through the mobile app compared to reports by clients at exit. 25,454 (47.2%) malaria diagnoses were reported by outlets through the mobile app. 2,462 (42.8%) clients who consented to an exit interview also reported having an mRDT. Both data sources showed similar demographics for those who tested. We noted important differences in the experiences of testing and adherence reported by outlets compared to clients; 11.0% of clients had positive mRDT reported in the app by the outlets compared to 35.3% from exit interviews. 97% of test positive patients received a first-line ACT as reported by the outlet but only 77% by client report. For test-negative clients, 35% received an ACT based on outlet reports compared to 25% by client report. Among 109 clients randomly selected for re-test at exit, nearly two thirds of those who reported a positive test from the shop had a negative mRDT at exit. Contrasting outcomes reported by the provider and the client highlight barriers to improving testing and adherence for malaria as well as challenges for monitoring case management in the retail sector, including accurate communication of results to the client, poor confidence in a negative result and reluctance to withhold antimalarials from test-negative clients.

6795

COMPARING MALARIA RAPID DIAGNOSTIC TEST AND PCR FOR DETECTION OF PLASMODIUM FALCIPARUM INFECTIONS IN SCHOOL MALARIA PARASITAEMIA SURVEY IN TANZANIA

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Malaria rapid diagnostic tests (mRDTs) are increasingly utilized in school malaria parasite surveys as part of national monitoring and evaluation efforts. However, mRDTs based on histidine-rich protein2 (HRP2) detection may yield false positives due to persistent antigenemia after effective antimalarial treatment, and false negatives due to low parasitemia or HPR2/3 gene deletion. In 2017, we evaluated HRP-II's diagnostic performance against polymerase chain reaction (PCR) for detecting Plasmodium falciparum infection in 17,051 primary schoolchildren across eight regions in Mainland Tanzania. Based on PCR the prevalance of Plasmodium falciparum malaria infection was 19.2% (95% CI 18.6-19.8). Compared to PCR, mRDT had a sensitivity of 76.2% (95% CI = 74.7-77.7) and specificity of 93.9% (95% CI = 93.5-94.3). At the conference, we will present the contribution of HRP2/3 to false positive results. Thus, PCR and other molecular methods should be considered as additional diagnostic tools for use in schools and other epidemiological surveys.

6796

COMPARISON OF TWO METHODS FOR DETECTION OF GAMETOCYTES IN BURKINA FASO YOUNG CHILDREN WHO RECEIVED THE MALARIA VACCINE CANDIDATE BK-SE36

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Plasmodium falciparum gametocyte is the only stage in the malaria parasite life cycle that is transmissible from the human host to the mosquito vector. As their density in peripheral blood is typically low, gametocytes are often undetected by conventional light microscopy of thick blood smears. RNA-based molecular detection method, described as more sensitive, remains however a challenge in remote field settings. In this study, we compared two detection methods of gametocyte, namely Light Microscopy (LM) and Reverse Transcription Polymerase Chain Reaction (RT-PCR) using blood samples of participants of a clinical phase Ib trial assessing the BK-SE36 malaria blood-stage vaccine (registry PACTR201411000934120). Peripheral blood samples from healthy participants were obtained from two age cohorts: 25-60-month-old (n=54) and 12-24-month-old (n=54) children. Gametocyte detection using LM and RT-PCR was conducted on a total of 756 samples collected from the 108 subjects attending 7 clinical

trial scheduled visits. RT-PCR was sensitive, specific, and superior to LM. Overall, 6.62 % of the samples from all visits were gametocyte positive by LM, whereas gametocyte positivity by RT-PCR was more than three-fold higher (6.62 vs 22.19 %, p = 0.0164). When collected prior to the first vaccination, 12.9% of the samples were positive by LM, vs. 19.4 % by RT-PCR. Both methods showed a decrease in gametocyte prevalence after two vaccinations, still with higher positivity when assessed by RT-PCR: 2.77 and 17.3 % (p = 0.0002) for LM and RT-PCR, respectively. The difference in detection method results was also observed when the analysis was done per age cohort (cohort1: 3.85 and 5.77 % [p = 0.032] and cohort 2: 1.92 and 28.85 % [p < 0.001] for LM and RT-PCR, respectively).The present study compares standard LM and RT-PCR for gametocyte detection using samples collected during a clinical trial. The study confirms the utility of RT-PCR in remote field settings.

6797

PERFORMANCE EVALUATION OF CONVENTIONAL RDT, HIGHLY SENSITIVE RDT, AND POLYMERASE CHAIN REACTION TO IDENTIFY MALARIA INFECTION AMONG PREGNANT WOMEN ATTENDING FIRST ANTENATAL CARE VISITS IN CHADIZA DISTRICT, ZAMBIA

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Antenatal Plasmodium falciparum infection can cause placental malaria and adverse pregnancy outcomes. In high transmission settings, pregnant women may harbor low density infections that are undetectable with conventional rapid diagnostic tests (cRDTs), but which can still lead to adverse pregnancy and birth outcomes. Understanding the degree to which a more sensitive RDT can detect asymptomatic infections in pregnancy has implications for earlier treatment to improve birth outcomes. We assessed the sensitivity of a high-sensitivity rapid diagnostic test (hsRDT) and cRDT versus polymerase chain reaction (PCR) during routine surveillance of pregnant women at their first antenatal care (ANC) visit in Chadiza District. From September to October 2020 and December 2021 to March 2022, consenting women attending their first ANC at 21 facilities were tested with both the NxTek Eliminate RTD (hsRDT, Abbott 05FK140) and either the SD Bioline or First Response cRDT (similar sensitivities). A dried blood spot sample was collected for the detection of malaria by PCR and was used as the gold standard for all outcomes. A total of 1,396 women were assessed by all three tests. Malaria prevalence was 13.5% (95%CI: 11.7 - 15.4) by cRDT, 14.5% (95%CI: 12.7 - 16.4) by hsRDT, and 16.8% (95%CI: 14.8 - 18.8) by PCR, while cRDT sensitivity and specificity was 64.1% (95%CI: 57.6 - 70.3) and 96.7% (95%CI: 95.5 - 97.7) respectively, and 65.0% (95%CI: 58.5 - 71.1) and 95.7% (95%CI: 94.4 - 96.8) for hsRDT. Prevalence by PCR was markedly different when stratified by gravidity, with 21.0% (95%CI: 17.3 - 25.2), 19.3% (95%CI: 15.0 - 24.2), and 12.8% (95%CI: 10.4 - 15.6) for primigravida, secundigravida, and multigravida (3+ prior pregnancies), respectively. Similar results were demonstrated with conventional RDT and HSRDT. Smaller than desired sample size precluded finding a significant difference between cRDT and hsRDT. Considering the potential life-long impact of poor birth outcomes, larger studies to better define the sensitivity difference, as well as a cost-benefit analysis, are warranted to assess the potential impact/utility of hsRDT in pregnancy.

6798

REINFORCING ADHERENCE TO NATIONAL GUIDELINES ON MALARIA CASE MANAGEMENT IN PRIVATELY-OWNED HEALTH FACILITIES: A CASE STUDY FROM OYO, NIGERIA

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High-quality health services necessitate delivering the right care and correct treatment, at the right time to the needs and preferences of service users, while minimizing harm and resource waste. In Nigeria, private health facilities (PHF) account for at least a third of the country's 34,000 health institutions, and 50% of patients with a fever seek care in highly unregulated privately owned health establishments (NMEP, 2018). Given these large proportions, this study aims to examine the effect of capacity-building efforts on the quality of malaria care at 128 PHF reporting into the National Health Management Information System that were selected based on high patient load and geographical spread in three senatorial districts of Oyo state. Two clinicians at each PHF (n = 256) were trained on malaria case management using the updated guidelines and on the prevention of malaria in pregnant women, with monthly supportive supervision for one year post training. A pre (Jan -Dec 2020)-and post (Jan-Dec 2022) (twelve months before and after the intervention) Wilcoxon signed rank test at a 95% confidence level with an alpha value of 0.05 was undertaken to assess malaria quality-of-care indicators. The facility-specific findings revealed that the rate of fever testing and the proportion of confirmed uncomplicated malaria treated in accordance with national guidelines increased from 85% to 98% ($p<0.05$) and 96% to 100% ($p<0.05$) respectively, while clinically diagnosed malaria decreased from 15% to 2% ($p<0.05$). The proportion of pregnant women receiving intermittent preventive treatment in pregnancy (second and third dose (IPTp2 & IPTp 3)) increased from 44% to 63% ($p <0.05$) and 12% to 35% ($p<0.05$) respectively. The outcomes of this analysis suggest the necessity of capacity building and on-the-job supportive supervision of private sector providers to improve the quality of malaria care. There is also a need for the government to reinforce regulatory oversight towards ensuring adherence to national guidelines on malaria case management to build sustainable quality malaria services in the private sector.

6799

MULTIPLEXED DROPLET DIGITAL PCR-AMPLICON SEQUENCING TO UNDERSTAND PLASMODIUM VIVAX TRANSMISSION IN THE ETHIOPIAN HIGHLANDS

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Genomic epidemiology has become a key methodology to understand malaria transmission, but few protocols are available for species other than Plasmodium falciparum. We developed a novel genotyping protocol for Plasmodium vivax targeting 44 microhaplotypes selected by screening publicly available genomes to find highly variable regions. Multiplexed amplification was done by droplet digital PCR (ddPCR) and followed by amplicon sequencing (AmpSeq). We applied our assay to 43 samples collected in Gondar (Ethiopian highlands) between November 2019 and

October 2020, with further samples currently being sequenced. Ethiopia accounts for 12% of the global cases of P. vivax, and the highlands are known for heavy seasonal migration of laborers from the lowlands in June-November (≈400,000 laborers each year). Their return is associated with an increase in malaria cases. We aimed to understand the proportion of imported and locally transmitted cases, and genetic distinctions among parasite populations. 37/44 markers were observed in all 43 samples, regardless of parasite density (from 1 to >100 parasites/μL). We observed 474 high quality SNPs, and each sample had a unique haplotype (Hd=1). 35/43 samples carried multiple clones. 25 samples had genomic similarity higher than 85%, clustering into one group. One of these individuals reported travel to the lowlands before symptoms occurred. This could indicate importation of an infection from the highly malarious lowlands. 18 samples did not show high similarity to any other sample. Multiple samples carried SNPs possibly conferring drug resistance. 27/43 samples carried the Y976F mutation in pvmdr1, 13/43 the A383G mutation in pvdhps, and 2/43 the S58R mutations in pvdhfr, indicating potential resistance against chloroquine (Y976F), sulfadoxine (A383G), and antifolates (S58R). In conclusion, our new assay is suitable to elucidate P. vivax transmission networks and showed that transmission in the highlands is high and largely independent from importation from the lowlands. Half of parasites are potentially resistant against the current first-line treatment.

6800

BRAIN ENDOTHELIAL SECRETORY BIOMARKERS FOR SEVERE AND CEREBRAL MALARIA

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Severe malaria is associated with multiple syndromes, including cerebral malaria (CM), which is associated with a high risk of death (~18%). Currently, there are no validated biomarkers that can help in the diagnosis or predict the risk of developing severe or CM. Most of the proposed biomarkers to date are molecules secreted by endothelial or immune cells in response to inflammatory stimuli. While inflammation is an important contributor to severe and CM, the role of Plasmodium falciparum-infected erythrocytes interactions with the endothelium has not been explored as a trigger for endothelial secretion of potential biomarkers.To identify biomarkers specifically secreted by endothelial cells in response to P. falciparum, we have performed the transcriptomic analysis (RNAseq) of human brain microvascular endothelial cells (HBMEC) incubated with P. falciparum infected red blood cells (RBC) lysates compared to control RBC. Selection of genes upregulated in response to the parasite coding for proteins that are predicted to be secreted from endothelial cells, yielded 14 candidate genes. Each candidate was tested at the protein level, finding that 8 of the candidate proteins were secreted by HBMEC in response to P. falciparum infected RBC lysates (ADAMTS18, Angiopoietin-like 4, BDNF, Brevican, Erythroferrone, Inhibin-βE, KiSS-1, Reelin). We then determined the level of the 8 selected candidate biomarkers in the plasma of a cohort of Mozambican children with non-severe (n=128) and severe (n=136) malaria, including CM cases (n=23). This analysis identified 2 candidate biomarkers that significantly differentiate the groups of non-severe and severe malaria: ADAMTS18 (AUROC 0.77, p<0.0001) and Angiopoietin-like 4 (AUROC 0.67, p<0.0001); and 2 candidate biomarkers that differentiate the groups of severe malaria (caused by any other complication but CM) and CM: Angiopoietin-like-4 (AUROC 0.68, p<0.005) and Inhibin-βE (AUROC 0.70, p=0.0024). A biomarker signature that could accurately predict or identify the development of severe and/or CM would facilitate rapid and accurate diagnosis of patients resulting in improved care.

6801

COMPARATIVE ANALYSIS OF PRIMARY HEALTH CARE PROVIDERS' ADHERENCE TO PARASITOLOGICAL DIAGNOSIS OF UNCOMPLICATED MALARIA USING BEHAVIORAL ECONOMICS PROTOTYPES IN AKWA IBOM, NIGERIA

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Malaria is a major global public health problem with an estimated 232 million annual cases. Nigeria accounts for 27% of the 2022 global burden. The United States Presidents' Malaria Initiative for States (PMI-S) project partners with State Malaria Elimination Programmes (SMEPs) to provide comprehensive malaria case management in Nigeria, consisting of parasitological confirmation of suspected cases and appropriate treatment of confirmed cases using quality-assured antimalarials. The Behavioral Economics Prototypes (BEP) are decision making-centered delivery approaches to improve health provider adherence to testing, differential diagnosis, and treatment of confirmed malaria cases in line with national guidelines. A study aimed to analyze health providers' adherence to parasitological diagnosis of uncomplicated malaria cases in selected Primary Health Centers (PHCs) implementing BEP in Akwa Ibom state. PMI-S collaborated with the SMEP to train 355 health providers from 275 PHCs on the application of BEP for fever case management using a stepwise cascade approach with on-site post-training and 1 year and 6 months follow-up supportive supervision. Fifty BEP facilities were randomly selected from those trained using inclusion criteria (data availability, no stock outs for malaria rapid diagnostic test kits (RDT)) during the study period. Quantitative data (2020 pre-BEP and 2022 during BEP implementation) from the National Health Management Information System were analyzed for adherence to parasitological diagnosis with RDTs using Wilcoxon rank sum test with an alpha value of 0.05. Results showed a statistically significant increase in testing rates (W=771, p-value =9.9 x 10 -4), 94% before to 99% after 2 years of intervention, and decrease in test positivity from 73% to 62%, which was also significant (W=1637, p-value =3.0x 10-4). The findings reinforce that scaling up BEP could improve testing of fever cases for malaria, leading to correct identification of cases which could improve treatment services. However, further research could be conducted to control for effects of possible confounders and determine causality.

6802

EVALUATION OF THE STANDARD G6PD RAPID TEST FOR THE DETERMINATION OF THE ENZYMATIC ACTIVITY OF G6PD

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The 8-aminoquinoline drugs, primaquine and tafenoquine, are effective against the liver-stage ofPlasmodium vivax, specifically the hypnozoites. However, they can cause severe hemolytic anemia inpeople with Glucose-6-Phosphate-Dehydrogenase (G6PD) deficiency. Thus, the WHO recommends aquantitative assay to assess the enzyme activity before prescription.The objective of this study was to evaluate the performance of the "STANDARD G6PD" from SDBIOSENSOR, a rapid quantitative test for the determination of G6PD activity, compared to theenzymatic method used as gold standard. A panel of 166 individuals has been selected based on previousG6PD results in order to represent all levels of G6PD activities and obtain three groups of individuals(36 severe deficient, 18 intermediate and 112 normal). In addition, a validation of methods according tothe ISO 15189 standard for medical biology has been conducted.The sensitivity/ specificity values [95% confidence intervals] of the rapid test to detect deficient malesand females were 100% [87-100]/ 100% [75-100] and 88% [79-97]/ 89% [82-96], respectively.Regarding intermediate females, it was of 61% [39-84]/ 82% [73-91]. The semiquantitativeinterpretation of the results would also been presented. A next-generation sequencing of the entire G6PDgene has been done to document the misclassified results. On deficient samples, the repeatability and reproducibility of the method determine a coefficient ofvariation (CV) at 9.4 and 9.7%, respectively. A R^2 of 0.87 has been obtained when comparing the resultsobtained in the field from venous or capillary blood. A four days storage between 2-8°C did not impactsample results beyond the CV, whatever the level of G6PD activity. According to the robustness of thetest, the incubation time of the sample in the buffer should stay under 5 minutes.The deployment of such a rapid, easy-to-use and implement method would be a major step forward inthe elimination process of P. vivax nowadays conducted in some countries of the Guiana Shield.

6803

APPLICATION OF MACHINE LEARNING IN A RODENT MODEL FOR RAPID AND ACCURATE PARASITE COUNTS

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Rodent malaria models (e.g., Plasmodium yoelli and P. berghei) serve as important preclinical antimalarial and vaccine testing tools. Efficacy measurements of these models often require manually counting parasite-infected red blood cells (RBCs), a time-consuming and repetitive process. We have developed machine learning (ML) software to expedite these studies by automating the counting of Plasmodium-infected RBCs in rodents. Previous ML methods created by our group, designed to count P. falciparum-infected RBCs in humans, accurately measure parasitemia in humans but need to be optimized to measure parasitemia in rodent models. We retrained our ML model to target P. yoelii, instead of P. falciparum, in mouse RBCs, which are much smaller than human RBCs. Our improved algorithm reliably measured P. yoelii-infected RBCs at a wide parasitemia range (0.13-74.12%). Automated parasitemia measurements strongly correlated with manual results (r = 0.996). The program was highly accurate for parasitemia >1%, with a median error rate of 2.06% (mean error rate= 6.74%). Low parasitemia (<1%) affected count accuracy (up to 2-fold). However, our new software was designed to allow optional user verification of infected RBCs and to make corrections, an especially quick process at parasitemia <1%. The software is being developed as a stand-alone desktop application for Windows and Mac OS. The dataset is currently being trained to differentiate between parasite stages and between reticulocytes and mature RBCs. This approach can be applied to other rodent malaria-infected RBCs, and we are currently verifying the program's accuracy counting P. berghei-infected RBCs. Automation by ML for quick and accurate quantitation of blood-stage parasitemia will help in the rapid evaluation of novel vaccines and antimalarials in an easily accessible in vivo malaria model.

6804

SPATIAL HETEROGENEITY OF THE DISTRIBUTION OF PFHRP2/3 GENE DELETION IN ETHIOPIA AND CURRENT ALTERNATIVES TO EXCLUSIVE HRP2-BASED RDTS

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Plasmodium falciparum (Pf) parasites with pfhrp2/3 gene deletion are fast expanding in the Horn of Africa. Following reports of very high prevalence of gene deletion in neighboring Eritrea and Djibouti and small-scale studies that highlighted its presence in Ethiopia, we have done a nationwide survey (35 districts) to examine its prevalence and tested alternative RDTs. Of microscopy confirmed samples (n=6,848), 12% were negative using SD BIOLINE HRP2-based RDT and this varied from 0% (south Ethiopia, border with Kenya) to 47% discordance (northwest Ethiopia, border with Eritrea and Sudan). The study informed a nationwide switching to a non-HRP2-based RDT. The next question was what the current alternatives were. Informed by the survey, we evaluated the performance of candidate RDTs (n=3) in districts with varying rate of discordance (n=6) among febrile patients (n=1,800). Overall, 37% of the patients were microscopy positive for Pf of whom 24% were missed by SD BIOLINE. BIOCREDIT double line Pf RDT (HRP2 and LDH) detected all infections detected by microscopy except 3% with its LDH-based counterpart (both Pf and Pv) missing 5% of these infections. Overall, compared to microscopy, SD BIOLINE RDT showed poor performance (sensitivity 77%, 75-79%; specificity 97%, 96-98%) whilst the Pf double line (sensitivity 97%, 96-98%; specificity 93%, 92-94%) and Pf/Pv LDH (sensitivity 94%, 93-95%; specificity 96%, 95-97%) BIOCREDIT RDTs had improved performance. Overall prevalence of digital PCR based pfhrp2 gene deletion was 18% (9-26%) and pfhrp3 deletion was 49% (13-75%). Pfhrp2 gene deletion explained 60% of the discordant data with the remaining confirmed to have low antigen concentration (using multiplex bead based assay). HRP2 antigen concentration was higher in the RDT positive (median 1,231pg/mL; IQR 715-1363; p=0.001) than RDT negative samples (8.3; IQR 7.5-15.6). In conclusion, the distribution of pfhrp2/3 gene deletion is highly heterogeneous in Ethiopia and this was evident at lower geographical scale. The pfhrp2/3 gene deletion explains most of the discordance of HRP2-based RDTs. Improved LDH-based RDTs are good alternatives.

6805

PLASMODIUM FALCIPARUM HISTIDINE-RICH PROTEIN 2 GENE DELETION SURVEILLANCE IN SENEGAL

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Histidine-rich protein 2 (HRP2)-based rapid diagnostic tests (RDTs) are recommended to diagnose P. falciparum malaria at the heath post level in Senegal. However, deletion of the genes pfhrp2 and pfhrp3 has been reported to cause false-negative results in Asia, America, and recently Africa. Loss of this diagnostic tool would constitute a real challenge for malaria control and undermine elimination efforts. Here, we investigated the evidence for pfhrp2 deletions in P. falciparum in Senegal. This study was conducted during the 2021 transmission season at sites located in four of Senegal's 14 regions (Kolda, Kédougou, Kaolack and Diourbel). We enrolled 1396 febrile patients who underwent RDT. Giemsa-stained slides were performed for microscopy confirmation, and a dried blood spot was collected for PCR analysis to resolve discrepancies between RDT and

microscopy. pfmsp2 genotyping was performed to check for the presence of malaria DNA. pfhrp2 gene genotyping was done using the one-step PCR method (CDC). Among the 763 total RDT negative samples, 29 (3.8%) were positive by PET-PCR. Of the 29 PCR-positive samples, microscopy identified 7 P. falciparum infections (parasite densities ranging 40 to 8700 parasites per microliter), 1 P. malariae and 1 P. ovale, while 20 were negative by microscopy. Of the 7 P. falciparum, only 2 (0.32%) were identified as potentially pfhrp2 deleted parasites. Validation of these findings using Oxford Nanopore Technology sequencing methods to confirm and map any deletion is ongoing. These findings suggest a very low prevalence of pfhrp2 deleted parasites in Senegal. Continued surveillance as part of the process of quality control and assurance of malaria diagnosis in the country is ongoing both detect and monitor changes in the frequency of any detected pfhrp2 or pfhrp3 gene deletion that may undermine efforts to control and eliminate malaria in Senegal. Regular surveillance is recommended to ensure appropriate use of malaria RDTs.

6806

DETECTION AND QUANTIFICATION OF PLASMODIUM VIVAX DNA: CONCORDANCE BETWEEN PCR RESULTS ON PLASMA AND BLOOD PELLET SAMPLES FROM PATIENTS IN SENEGAL

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Current malaria diagnosis relies mainly on microscopy and rapid diagnostic tests, both having shown several limitations in the detection of non-falciparum species, though the global agenda for malaria elimination and eradication does not preclude these species. In Senegal, the use of molecular diagnostic on long-term archived sera samples has been key to the discovery of Plasmodium vivax. To ensure the reliability of the diagnosis of P. vivax from plasma or serum samples as an alternative to the preferred red blood cells, our study evaluated the detectability and quantification of P. vivax gDNA in blood pellets and plasma samples from febrile individuals. Blood samples obtained from 616 febrile patients living in Kolda, Tambacounda, and Kedougou regions in Senegal, were first screened for Plasmodium species composition by 18S ssrRNA-based nested PCR. Paired blood pellets and plasma samples were selected from a subset of 50 P. vivax-positive patients matched by age and sex with 50 P. vivax-negative patients, and subjected to a cytochrome b-based qPCR to compare the detection and quantification of P. vivax genomic DNA between the two specimen types. We report 1.8% and 14.77% of single and mixed P. vivax infections in the study population, and a high concordance (84%) between the qPCR detection of P. vivax genomic DNA from paired blood pellets and plasma samples. All P. vivax negative samples from the blood pellets were also confirmed plasma-negative, and parasitaemia in blood pellets was higher compared to plasma samples. The results support investigations of P. vivax infections in archived plasma collections with a high degree of confidence to generate additional data on the neglected P. vivax malaria, and ultimately guide strategies to control the disease.

6807

INTEGRATED FACILITY-BASED REFRESHER TRAINING AND, SUPPORTIVE SUPERVISION FOR STRENGTHENING HEALTHCARE PROVIDERS' CAPACITY FOR EFFECTIVE MALARIA CASE MANAGEMENT, PRODUCT SUPPLY MANAGEMENT AND SURVEILLANCE IN NIGERIA

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Malaria still remains an important public health disease with high burden for which high impact is required in Nigeria. A changing epidemiology of malaria is now accepted with decline in prevalence from 42% in 2010 to 22.5% in 2021. Notwithstanding this decline nationally, malaria is heterogeneous and varies in prevalence across the country. Effective malaria case management ensures that all malaria-suspected patients are diagnosed early, treated promptly and recorded. However, parasitological confirmation is low after a decade of policy implementation. Parasitological testing is done routinely with microscopy or malaria rapid diagnostic tests (RDTs) that are meant to expand access to testing as they are used in the ubiquitous Primary Health Centres (PHCs), Health Posts and in some medicine retailers in the informal private sector. There are challenges in the implementation of quality diagnosis in health facilities as testing remains low, behind artemesinin combination therapies (ACTs), lack of confidence in RDT results, poor quality of malaria microscopy, poor records, long turn-a-around time for microscopy, poor performance of RDTs etc. These training interventions are expensive though imperative. It was instructive that an integrated approach of strengthening capacity of healthcare workers who provide malaria case management services will need additional capacity in data quality, product supply management, monitoring and evaluation (M&E) to address the myriads of challenges in the health facilities. A sustainable, cost-effective, impactful implementation of refresher training during on-the-job supportive supervision at the facilities is invaluable compared with stand-alone external quality assurance approach. Local capacity within the areas was additional benefits of leadership among the supervisors employed. With funding support from The Global Fund, an integrated capacity strengthening package was implemented for healthcare providers with innovation and corrective actions; It has great potential for scaling effective malaria case management in Nigeria.

6808

EXPANDING COMMUNITY CASE MANAGEMENT OF MALARIA TO ALL AGES CAN CONTRIBUTE TOWARDS UNIVERSAL ACCESS TO MALARIA DIAGNOSIS AND TREATMENT: RESULTS FROM A CLUSTER RANDOMIZED TRIAL

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Global progress on malaria control has stalled in recent years, in part due to challenges in universal access to malaria diagnosis and treatment. Community health workers (CHWs) can play a key role in improving access to malaria care for children < 5 years (CU5), but national community health policies rarely permit them to treat older individuals. We conducted a two-arm cluster randomized trial in rural Madagascar to assess effects of expanding malaria community case management (mCCM) to all ages on health care access and use. Thirty health centers and their associated CHWs in Farafangana district were randomized 1:1 to mCCM expansion (intervention), plus conventional integrated CCM (iCCM) for CU5, or to existing iCCM (control) for CU5 only. Both arms were supported with CHW trainings on malaria case management, community sensitization on free malaria care, monthly CHW supervision and reinforcement of malaria supply chains. Cross-sectional household surveys in ~1600 households were conducted at baseline (Nov-Dec 2019) and endline (Nov-Dec 2021). In addition, data were collected from health center and CHW registers for 36 months (2019-2021). Intervention impact was assessed via difference-in-differences analyses for survey data and interrupted time-series analyses for health system data. Rates of care seeking for fever and malaria diagnosis more than doubled in both arms (from 25% to over 50%), driven mostly by increases in CHW care. mCCM expansion yielded additional improvements for those over 5 years in the intervention arm (Rate ratio for RDTs done in 6-13-year-olds (RRRDT6-13yrs)=1.65; 95% CI 1.45-1.87; RR for RDTs done in those 14+ years (RRRDT14+yrs)=1.46; 95% CI 1.30-1.63), but increases were statistically significant only in health system analyses. mCCM expansion was associated with larger increases for populations living further from health centers (RRRDT6-13yrs=1.21 per km; 95% CI 1.19-1.23). Expanding mCCM to all ages can contribute to universal access to malaria diagnosis and treatment. In addition, strengthening community health and supply chain systems can achieve significant improvements even absent mCCM expansion.

6809

DIGITALLY-ENHANCED RAPID MALARIA TESTING USING ARTIFICIAL INTELLIGENCE (AI) TO SUPPORT QUALITY CONTROL WITH COMMUNITY HEALTH WORKERS IN RWANDA

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Following the WHO's guidance for parasitological diagnosis of all suspected malaria cases, from 2010 to 2020, the use of malaria rapid diagnostic tests (mRDTs) increased 10-fold across sub-Saharan Africa. While this scale-up was an important step towards improved malaria case management and surveillance, RDT misadministration and misinterpretation errors remain a concern amongst community healthcare workers (CHWs). Traditional data quality assurance (QA) methods rely heavily on visits to health facilities and communities, and assume patient register data is accurate, despite reports of over-treatment and a lack of provider confidence in negative RDT results. In Rwanda, CHWs contribute to the case management of more than 60% of uncomplicated malaria cases exclusively using nationally recommended RDTs for diagnostic testing and artemisinin-based combination treatments (ACTs). However, there is paucity of evidence around this statistic and weak QA systems. This study investigates whether a digital application (app) supporting CHWs in Rwanda could augment QA/QC efforts, providing a way to facilitate high quality community mRDT administration and real time data surveillance to assess the accuracy of malaria test positivity rate (TPR). To date, 200 CHWs have completed 4,388 tests using the app with positivity rates of 15.2% P.f positive, 2.1% Pan positive and 8.5% P.f/Pan positive. Baseline CHW survey results indicate over 90% of CHWs are supportive of using an app in their malaria testing flow and are excited about its potential to provide proof for their work. Final results available in July 2023 will assess the accuracy of CHW RDT interpretations against a trained group of RDT readers (Panel Read ground truth) and artificial intelligence algorithms (AI), indicating AI's potential role in supporting timely overall TPR reporting accuracy for CHWs. This work has broader impact across disease areas (including other neglected tropical diseases), supporting decision-making and accurate reporting, and augmenting investment in mRDT AI technology that can be a multiplier for overall community health and febrile epidemic surveillance.

6810

EFFICACY OF ARTEMETHER-LUMEFANTRINE, ARTESUNATE-AMODIAQUINE, AND DIHYDROARTEMISININ-PIPERAQUINE FOR THE TREATMENT OF UNCOMPLICATED PLASMODIUM FALCIPARUM MALARIA AMONG CHILDREN IN THE CENTER AND NORTH REGIONS OF CAMEROON, 2021-2022

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Since 2019, treatment for uncomplicated falciparum malaria in Cameroon has been one of three first-line therapies: artesunate–amodiaquine (ASAQ), artemether-lumefantrine (AL), and dihydroartemisinin-piperaquine (DP). In accordance with WHO's guidance and standard protocol to routinely test antimalarial drug efficacy, we evaluated all three treatments in children 6 to 120 months in Cameroon's Center and North regions from April 2021 to September 2022. In the Center, 178 patients were randomly assigned either ASAQ (n=89) or AL (n=89); in the North, where seasonal malaria chemoprevention (SMC) is implemented, 203 patients randomly received either AL (n=102) or DP (n=101). Clinical and parasitological responses were monitored for 28 (AL and ASAQ) or 42 (DP) days. Molecular correction was performed on 52 late treatment failures using PCR analysis of msp1 and msp2 genes to differentiate recrudescence from reinfection. For AL, Kaplan-Meier PCR-corrected efficacy was 96.6% (95% CI 93.0-100%) in the Center and 93.8% (89.2-98.7%) in the North. PCR-corrected efficacy of ASAQ in the Center was 100%. PCR-corrected efficacy for DP in the North was 90.5% (84.8-96.6%). Amplicon sequencing of 104 (52 day zero and 52 day of failure) samples was performed on pfk13, pfmdr1, and pfcrt genes. Results showed no evidence of pfk13 mutations associated with resistance. Pfmdr1 86Y was found only in the North at a frequency of 11.2%, while 184F was found in the North and Center at frequencies of 55.0% and 76.1%, respectively. Pfcrt 76T was detected only in the North at a frequency of 21.5%. We observed a high frequency of wild type pfcrt K76 and pfmdr1 N86 in the Center region. AL, ASAQ, and DP remain efficacious in these areas of Cameroon, but continued efficacy monitoring is essential to facilitate data driven malaria treatment policies. In particular, the 86Y and 76T mutations in the North warrant further investigation, as they could be due to drug pressure from the amodiaquine component of SMC implemented annually in the region since 2016.

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THERAPEUTIC EFFICACY OF ARTESUNATE-AMODIAQUINE AND ARTEMETHER-LUMEFANTRINE FOR UNCOMPLICATED FALCIPARUM MALARIA TREATMENT IN FOUR SENTINEL SITES OF CÔTE D'IVOIRE, 2021

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In Côte d'Ivoire, artesunate-amodiaquine (ASAQ) and artemether-lumefantrine (AL) have been used as first-line treatment for uncomplicated malaria since 2005. The World Health Organization recommends regular therapeutic efficacy studies (TES) to monitor the efficacy and safety of ACTs. From April to October 2021, a TES was conducted to assess treatment efficacy and safety of ASAQ and AL for uncomplicated malaria and to determine the polymorphisms of molecular markers of drug resistance in 4 sites: Aboisso, Abengourou, Bouake, and San-Pedro. Participants were treated with standard doses of each ACT and monitored for 28 days. Genotyping was done to differentiate recrudescence from reinfection in case of treatment failure. Polymorphisms in the Pfkelch13, Pfcrt, Pfmdr1, Pfdhfr, Pfdhps and Pfatp6 genes were assessed in pretreatment and treatment failure samples. A total of 704 children were treated with AL (n=353) or ASAQ (n=351). There was one ASAQ early treatment failure in Aboisso. The 28-day PCR-corrected Kaplan–Meier estimates for AL were 97.7% (95% CI: 91.1-99.4%) in Abengourou, 96.6% (95% CI: 89.7-98.9%) in Aboisso, 96.5 (95% CI 89.6-98.9%) in Bouake and 94.3% (95% CI: 86.9-97.6%) in San-Pedro. For ASAQ, efficacy was 100% (95% CI: 95.9-100%), 98.8% (95% CI: 91.8-99.8 %), 97.7% (95% CI: 91.1-99.4%) and 97.7% (95% CI: 91.0-99.4%) in Abengourou, Bouake, San-Pedro and Aboisso, respectively. No serious adverse event was reported in either study arm. No resistance-associated mutations in the Pfk13 gene were found in the 196 successfully sequenced samples. The CVMNK wild haplotype of Pfcrt was found in over 95% of samples in all sites except in Bouake (50%). The Pfdhfr triple mutant (51I/59R/108N) was the predominant allele in all sites. The majority of isolates from all four sites carried Pfdhps simple mutation 437G. Pfmdr1184F allele of reduced susceptibility to lumefantrine was found in 32.5%, 29.0% and 10.6% of samples in Abengourou, San-Pedro and Aboisso, respectively and was not found in Bouake. AL and ASAQ continue to be efficacious in Côte d'Ivoire. Continued monitoring is critical to inform evidence-based malaria treatment policies.

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AN IN VIVO SCREEN REVEALS NOVEL VULNERABILITIES IN THE MOSQUITO STAGES OF PLASMODIUM FALCIPARUM

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Progress against malaria has plateaued in recent years, necessitating new strategies to combat this deadly disease. We recently demonstrated that Plasmodium falciparum parasites can be directly targeted within the Anopheles vector by allowing mosquitoes to land on a surface coated with the antimalarial cytochrome bc1 (Cyt B) inhibitor atovaquone. This initial finding provided proof-of-principle evidence for novel mosquito-targeted antimalarial interventions. To identify additional inhibitors of mosquito stage P. falciparum, we performed an in vivo mosquito-targeted screen of diverse antimalarials and identified a number of active compounds with distinct modes of action. In particular, we found that the endochin-like quinolones (ELQs) were exquisitely potent via pre-infection mosquito exposure. ELQs also target Cyt B, a component of the parasite electron transport chain essential for coenzyme Q (CoQ) redox and mitochondrial membrane potential. Our initial screen identified both CoQ oxidation (Qo) and reduction (Qi) site inhibitors, and we focused on inhibitors of each site for further translational development. We performed a first in-mosquito preliminary structure activity relationship study and found that both prodrug moieties and specific quinolone core substituents greatly improved tarsal activity. To assess the compatibility of these compounds with bed net like formulations, we generated low density polyethylene films incorporated with our most active hits: ELQ453 (Qo) and ELQ613 (Qi). Allowing mosquitoes to land on polyethylene films with as little as 0.1% w/w ELQ strongly inhibited P. falciparum infection. We also assessed the propensity for ELQ resistance development and transmission. We found that blood stage selection with Cyt B Qo site inhibitors led to a variety of target-site mutations, which all had impaired sporogony and produced significantly fewer sporozoites. Taken together, the remarkable activity of ELQs against mosquito stage P.

falciparum and the impaired transmissibility of resistant mutants highlights the promise of these compounds for future mosquito-targeted antimalarial interventions.

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THERAPEUTIC EFFICACY OF ARTEMETHER-LUMEFANTRINE AND DIHYDROARTEMISININ-PIPERAQUINE FOR THE TREATMENT OF UNCOMPLICATED PLASMODIUM FALCIPARUM MALARIA IN MALI, 2020-2022

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The National Malaria Control Program in Mali recommends artemether–lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) for the treatment of uncomplicated malaria. The WHO recommends regular monitoring of drug efficacy to support national treatment policies and practice. From August 2020 to February 2022, we conducted an in vivo study of clinical and parasitological responses to AL and DP in Dioro, Missira and Sélingué sites using the standard WHO therapeutic efficacy study protocol. A total of 420 children (160 in Dioro, 160 in Missira, and 100 in Sélingué) between 6 months and 16 years of age with uncomplicated Plasmodium falciparum malaria and a prevalence of 2,000–200,000 asexual parasites/µL were enrolled, randomly assigned to either AL or DP, and followed up for 28 days (for AL) and 42 days (for DP). Late treatment failures were genotyped to differentiate recrudescence from reinfection using msp1, msp2, and glurp. In AL patients, Day 3 positivity rates were 2.6%, 7.2%, and 0% in Dioro, Missira, and Sélingué, respectively. For DP, Day 3 positivity was 3.2% in Dioro, 7.9% in Missira, and 0% in Sélingué. Uncorrected and PCR-corrected efficacy at day 28 for AL and day 42 for DP were calculated. For AL, day 28 corrected efficacy was 97.3% (95% CI 90.6–99.7%) in Dioro, 98.5% (92.1–100.0%) in Missira, and 100% (92.0–100.0%) in Sélingué. At day 42, corrected efficacy for DP was 94.4% (86.2–98.4%) in Dioro, 98.2% (90.4–100.0%) in Missira, and 100.0% (91.2–100.0%) in Sélingué. Efficacy was above the WHO cutoff for all sites and drugs. Known markers of resistance in Pfk13, Pfmdr1, and Pfcrt genes were assessed in 23 paired samples (day zero and day of failure) using Sanger sequencing. No mutations associated with artemisinin resistance were identified in the Pfk13 gene. For Pfmdr1 (86, 184 and 1246 positions), the NFD haplotype was the most common; it was found in 57.1% of isolates. For Pfcrt, the CVIET haplotype was most common, with a frequency of 37.5%. Findings signify that both AL and DP remain effective for uncomplicated malaria treatment in our three study sites in Mali.

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PHARMACOKINETICS OF PIPERAQUINE WHEN USED AS MALARIA CHEMOPREVENTION IN HIV-INFECTED CHILDREN ON ANTIRETROVIRAL THERAPY IN UGANDA

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Dihydroartemisinin-piperaquine (DHA-PQ) is increasingly used for malaria treatment and considered for chemoprevention where malaria and HIV co-infection are common. PQ is metabolized by cytochrome p450 CYP3A4 leading to drug-drug interactions (DDI) between DHA-PQ and antiretroviral therapy (ART) when co-administered. Suboptimal or elevated pharmacokinetic (PK) exposure may result with efavirenz (EFV)- and lopinavir/ritonavir (LPV/r)-based ART, respectively, compromising efficacy, toxicity, and risking drug resistance. The recently recommended ART, dolutegravir (DTG), has not been extensively evaluated for DDIs. We therefore conducted a prospective open-label PQ PK study in the context of EFV-, LPV/r- and DTG-based ART regimens among HIV-infected Ugandan malaria-uninfected children alongside HIV-uninfected controls. PK sampling was performed over 42 days with quantification by LC tandem MS. 30 HIV-uninfected children at each of the two age groups (3-10 and 11-17 years), and 90 HIV-infected children (n=30 on each regimen) provided PK results. PQ exposure was significantly reduced in children on EFV vs controls, as measured by AUC 0-day21, AUC 0-day28, and AUC 0-day42, (4.17, 4.33, 4.47 vs 11.2, 12.5, 14.6 hr*ug/mL; GMR: 0.372, 0.346, 0.306), and Day 21, 28, and 42 PQ levels (2.24, 1.03, 0.757 ng/mL vs 14.9, 6.41, 9.34 ng/mL; GMR: 0.150, 0.161, 0.081, respectively); all p-values <0.0001. In contrast, LPV/r-based ART increased PQ exposure as compared to controls; AUC 0-day21, AUC 0-day28, and AUC 0-day42, (36.7, 41.6, 49.7 hr.ug/mL; GMR: 3.28, 3.33, 3.40), and Day 21, 28, and 42 PQ levels (47.0, 17.6, 17.8ng/mL; GMR: 3.15, 2.75, 1.91, respectively); all p-values <0.0001. DTG-based ART reduced Day 28 and 42 PQ levels as compared to the controls at 11-17 years (5.44, 5.01 ng/mL vs 8.01, 13.8 ng/mL; GMR: 0.679, 0.363, p-values: 0.0199 and <0.0001, respectively). HIV-infected children on EFV- and LPV/r-based ART have opposing effects on PQ exposure, which may impact efficacy and toxicity, respectively, while reductions in the terminal PQ exposure in those on DTG-based ART may reduce the duration of post-treatment chemoprophylaxis.

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EVALUATION OF IVERMECTIN AND METABOLITES AS AN ANTIMALARIA THERAPY AGAINST PLASMODIUM FALCIPARUM LIVER STAGE

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Malaria remains a major global public health threat due to prevalence of drug-resistances and failure to frontline antimalarial therapy, hindering the global efforts to control and eliminate the disease. Almost none of the available antimalarial drugs are efficacious against the liver stage of Plasmodium falciparum, which is the initial stage of infection that leads to disease causing blood stage infection. The only currently FDA-approved class of drug capable of eliminating Plasmodium liver stage parasites are the 8-aminoquinolines and this drug class has its own limitations due to potential hemolytic activity in people with favism and therefore not suitable for mass drug administration. Due to these limitations, there is a critical need for safer and more efficacious drugs that can prevent liver

stage development of malaria parasites. Ivermectin is an approved broad spectrum antiparasitic drug that has been proposed as a novel malaria transmission control tool to kill mosquito vectors that transmit malaria and aid malaria elimination. Recent studies have revealed ivermectin inhibits liver-stage development of P. berghei, a rodent malaria laboratory model, suggesting this drug may be an effective antimalarial drug. However, ivermectin is known to be metabolized by cytochrome P450 3A4 enzyme, which exhibits polymorphism among different individuals to potentially alter the efficacy against Plasmodium, emphasizing the importance of understanding the metabolism of ivermectin and its metabolites. We established a robust in vitro liver assay to study the liver stage development of human malaria parasites in primary human hepatocytes that can be used to evaluate the potential impact of these metabolic differences on ivermectin's anti-liver stage efficacy. This model can be used to evaluate the metabolism of ivermectin in hepatocytes from different donors and its efficacy against P. falciparum liver stages.

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A PHASE 2A TRIAL OF SJ733 FOR PLASMODIUM VIVAX MALARIA

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SJ733 is currently being developed for treatment of acute uncomplicated and severe malaria. Phase 2a trial with a 3-dose schedule of SJ733 (600 mg daily doses) in Peru demonstrated that SJ733 cured blood stage P. vivax malaria in 95% of cases at a 14-day endpoint but did not cure latent liver stage disease. In this trial 80% of patients had undetectable parasitemia within 48 h of initiating therapy. No drug-related adverse events were observed and efficacious exposures of SJ733 were maintained for over 100h. This study strongly suggests that combining SJ733 in a combination drug with a liver-stage active partner would provide for 3-day schedule radical cure of P. vivax malaria.

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ARTESUNATE PYRONARIDINE IS A SAFE AND EFFICACIOUS TREATMENT FOR PLASMODIUM FALCIPARUM AND P. VIVAX IN ETHIOPIA WITH A STRONG TRANSMISSION REDUCING ROLE IN P. VIVAX

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The emergence and spread of drug-resistant parasites in Africa threaten the recent gains in malaria control. Plasmodium falciparum (Pf) and P. vivax (Pv) are sympatric in Ethiopia. Single-dose primaquine (PQ) for Pf and radical cure for Pv are included in its guidelines. We examined the safety and efficacy of Artesunate-pyronaridine (AP) as an alternative for both Pf and Pv and compared it with the current first-line treatments for Pf (artemether-lumefantrine, AL) and Pv (chloroquine, CQ). The transmission-reducing effect of AP and CQ was evaluated using mosquito feeding assays in four arms (n=60) that included a standard (day 0) and delayed (day 3) PQ administration. Day 42 treatment success rate was the same between AL (92%, 76/83) and AP (92%, 80/87) for Pf whilst for Pv AP (98%, 83/85) was higher than CQ (91%, 69/76). This was the same between the two arms of Pf starting from day 1 (p=0.82). No signs of early treatment failure were observed. For Pv, a significant difference (p=0.001) was observed between the two arms; AP cleared the vast majority of parasites on day 1 (95%) whilst CQ cleared parasites in only 80% of patients on day 1. These observations remained the same after PCR correction. Using amplicon-based NGS, an expansion of R622I pfk13 mutation (47%) was observed together with novel mutations (K189T, E401Q, and M18I). The very high rate of the pfmdr1 N86 (98%) and Y184F (99%) alleles hint at potential lumefantrine resistance. The HRP2-based RDT missed 41%(82/199) of Pf infections detected by microscopy, of which digital PCR-based typing confirmed 78% as the pfhrp2 gene deleted 95% of pfhrp3 deleted. All isolates that carried the R622I mutation were also pfhrp2 deleted. Overall mosquito infectivity before treatment was 92%(55/60) with no difference between the four arms. On day 1 after treatment, infectivity to mosquitoes was observed mainly in the CQ arms with delayed (47%, 7/15) and standard (20%, 3/15) PQ. Only one patient was infectious after treatment with AP (7%, 1/15), in the delayed PQ arm. AP is a safe and efficacious alternative treatment for both Pf and Pv. The expansion and co-occurrence of R622I mutation with pfhrp2 deletion is worrisome.

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THE ANTIPLASMODIAL ACTIVITY OF PUTATIVE COMPOUNDS TARGETING PLASMODIUM SPP. AURORA KINASE-2

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Malaria remains a heavy worldwide burden on public health and socioeconomic in tropical and subtropical regions. The emergence of resistant strains to almost all recommended treatments turns needed the discovery of novel antimalarial therapies with novel mechanisms of action. PfArk-2, a serine/threonine kinase protein related to the Aurora family, has been identified in P. falciparum's kinome and shown to be essential for the parasite's development in different stages of its life cycle. Thus, PfArk-2 is an attractive approach for developing new multi-stage antimalarials. The aim of this work was to validate experimentally inhibitors against PfArk-2 identified using chemoinformatics strategies based on molecular volume and shape models. After developing and validating the computational model, a virtual screening in the ChemBridge commercial library was performed, and six compounds were acquired and tested in vitro. SYBR Green fluorimetric assays were used to evaluate in vitro antimalarial activity. The cytotoxicity was assessed via the MTT assay, and inhibition of oocyst conversion was analyzed using P. berghei Ooluc strain. The compounds were initially tested at a concentration of 5 μM against the chloroquine-sensitive 3D7 strain, showing > 80% of parasite growth inhibition. Among them, LDT715-720 compounds presented EC50< 100 nM for both 3D7 and Dd2 (chloroquine-resistant) strains. Additionally, cytotoxicity assays on COS-7 and HepG2 mammalian cells indicated low toxicity. Moreover, five compounds are able to inhibit at least in 80%. late-stage P. falciparum gametocytes in vitro Furthermore, LDT-719 and LDT-720 showed inhibition over 90% at 10μM for in vitro P. berghei oocysts development. Preliminary morphological analyses revealed that the most potent compound, LDT-715 has a fast action, acting in the early stages of asexual parasite development. In summary, the virtual screening model proved to be successful in identifying five active compounds (EC50 < 100nM) against P. falciparum, which demonstrated low cytotoxicity to mammalian cells and multistage properties.

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THERAPEUTIC EFFICACY OF PYRONARIDINE-ARTESUNATE (PYRAMAX®) AGAINST UNCOMPLICATED PLASMODIUM FALCIPARUM INFECTION AT HAMUSIT HEALTH CENTER, NORTHWEST ETHIOPIA

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Malaria remains a major public health problem. Early cases detection and prompt treatment are important malaria control strategies implemented in many endemic countries, including Ethiopia. ACT is currently recommended by the World Health Organization (WHO) for the management of uncomplicated Plasmodium falciparum and P. vivax malaria. However, the emergence and rapid spread of drug-resistant plasmodium strains presents a major challenge to malaria control and elimination efforts. Pyronaridine-artesunate (Pyramax) is an artemisinin-combination therapy shown to have good efficacy for uncomplicated malaria in large-scale clinical trials conducted in Asia and Africa. This study reports the first therapeutic efficacy profile of pyronaridine-artesunate for uncomplicated P. falciparum in Ethiopia.This single-arm prospective study with 42-day follow-up period was conducted from March to May 2021 at Hamusit health center using the WHO therapeutic efficacy study protocol. A total of 90 adults ages 18 and older with uncomplicated falciparum cases consented and were enrolled in the study. A standard single-dose regimen of pyronaridine-artesunate was administered daily for 3 days, and clinical and parasitological outcomes were assessed over 42 days of follow-up. Thick and thin blood films were prepared from capillary blood and examined using light microscopy. Hemoglobin was measured and dried blood spots were collected on day 0 and on the day of failure.Out of 90 patients, 86 (95.6%) completed the 42-day follow-up study period. The overall PCR-corrected cure rate (adequate clinical and parasitological response) was very high at 98.9% (95% CI: 92.2-99.8%) with no serious adverse events. The parasite clearance rate was high with fast resolution of clinical symptoms; 95.6% and 100% of the study participants cleared parasitemia and fever on day 3 respectively. The mean hemoglobin concentration was significantly increased ($p < 0.001$) on day 14 compared to that on day 0. Pyronaridine-artesunate was highly efficacious and safe against uncomplicated P. falciparum in the study population.

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MUTATION OF THE PLASMODIUM FALCIPARUM FLAVOKINASE CONFERS RESISTANCE TO ANTI-PLASMODIAL RIBOFLAVIN ANALOGUES

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Not much is known about the requirements of the intraerythrocytic stage of Plasmodium falciparum for riboflavin (vitamin B2). We have recently shown that the riboflavin analogues, roseoflavin and 8-aminoriboflavin, potently inhibit malaria parasite proliferation and that they do so by targeting riboflavin metabolism and/or utilisation. To investigate their mechanism of action, we generated resistant parasites by in vitro evolution in the presence of roseoflavin. These parasites were resistant to roseoflavin (six-fold) and 8-aminoriboflavin (50-fold). Whole genome sequencing of cloned parasites revealed a mutation (L672H) in flavokinase (PfFK); the enzyme responsible for converting riboflavin into the essential enzyme cofactor flavin mononucleotide (FMN). To determine the role of this mutation in the resistance phenotype, we generated parasites episomally-expressing GFP-tagged versions of the wild-type or mutant flavokinase. Parasites expressing mutant PfFK-GFP had a three-fold higher roseoflavin IC50 value compared to parasites expressing the wild-type flavokinase. This is consistent with the mutation being responsible for the resistance phenotype. Immunopurified PfFK-GFP phosphorylated riboflavin into FMN. Riboflavin, roseoflavin and 8-aminoriboflavin were found to have a similar KM for the wild-type flavokinase (KM ~ 1.2 µM). However, the L672H mutation reduced the flavokinase binding affinity for both roseoflavin and riboflavin by 13-30 times (KM = 38 and 16 µM), respectively. In addition, we found that 8-aminoriboflavin is no longer a substrate of the mutant flavokinase. Our study shows that PfFK is a viable target for the development of a novel antimalarial.

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ANTIPLASMODIAL ACTIVITY OF NOVEL HETEROCYCLIC COMPOUNDS USING IN SILICO AND IN VITRO ASSAYS

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Resistance to artemisinin and/or their partner drugs has become a major thread to achieve malaria eradication. The development of new antimalarials is paramount to keep the goals on reduction of malaria cases in endemic regions. The search for quality hits has been challenging as many inhibitory molecules may not progress to the next development state. Combined strategies using in silico and phenotypic approaches may improve the detection and selection of hits likely to progress through the pipeline as drug candidates. The aim of this work was to screen an in-house library of heterocyclic compounds (RGHC) for antimalarial activity using computational predictions and phenotypic techniques to find quality hits. The novel heterocyclics were synthetized based on biologically active templates. The physicochemical and drug likeness properties (ADMET) of RGHC library were evaluated in silico and compounds were selected for a structure-based analysis. Seven Plasmodium target proteins were chosen from the drug bank database and ligands and receptors processed using computer tools (Chimera UCSF and Open Babel) before being subjected to docking analysis with Autodock Vina. Growth inhibition of P. falciparum (3D7) cultures was tested by SYBR green assays and toxicity was assessed in the G. mellonella in vivo model. From a total of 792 compounds, 364 (45.9%) showed good membrane permeability, oral /gastrointestinal bioavailability and complied with the Lipinski rule of five. Seventeen (2.1%) compounds were detected as PAINs structures, 341 compounds with favorable drug likeness profile were selected for analysis. Eight compounds showed IC50 ranging from 0,175- 0,990 µM, these compounds belong to the same series of pyridines. Preliminary toxicity assays showed low toxicity in the Galleria model in at least 4 compounds complying with drug likeness properties. Two inhibitory compounds showed good binding energies with 1-cys peroxiredoxin, and the calcium dependent protein kinase-4 and the other two compounds with the haloacid dehalogenase-like hydrolase and plasmepsin 2, suggesting potential antimalarial activity.

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EVALUATING THE EFFECT HETEROGENEITY OF MALARIA CAMP INTERVENTIONS IN HARD-TO-REACH AREAS OF ODISHA STATE, INDIA

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Odisha state has the highest burden of malaria in India with a large tribal population living in hard-to-reach areas. The Odisha State Malaria Control Program introduced 'malaria camps' in 2017 targeting remote villages to perform mass screening and treatment, enhance vector control and educate the population. To better understand the heterogeneity of intervention effects, we combined data on intervention outcomes and the target population's socioeconomic and demographic characteristics with entomological and remotely-sensed data on climate and environmental factors for the study villages. We created four outcome variables: Plasmodium RDT+, which was further divided into symptomatic cases RDT+/fever+ and asymptomatic infection RDT+/fever-; and subpatent malaria RDT-/PCR+. We applied XGboost, a machine learning algorithm, on each study outcome, operationalizing the remaining variables as model features, to investigate the factors contributing to intervention effect heterogeneity. The Shapley additive explanation post-processed model interpretation framework was used to interpret the models. The model exhibited the best predictive performance in identifying subpatent infections, with 75% recall and 87% balanced accuracy. All feature classes contributed as important features to the model, with particular importance on anthropometric (age, sex, weight, height, BMI, body temperature), sociodemographic (number of occupants in the household) and behavioral characteristics (sleeping without bednet, knowledge of malaria symptoms), malaria history, climactic factors (precipitation and temperature in previous quarter), entomological characteristics in study villages (Anopheles and Culex counts), and serological features (antibodies to PfRh22030 and PfMSP2Ch150 antigens). The model's relatively good performance in predicting subpatent infection suggests that it has the potential to guide development of more targeted and effective interventions to reduce subpatent reservoirs. Such improvements are likely to enhance intervention cost-effectiveness and contribute to the malaria elimination goal by 2030.

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IMPLEMENTATION OF A NEW VECTOR SURVEILLANCE SYSTEM TO ANTICIPATE THE IMPACT ASSESSMENT OF THE NOVEL GENETIC TECHNOLOGIES IN BURKINA FASO

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New approaches based on the release of genetically-modified sterile male mosquitoes to control natural populations are proposed as the most promising strategies for malaria control. To effectively assess the impact of these interventions in endemic settings, vector surveillance systems that address practical issues of malaria control must be established. However, in most sub-Saharan African countries vector surveillance is generally not, or under-funded and limited resources are allocated to support the development and enhancement of adequate capacities for effective entomological surveillance within national malaria control programmes (NMCPs). Thus, vector surveillance systems remain weak, fragmented between research institutes, universities, and the national programmes, and lack appropriate coordination, although such systems are urgently needed. In Burkina Faso, we have brought together all relevant stakeholders from the NMCP, the Ministry of Health, research centres, universities to develop a better approach to establishing sustainable system with increased local participation, ownership and integration of vector control implementation, surveillance, and operational research for malaria elimination. Here we present the impact of the training in malaria vector surveillance and monitoring of vector control interventions to anticipate the envisaged use of gene drive technology to supress vector populations in Burkina Faso setting. Newly trained entomologists, including 70 health promotion officers deployed in the peripheral health districts, 13 others in the intermediate level of the health regions and 9 in the central level of decision making in the NMCP, were assessed on practical techniques and methods for collecting adult mosquitoes and larvae in the field. The results show that our approach is quick, unexpensive, and accurate, with a high mosquito and larval sampling performance, which makes it a promising system for very large-scale mosquito genetic surveillance to assess the impact of implementations for vector control.

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INVESTIGATING FACTORS ASSOCIATED WITH VECTORS DENSITIES, COMPOSITION AND BITING PATTERN ACROSS DIFFERENT SETTING OF TANZANIA TO INFORM CONTROL STRATEGIES

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Major malaria interventions, such as ITNs and IRS, are becoming less effective due to changes in mosquitoes behavior and insecticide resistance. In Tanzania's northern, western, and southern regions, where malaria still caused significant child mortality, complimentary approaches are still needed to address the problem. This study aims to determine malaria vectors species abundance, and investigate their biting patterns, to inform complementary malaria vector control strategies. The present study utilized mosquito electrocuting trap (MET) to collect Anopheline mosquitoes from 32 districts in Tanzania. Zero-inflated mixed-effect regression model were used to determine mosquito abundance and biting patterns. Independent variables such as windows screening, eaves opening, roof type, livestock, land use were fitted in the model to assess the associated risk of mosquito abundance. The study examined factors associated with mosquito abundance in primary malaria vector species, An. gambiae indoor (23.5%) and outdoor (35.6%) and An. funestus indoor (75.4%) and outdoor (63.0%) respectively. Iron roof (OR=0.5, p=0.0004), Rice farm (OR=0.18, p=0.0003), cooking outdoors (OR=0.45, p=0.0012), absence and partial window screen (OR=0.2, p=0.042 and OR=4.2, p=0.015) respectively, were found to be significant predictors of mosquito abundance. An. funestus bites indoors during the night (0300 - 0400 hrs) and early morning (0500 - 0600 hrs), while A. gambiae prefers to bite at night (2100 -2200 hrs) and midnight (2300 - 0000 hrs). An. funestus tends to bite outdoors just about midnight (2300 - 0000 hrs), while An. gambiae bites outdoors during night (0100 - 0200 hrs). While ITNs and IRS can prevent most indoor exposures, significant malaria transmission risk remains outdoors, during communal gatherings and certain activities like cooking and storytelling, especially in rural and low-income households. Addressing this persistent exposure requires scalable approaches that complement ITNs, particularly targeting outdoor-biting mosquitoes. Complementary interventions should prioritize low-income families.

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A SUSTAINABLE MALARIA CONTROL BLUEPRINT: 20 YEARS OF CHALLENGES, LESSONS AND ACHIEVEMENTS

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Bioko Island Malaria Elimination Project (BIMEP) was conceived in 2004 through a public-private partnership (PPP) funding mechanism to address the high malaria burden on Bioko Island. Some of the key approaches adopted by the BIMEP's sustainable malaria control framework include robust data information systems, flexible programmatic decisions, long-term funding, strong academic partnerships, detailed documentation of programmatic impact, staff retention, capacity building, and best practices. As a result, the project has seen sustained gains despite major challenges. This study aims to examine the BIMEP's footprint through a comprehensive analysis of impact (e.g. parasite prevalence, morbidity, and mortality rates, entomological collections), outcome (e.g. intervention coverage) and process (e.g. productivity) indicators and how they have changed across two decades of implementation. This insight will underscore the importance of adaptive management and PPP in improving and sustaining the implementation of interventions, such as indoor residual spraying, long-lasting insecticide-treated nets, artemisinin-based combination therapy, larval source management and case management and diagnosis practices. The analyses will look at temporal and spatial trends in an attempt to highlight the most significant achievements, the greatest challenges remaining and the most important lessons learned in one of the longest lived malaria control programs in sub-Saharan Africa.

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PRIVATE PROVIDERS ACCEPTANCE OF SOCIAL MEDIA REPORTING TOOLS FOR MALARIA CASE NOTIFICATION AND SURVEILLANCE IN MYANMAR

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Myanmar aims to eliminate malaria by 2030. To meet elimination targets, all malaria cases must be reported within 24-hours. Case-based reporting began in 2019 but remains challenging due to lack of standardized mechanism and using inefficient methods like SMS and phone calls. In 2021, we developed social media chatbots running on Facebook Messenger and Viber and connected to DHIS2, allowing private providers and field supervisors of malaria community volunteers to report surveillance data within 24-hours. Volunteers have limited access to internet therefore their supervisors used the chatbots for case notification. From July 2021 to date, 1349 malaria cases have been notified by 486 private providers and 5475 cases by 40 field supervisors covering 1116 volunteers. We conducted qualitative interviews with 8 providers and 8 supervisors in Q1 2023 to understand users' experiences with the new tools and identify future support needs and opportunities for further scale-up. Data were analyzed in a workshop setting. Chatbot approach was favored by users for malaria case notification and surveillance: users preferred chatbots to aggregate reporting on paper. Digital notification was perceived as quick, low-cost, and simple to perform, lowering the record-keeping burden. The chatbots were compatible with almost all phone and tablet models. Saving time, real-time notification and ability to respond confirmed cases for malaria elimination were most mentioned motivating factors. Delayed user registration on the chatbot systems also resulted in missed or delayed case notification. Poor provider digital literacy, internet connectivity, and time limitations were cited as the main barriers of consistent use. The study indicated that private sector can play a crucial role in disease surveillance and innovative digital tools can enhance the effectiveness and timeliness of malaria surveillance efforts in Myanmar. Malaria has been a trailblazer in the use of digital tools for disease surveillance, setting an example for other disease to follow and thus expansion of the system to support horizontal health system approaches appears promising.

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PLANS TO ALIGN MALARIA INTERVENTIONS WITH EPIDEMIOLOGICAL MICROSTRATIFICATION IN MADAGASCAR IN 2023

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Malaria in Madagascar is epidemiologically and geographically heterogeneous, with an average incidence of 56.7 ‰ in 2022. This study examines how the exploitation of microstratification aims to tailor malaria elimination strategies in Madagascar. Routine malaria data disaggregated by districts from 2018-2022 distinguished four epidemiological strata: (i) DNRS4 (District Risk Level 4) or High Risk Stratum (average annual incidence ≥ 100 ‰, for 59 districts); (ii) DNRS3, Moderate Risk Stratum (annual incidence between 50-99 ‰, for 24 districts); (iii) DNRS2, low-risk stratum (annual incidence ranges from 1 - 49 ‰, counting 21 districts); (iiii) DNRS1, very low-risk stratum (persistent annual incidence <1 ‰, in 10 districts). The successful piloting of microstratification with operational decentralization in the three elimination districts has allowed the NMCP to scale up in the new NSP 2023-2027, identifying interventions appropriate to the communes according to their stratum and WHO recommendations: For the DNRS1, decentralized surveillance is a priority to move towards elimination (active investigation around cases with Social Behavior Change to face malaria, entomological and parasitological surveillance, formative supervision); targeted residual insecticide spraying and the distribution of insecticide-treated nets or ITNs as vector control, coupled with integrated management of the environment and monitoring of the resistance of vectors and of parasites. In addition to the interventions in DNRS1, specific activities for the high-risk stratum DNRS4 are identified: passive detection and treatment of cases; ITN in mass and continuous campaigns, preventive treatment of malaria for pregnant women or IPTp; and as an innovation, seasonal chemoprevention Same routine interventions for DNRS 2 and 3, but without SMC. Thanks to microstratification that allowed for targeted and community-based interventions, the 2 eliminating districts have maintained their status and are moving towards elimination (Incidence of 33, 4‰ in 2018 and 57,7in 2022).

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FROM ENDEMIC TO EPIDEMIC: A STRUCTURED DISTRICT LEVEL ASSESSMENT OF MALARIA IN THE ELGON REGION OF EASTERN UGANDA

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With an estimated 5% of global cases, Uganda carries the third largest burden of malaria cases in the world. Despite years of focus on malaria control by Uganda's Ministry of Health and international partners, from 2021 to 2022, the malaria incidence rate increased dramatically from 206 to 271 cases per 1000 population, respectively. We aimed to establish the gaps that exist in malaria prevention, detection, and response in the high burden Elgon region of eastern Uganda, comprising 16 districts and 1 city. We collected data from the Ugandan Ministry of Health District Health Information Software 2 database to identify districts and demographics with the highest incidence of malaria within the Elgon region. We then adapted a structured district assessment tool from an existing WHO malaria surveillance assessment. We used the structured Malaria District Assessment Tool to conduct key informant interviews at the district level to gather both qualitative and quantitative data from district health officers, malaria focal persons, and vector control persons within each high burden

district. We analyzed the qualitative data using immersion crystallization methodology with multiple independent reviewers extracting major and minor themes within the frameworks of prevention, detection, and response capabilities. Within the category of prevention, the main theme extracted was a lapse in vector control strategies. The major themes extracted from the categories of detection and response were lack of logistical support and chemotherapeutics. Of the 10 districts assessed, 7 (70%) had inadequate access to insecticide treated nets, 3 (30%) had no active indoor residual spraying program in place, and 8 (80%) had limited or no rapid diagnostic tests available. The mean (SD) time from last resupply for anti-malarial medications from the central governmental supply was 117 (± 9) days. The extracted themes highlight key areas ripe for intervention to better equip high burden districts in eastern Uganda experiencing a dramatic rise in malaria.

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THE TRAJECTORY OF MALARIA CARE OF CHILDREN UNDER FIVE YEARS WITH FEVER, FROM AN ANNUAL CROSS-SECTIONAL HOUSEHOLD SURVEY WITHIN PROGRAM AREAS OF THE ISDELL:FLOWERS CROSS BORDER MALARIA INITIATIVE IN ZAMBIA

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The Zambia National Malaria Strategic Plan 2022-2026 has the goal of ensuring 100% of suspected malaria cases are tested and 100% confirmed cases are treated within 24 hours with an antimalarial. Achieving this goal relies not only on strong health systems and availability of commodities, but also on proper care-seeking behavior within the at-risk population. This study assessed the trajectory of care of children under five years with fever in the previous two weeks within program areas of the Isdell:Flowers Cross Border Malaria Initiative (IFCBMI), an implementing partner of Zambia's National Malaria Elimination Centre, as reported by caregivers in an annual cross-sectional household survey conducted from May-June 2021 (n=2541) and April-May 2022 (n=1982). From 2021-2022, results showed nonsignificant changes in care-seeking behavior and in provision of malaria tests to children <5 with fever but showed a significant increase in the proportion of children who received Coartem after testing positive for malaria. Specifically, in 2022, 87.6% (84.5% - 90.2%) of respondents whose child <5 had a fever in the previous two weeks sought care for their child from a health facility or community health worker (CHW) but only 65.5% (61.3% - 69.5%) did so within 24 hours of fever onset, compared to 89.7% (- 2.1%, p=0.419) and 65.7% (-0.2%, p=0.935) in 2021, respectively. Among those children <5 with fever who sought care from a health facility or CHW, 88.4% (85.1% - 91.1%) received a malaria test, compared to 86.4% (+2.0%, p=0.251) in 2021. Of those febrile children who were tested, 62.9% (58.3% - 67.3%) tested positive for malaria, compared to 65.9% (-3.0%, p=0.361) in 2021. Of those children who tested positive for malaria, 95.3% received Coartem for treatment in 2022, a significant increase from 87.7% (+7.6%, p=0.002) in 2021. These data comprise part of an annually conducted survey on malaria-related knowledge, attitudes, and practices, utilized by government and local community planners for malaria goal setting. Data to be collected in April-May 2023 will again measure these indicators and assess changes relative to 2022 results.

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COMPARATIVE EFFECTIVENESS TRIAL OF TWO INTEGRATED COMMUNITY CASE MANAGEMENT TECHNIQUES FOLLOWING WITHDRAWAL OF INDOOR RESIDUAL SPRAYING IN NE UGANDA

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In standard integrated community case management (ICCM), caregivers approach community health workers (CHWs) for testing and treatment for malaria in under-5s. Proactive ICCM (ProCCM) expands on iCCM with proactive weekly or biweekly household visits by VHTs and case management for all ages. We present results of a prospective two-year trial comparing the effectiveness of ICCM vs. ProCCM at maintaining malaria reduction or preventing resurgence. Indoor residual spraying with pirimiphos-methyl occured four times in the high-transmission district of Katakwi in NE Uganda, with the final round in December 2018. At trial baseline, all-ages malaria prevalence by microscopy was 10%. In 55 villages in the former IRS area, we performed a community-randomized comparative effectiveness trial of the combination of PermaNet 3.0 deltamethrin- piperonyl butoxide (PBO) long-lasting insecticide treated nets (LLINs) and either ICCM or ProCCM. A total of 27 villages were randomized to iCCM + PBO nets and 28 villages to ProCCM + PBO nets using covariate-constrained randomization. The primary outcome of community-level cross-sectional Pf prevalence measured at baseline, midline and endline. PBO nets were distributed in July 2019, while CHWs were trained in August 2019 and acting to protocol by November 2019. Malaria incidence data was recorded weekly by CHWs in both arms using mobile devices, while arm-specific incidence data from health facilities was collected using village of residence. Entomological adult collections were also performed in 180 observation households. Community level cross-sectional Pf prevalence surveys were conducted at baseline April 2019, midline July/August 2020 (delayed by pandemic restrictions), and at endline August 2021. Even after accounting for seasonal differences, malaria prevalence under IRS protection at baseline increased dramatically to pre-IRS levels (30%) in both arms by study endline. Analysis of surveys found no difference in Pf prevalence between arms, despite increased treatment per capita in ProCCM. In high transmission, the combination of PBO LLINs and ProCCM may not be sufficient to control malaria.

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COMMUNITY PERCEPTIONS OF PROACTIVE MALARIA COMMUNITY CASE MANAGEMENT IN CHADIZA DISTRICT, ZAMBIA

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Zambia has successfully implemented malaria community case management (CCM) through passive and reactive case detection by community health workers (CHW) since 2011. With the goal of malaria elimination, in 2021 the National Malaria Elimination Centre implemented

a trial to measure the impact of proactive CCM (ProCCM) compared to routine CCM on malaria incidence and prevalence in Chadiza District, Eastern Province. ProCCM entails weekly visits by CHWs to all households in a community to identify people with malaria symptoms, offer diagnostic testing, and treat those with positive tests. As part of this trial, we conducted a qualitative midline assessment to describe the feasibility and acceptability of ProCCM. We interviewed 12 CHWs, 6 provincial and district staff, 9 health facility (HF) staff, and 72 community members from 6 ProCCM and 6 routine CCM clusters. All respondent groups preferred ProCCM to routine CCM, reporting it reduces distance travelled to seek care and provides care to people with poor health seeking behavior. Most CHWs and HF staff perceived the intervention arm to have less malaria compared to the control arm. Most community members preferred at least one weekly visit. Six provincial, district, and HF staff and 5 CHWs felt that ProCCM negatively affected CHWs' livelihood, necessitating compensation. Four HF staff reported supervising ProCCM CHWs more frequently than before the trial, which 2 saw as an additional, albeit manageable, time commitment. District and HF staff noted an increase in rapid diagnostic test and artemisinin combination therapy consumption due to ProCCM. Other challenges included long distances covered by CHWs during visits, and the impact of the farming cycle on both households' and CHWs' availability to conduct visits. While these findings suggest that the ProCCM approach is accepted by the community, it requires more time and travel by CHWs compared to routine CCM. Intervention arm CHWs were provided with performance-based remuneration and bicycles after this assessment. Further analysis to assess the effect of remuneration on their performance will provide valuable insights into feasibility.

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ASSESSING MALARIA INCIDENCE IN PROACTIVE COMMUNITY MALARIA CASE MANAGEMENT (PROCCM): A RANDOMIZED CONTROL TRIAL IN CHADIZA DISTRICT, EASTERN PROVINCE, ZAMBIA

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Community health workers (CHWs) play a key role in the malaria control and elimination strategy in Zambia. As part of routine (passive) community case management (CCM), CHWs provide malaria services for persons of all ages seeking care for malaria symptoms using rapid diagnostic tests (RDTs), and treat positive individuals with artemisinin-based combination therapy (ACT). In 2021, we started a two-year cluster randomized controlled trial to determine the additional impact of proactive household malaria symptom screening, testing and treatment (ProCCM) on incidence of malaria. All 4,987 households in 33 intervention arm (IA) clusters began receiving weekly ProCCM household visits in addition to routine CCM; 4,714 households in 33 control arm (CA) clusters continued receiving routine CCM. CHWs in the IA reported weekly home visits via CommCare's mobile platform; CHWs in both arms abstracted weekly malaria data (tests and positive cases) for their clusters from passive CCM in their registers as well as checking health facility (HF) registers for visits by members of their community and reported these in a district health information system 2 (DHIS2) instance. From January-December 2022, 199,269 proactive home visits were conducted in the IA, testing 13,168 patients with malaria symptoms. Over this same period, 30,191 and 33,547 individuals in the intervention and control arms, respectively, were tested for malaria through passive CCM and at HFs. Cumulative malaria incidence for 2022 from all sources of testing was 512 cases per 1,000 population in the IA [ProCCM: 131 per 1K (25.5%); HF: 75 (14.7%); routine CCM: 306 (59.8%)] and 546 per 1,000 in the CA [HF: 101 (18.4%); routine CCM: 445 (81.6%)]. The malaria test positivity rate (TPR) for proactively tested cases in the IA was 26.1%; TPRs for passively tested cases (combined routine CCM and HF) were 33.2% and 39.6% in the intervention and control arms, respectively. Interim results indicate a shift in case management from facilities to communities in the intervention arm. Final trial results will include data through May 2023 and evaluate the intervention impact on parasite prevalence and incidence.

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EXPLORING STAKEHOLDERS' PERCEPTIONS OF THE BIOKO ISLAND MALARIA CONTROL AND ELIMINATION PUBLIC-PRIVATE PARTNERSHIP MODEL: A QUALITATIVE STUDY

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While malaria has historically been a major public health concern on Bioko Island, Equatorial Guinea, considerable progress has been made in recent years, owing largely to the effective implementation of a public-private partnership (PPP) through the Bioko Island Malaria Elimination Project (BIMEP). Knowledge of the opinions of project stakeholders regarding the elements leading to the project's success is scarce. This qualitative study will seek to investigate and better comprehend the perspectives of the various stakeholders participating in the BIMEP and to identify the essential success aspects that can inform future PPP projects for malaria control and beyond. Using a qualitative research design, we will conduct semi-structured interviews with a purposive sample of stakeholders, including representatives from government agencies, non-governmental organizations, private sector partners, healthcare providers, and community members. Data will be collected through in-person and virtual interviews, audio-recorded, transcribed verbatim, and analyzed using thematic analysis. The study will follow ethical guidelines, and all participants will provide informed consent. The analyses will concentrate on key topics, including: (1) the significance of a shared vision and well-defined objectives; (2) the value of strong collaboration and communication among stakeholders; (3) the role of local capacity building and community engagement; (4) the influence of effective project management, monitoring, and evaluation; and (5) the sustainability and scalability of the PPP model. The insights of the study can inform the value of PPP initiatives in global health as viable alternatives to supporting projects and programs.

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A CRITICAL SYSTEM PERSPECTIVE OF MALAWI'S HEALTH SURVEILLANCE ASSISTANTS' NEEDS AND OPPORTUNITIES

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Over the past 50 years, Health Surveillance Assistants (HSAs) have provided an increasing array of community-based health services for the largely rural population in Malawi, including frontline malaria and childhood disease management. Here we present the findings of a rapid assessment conducted at the end of two five-year national strategies—the National Community Health Strategy '17-'22 and National Malaria Strategic Plan '17-'22 for Malawi—aimed at understanding recent progress and describing current HSA program gaps and opportunities from a critical system perspective. In collaboration with the Ministry of Health's National Malaria Control Program and Integrated Management of Childhood Illness departments, in Q4 2022 we purposively sampled 2-3 districts in each region (Southern, Central, and Northern) to represent a range of geographies across Malawi. Within each district, two health centers were selected and for each health center, three village health clinics (VHCs) located in hard-to-reach areas were identified. From these VHCs, 39 HSAs were interviewed to share their views on various aspects of the community health system. Feedback described availability of malaria commodities but chronic stockouts of others for treatment of diarrhea and pneumonia. Similarly, HSAs noted a need for replacement of basic supplies and equipment—frequently rain gear and backpacks—and that shortages of printed registers and forms resulted in omission of key data during reporting, which is primarily paper-based. Supervision and in-service training to build and reinforce skills appeared to be infrequent and inconsistently implemented across districts. Additionally, nearly half of interviewed HSAs resided outside of their assigned catchment areas, compounding more widespread issues with transportation and limiting the hours in which HSAs could provide services. Despite challenges, however, HSAs demonstrated strong commitment to their roles, interest in acquiring knowledge and skills, and willingness to adopt digital tools as solutions—opportunities for further strengthening Malawi's community health system.

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STAKEHOLDER ANALYSIS, IN-DEPTH INTERVIEWS AND COMMUNITY SURVEYS ON EXPANDED ROLES OF MALARIA COMMUNITY HEALTH WORKERS IN CAMBODIA, THAILAND AND VIETNAM

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In the Greater Mekong Subregion, malaria community health workers tasked with promptly detecting and treating all malaria cases to prevent onward transmission are a key component of malaria elimination strategies. As malaria declines, expanding their roles to provide health services beyond malaria is essential to maintain accessible malaria services. Drawing on qualitative data, this study comparatively explores the prospects for role expansion across three countries (Cambodia, Thailand, and Vietnam). Data were collected as part of a multidisciplinary project. Stakeholder analysis, focus groups and interviews with policymakers and implementers, community members, and malaria workers were conducted in forested communities and local health facilities in near elimination settings. Across the sites, malaria workers often undertook various volunteer roles within the primary care system and many were multi-tasking these with agricultural work as their main income-generating activities. Compensation, contribution to and respect from their community, and career advancement motivated workers; however, concerns were raised regarding being overburdened, underpaid or underperforming due to inadequate internet connectivity, digital skills and devices in resource-limited settings. Proximity to malaria services largely influenced the community's uptake, particularly for forest goers who had limited access to alternative health providers. Alignment with health system integration (including politically-advocated guidelines, domestic ownership and local health priorities) has implications for implementation. Findings suggest that a sustainable approach for malaria CHWs requires tailoring their role packages based on local needs and their embedded role as a link between the health sector and the communities, while considering carefully their capacities and support requirements in the last mile towards elimination.

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EXPANDED ROLES OF COMMUNITY HEALTH WORKERS BEYOND MALARIA SERVICES IN THE ASIA-PACIFIC: A SYSTEMATIC REVIEW AND LANDSCAPING SURVEY

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In the Asia Pacific, community health workers (CHWs) are key to malaria elimination. However, support for, and uptake of, malaria services may decrease as malaria declines. To sustain malaria CHW services, expanding their roles beyond malaria and integrating them into the wider primary health system have been proposed. This project aimed to identify and characterize programmes with malaria CHWs in the region, describe the malaria and non-malaria services they provide, and explore programmatic characteristics and enabling factors that lead to effective and sustainable implementation. Searches were conducted in 6 databases, for grey literature, and in bibliographies of retrieved articles, from which data were extracted and analysed using thematic coding and descriptive analysis. To capture unpublished and updated information, a short survey was developed and distributed to national malaria programmes and implementing organizations in the Asia Pacific in 2021-2022. We identified 48 programmes in 18 Asia-Pacific countries with CHWs performing both malaria and non-malaria roles, most commonly provision of health education and direct care services for diarrhea, tuberculosis, and antenatal care/maternal and child health. While the review found limited published evidence of CHW impact on malaria or other disease outcomes, survey responses reveal that programmes often performed M&E and impact assessments internally and for funder reporting without publishing. M&E mechanisms, multi-sectoral stakeholder collaborations, adequate training and consistent supervision were key to effective programme implementation. Meanwhile, adequate policy and funding advocacy, tailored incentive packages, being responsive to target communities, and engaging with local health systems contributed to sustaining provision of health services by CHWs. Self-reported views of programme implementers attributed different strategies to sustainability, either integration of programmes into broader health services or expanding malaria CHW roles beyond malaria, will depend heavily on the primary health care system in each context.

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SUSTAINING MALARIA COMMUNITY HEALTH WORKER PROGRAMS WITH EXPANDED ROLES IN THE GMS: FINDINGS FROM IMPLEMENTER CASE STUDIES

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Throughout the Asia-Pacific region, many countries rely on community health workers (CHWs) to provide care for a range of health needs. In the Greater Mekong Subregion (GMS), Village Malaria Workers (VMWs)

have been essential to malaria elimination strategies. Yet as countries near elimination and the malaria burden declines, the role of VMWs in local health systems and communities is changing. There is a need to expand VMW roles to take on provision of health services beyond malaria. We aimed to understand the process and experience of VMW/CHW role expansion including implementation, financing, policy, and sustainability within the Asia-Pacific region. We documented VMW/CHW programs that included health services in addition to malaria. We conducted 21 key-stakeholder interviews from fifteen programs in eight countries within the Asia-Pacific region. Qualitative interviews were conducted virtually in English, audio-recorded, and findings analyzed using rapid-matrix analysis. Of the fifteen programs, five were government programs, six international non-governmental organization (INGO) programs, and two research programs. Program managers and technical advisors explained expansion processes, challenges, and opportunities. We found that integration can take place in multiple program domains and does not necessarily occur in all domains at once. We identified six entry points for VMW role expansion, including integrated policy and financing, as well as planning, assessments, and research. Operational entry points included the selection, training, and motivation, as well as management, supervision, and monitoring of CHWs. Enabling factors, such as decentralized management structures, health system linkages, namely commodity provision and referral procedures, as well as community engagement and hard to reach areas were also included. While there is not a linear or unique path towards integration, there are key considerations for the policy level, practical implementation steps, as well as enabling factors for countries in the GMS to take into account as they move towards sustainable, integrated VMW/CHWs.

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HIGH BURDEN OF ASYMPTOMATIC MALARIA AND ANAEMIA DESPITE HIGH ADHERENCE TO MALARIA CONTROL MEASURES: A CROSS-SECTIONAL STUDY AMONG PREGNANT WOMEN ACROSS TWO SEASONS IN A MALARIA-ENDEMIC SETTING IN GHANA

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Anaemia remains a serious concern among pregnant women, and thus, it is closely monitored from the onset of pregnancy through to delivery to help prevent adverse maternal and neonatal outcomes. In malaria-endemic settings, continuous low-level carriage of Plasmodium falciparum parasites is common and its contribution to maternal anaemia should not be underestimated. In this study, we evaluated the impact of adherence to malaria control measures (number of antenatal clinics (ANC) attended, supervised intake of sulphadoxine pyrimethamine (SP), and use of insecticide treated bed nets (ITNs)) on asymptomatic malaria and anaemia outcomes among pregnant women on ANC in hospitals in the Central region of Ghana. The study was conducted during two seasons; October-November 2020 (dry season, n=124) and May-June 2021 (rainy season, n=145). Among the women, there was a high adherence to the control measures for both seasons (ANC ≥3 visits; ~82.0%, intake of SP; ~80.0% and ITNs use; ~75.0%). Asymptomatic P. falciparum carriage was high for both seasons (44.4% for the dry season; 46.9% for the rainy season). Correspondingly, the occurrence of anaemia was high for both seasons (57.3% for the dry season; 68.3% for the rainy season) and was strongly predicted by carriage of P. falciparum parasites. Despite the high adherence to ANC protocols, asymptomatic P. falciparum infection was common and contributed to the high burden of maternal anaemia. Our findings emphasize the need for improved control measures that can clear asymptomatic/sub-microscopic P. falciparum infection and protect against malaria-induced anaemia among pregnant women attending ANC in malaria endemic-settings.

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HIGH COMMUNITY HEALTH WORKER USAGE WITH APPROPRIATE MALARIA MANAGEMENT IN A MODERATE PLASMODIUM FALCIPARUM BURDEN REGION OF CHADIZA DISTRICT, ZAMBIA, APRIL-MAY, 2021

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Community health workers (CHWs) are used to improve access to prompt and effective care, in particular malaria community case management (mCCM). We characterized care seeking for fever and malaria case management in Chadiza District, Zambia, in the context of an effectively scaled up mCCM program (1 CHW for ~500 people; >50% of malaria cases reported by CHWs) using a cross-sectional household survey. During a pre-intervention household survey from a trial of proactive mCCM, we randomly selected 33 households in each of 73 of 161 eligible communities. We asked all household members about fever in the past 2 weeks; those reporting fever were asked about healthcare seeking and interventions received. All participants received a malaria rapid diagnostic test (RDT). Weighted population estimates with 95% confidence intervals (CI) were used for all percentages, and chi-squared tests were used to assess significance. Analyses were stratified by age and RDT result. Among 11,185 consenting residents, 8.3% (95% CI 5.8-10.7%) reported fever in the last 2 weeks; children <5 years were most likely to report fever (12.4%, 8.2-16.6). Overall P. falciparum prevalence was 18.9% by RDT (16.4-21.4); prevalence was higher (33.7%, 26.4-40.9) among those with fever in the past two weeks. Care seeking from any source for fever was higher in the younger age groups: 67.3% (59.9-74.8) for children <5 years, 60.1% (52.6-67.6) for children 5-14 years, and 48.6% (38.4-58.7) for those >15 years. Among persons of any age that sought care, 76.2% (67.8-84.6) went to a CHW alone or in combination with another source (e.g., health facility, shop). Those who accessed a CHW were more likely to report receiving a malaria test (89.2%, 85.0-93.5) compared with non-CHW care (73.5%, 63.9-83.0). Of those with a positive RDT, a history of fever, and who sought care, 70.5% (60.2-80.8) reported receiving artemisinin-based combination therapy; percentages were similar for CHW and non-CHW care. Among care seeking participants, CHW usage was very high, and malaria management was appropriate. Further interventions are needed to maximize the percentage of febrile individuals who seek care.

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EVALUATION OF THE MANAGEMENT OF CHILDREN UNDER TEN YEARS OF AGE HOSPITALIZED WITH SEVERE MALARIA AT THE HEALTH CENTER OF TAMBACOUNDA, SENEGAL FROM 2018 TO 2021

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Malaria remains a public health priority in Senegal, particularly in Tambacounda where it is one of the main causes of infant mortality. The objective of this study was to evaluate the management of children under 10 years of age hospitalized at the Tambacounda health center for severe malaria and to identify factors associated with their recovery.A retrospective and descriptive study with analytical aims was conducted. An exhaustive recruitment of children aged 0 to 120 months hospitalized at the Tambacounda health center for severe malaria (with WHO criteria) between January 1, 2018 and December 31, 2021 was performed. Hospitalization records, hospitalization and treatment registers were the sources of collection.We enrolled 481 patients. The highest number of severe malaria cases was recorded in 2018 (33.1%). Peaks were always observed between October and November. The mean age was 65.6 +/- 29.2 months with a female predominance (53.4%). The majority of people were admitted from the outpatient clinic (57.2%) and 42.8% were referred from a peripheral health post. All patients had a positive rapid diagnostic test and/or a thick drop. The thick drop was negative in 5.2% of cases. Fever (88.9%) and vomiting (42.2%) were the most frequent reasons for consultation. Seizures (47.9%) and severe anemia (50.6%) were the most frequent signs of severity. All patients received an artesunate injection. The cure rate was 81.3%, baseline 10.2% and case fatality 5.0%. There was a statistically significant association between cure and no referral to a health post (OR = 1.85). Similarly, death was associated with the presence of at least 2 signs of severity (OR=1.81), seizures (OR=1.51), prostration (OR=2.77), cardiovascular shock (OR=6.67), laboratory signs of severity (OR=3.70), and hypoglycemia (<0.4 g/L) (OR=5.88). According to the NMCP follow-up grid, management was good in 47.8%, acceptable in 41.8%, and poor in 2.1% of cases.Children hospitalized at the health center for severe malaria with coma, prostration, cardiovascular shock and/or convulsions should be systematically referred to the next level to increase their chances of recovery.

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IMPACTS OF CYCLONE IDAI RELATED INFRASTRUCTURE DAMAGE ON MALARIA INCIDENCE IN SOFALA PROVINCE, MOZAMBIQUE

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Increases in the frequency and severity of storms is a hallmark of climate change. Climate change will have impacts on the incidence, prevalence, and geographic range of infectious diseases, particularly malaria and other vector borne diseases. One mechanism for these impacts is through changing the environmental suitability of vector habitats in endemic areas. Another mechanism is through infrastructure damage to households, schools, and healthcare facilities. This infrastructure damage leads to increased risk for interaction with infectious vectors and decreased access to community and health services. We conducted a retrospective study to quantify the infrastructural impacts of Cyclone Idai (2019) in the Sofala Province. As of 2019, Cyclone Idai was the largest tropical storm to make landfall in the southern hemisphere and the range of damage outside of the coastal region is still largely unquantified. We used satellite imagery in Google Earth Pro® to determine the number of schools and healthcare facilities damaged due to Cyclone Idai. We used a database of schools in the central corridor of Mozambique from OpenStreetMap and healthcare facilities from an open-source database of health facilities in sub-Saharan Africa. These databases included 71 schools and 98 healthcare facilities. These databases were supplemented with results from Google Earth Pro® searches. We created a database of damage to these facilities, documenting the severity of the damage (completely destroyed, partially destroyed) and time frame until fully repairing the damage. We spatially joined these to malaria incidence data from 2018 and 2019 to calculate the impact of infrastructure damage in each district on malaria incidence in 2019 and the change in malaria incidence between 2018 and 2019. We also included environmental variables (vegetation, elevation, and river area) and census variables (median age and housing materials) as potential confounders. We found that districts with high infrastructure damage was associated with a lower malaria incidence in 2019 in the aftermath of Cyclone Idai. This is likely due to lack of healthcare access due to this damage.

6842

UPDATING MALARIA RISK MAP OF KENYA BY PRE-SERVICE DIAGNOSIS OF THE MALARIA ASYMPTOMATIC INDIVIDUALS RECRUITED IN THE KENYA DEFENCE FORCES

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Malaria is among the leading causes of morbidity and mortality globally. The World Health Organization (WHO) Malaria Report 2020 estimates 241 million malaria cases in 2019 leading to 627 000 deaths in 87 malaria-endemic countries with Kenya harbouring 3.5 million (1%) and 107,000 (3%) of this burden, respectively. Over 60% of infections with Plasmodium species generate a malarial parasitaemia in the absence of fever or other acute symptoms, therefore regarded as asymptomatic or chronic malaria. This proportion of infections form a major reservoir for malaria transmission hence need to quantify for effective transmission control. The study aim was to conduct a countrywide testing of asymptomatic malaria burden, stop its dispersion among newly accessioned military forces and map the malaria risk across Kenya. Between 2016 and 2021, we conducted a comprehensive malaria testing and treating of healthy individuals comprising at least one per 4 – 5 Km2 land surface of the country, newly enrolled into the Kenya Défense Force (KDF). 12,715 consenting military recruits from 47 counties across Kenya were screened for malaria using both screening and confirmatory test methods between 2016 and 2021; 2,481 (2016), 2,481 (2017), 2,650 (2019), 2,110 (2020) and 3,993 (2021). 490/12715 (3.8%) otherwise healthy individuals tested positive for malaria and were treated. All cases detected were treated with artemether-lumefantrine antimalarial prior to recruit training commencing therefore deterring spread of migrant malaria. Malaria was detected in 46 out of the 47 counties including those where malaria had never been known to occur. Moreover, Marsabit, Baringo, Nakuru and Turkan counties showed 10-fold higher frequency of malaria than previously documented in malaria surveys. Detection of malaria in these otherwise healthy individuals sampled from across the country appear to suggest need to update the overall malaria risk map of Kenya. Successful partnership between the USAMRD-A/KEMRI and KDF demonstrates the value of timely diagnosis and treatment of malaria to prevent the spread of migrant malaria and prevent malaria-related loss time

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LLIN EVALUATION IN UGANDA PROJECT (LLINEUP2) - ASSOCIATION BETWEEN HOUSING CONSTRUCTION AND MALARIA BURDEN IN UGANDA: RESULTS FROM AN OBSERVATIONAL STUDY OF 32 DISTRICTS

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Well-built housing limits entry of mosquitoes and could complement other malaria control interventions to reduce malaria transmission. Evidence supporting the role of housing in malaria control is mounting, but few studies have assessed the community-level impact of modern housing on malaria. To investigate associations between improved housing and malaria burden, data from 64 communities in 32 districts across Uganda were analysed, covering approximately 30% of the country. Surveys were conducted between November 2021 and March 2022 in randomly selected households near health facilities with ongoing outpatient malaria surveillance. Houses were classified as 'improved' (synthetic walls and roofs, eaves closed or absent) or 'less-improved' (all other construction). Outcomes included individual and community-level parasitaemia in children aged 2-10 years and community-level malaria incidence (all ages). Associations between housing and parasitaemia were made using mixed effects logistic regression (individual-level) and multivariable fractional response logistic regression (community-level) and between housing and malaria incidence using multivariable Poisson regression. Overall, 4,893 children aged 2-10 years were enrolled from 3,518 houses (median: 53 houses per site); of these, 1,389 (39.5%) were classified as improved. Children living in improved houses had 58% lower odds (adjusted odds ratio=0.42, 95% CI 0.33-0.53, p<0.0001) of parasitaemia than children living in less-improved houses. Communities with >67% of houses improved had a 63% lower parasite prevalence (adjusted prevalence ratio 0.37, 95% CI 0.19-0.70, p<0.0021) and 60% lower malaria incidence (adjusted incidence rate ratio 0.40, 95% CI 0.36-0.44, p<0.0001) compared to communities with <39% of houses improved. Improved housing was strongly associated with a lower burden of malaria in individual children and communities across a wide range of sites in Uganda and should be utilized as an intervention to control malaria.

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DISTRIBUTION OF MALARIA INFECTIONS AND RISK FACTORS IN SELECTED REGIONS OF TANZANIA WITH VARYING TRANSMISSION INTENSITIES

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Despite recent reduction in malaria morbidity and mortality in Tanzania, asymptomatic malaria cases create a significant reservoir of infections behind transmission. Estimating the burden of the malaria in population and identifying areas with elevated risk is important for targeting malaria control in Tanzania. This study analysed the distribution of malaria infection among individuals in selected villages in Tanzania and identified the risk factors of malaria distribution. A cross-sectional study was conducted in seven from three districts of Tanzania, between May and June 2022. This study involved 1,558 households and 4,379 individuals. Logistics regression model was used to determine malaria infection association and presented using odds ratio and 95% confidence interval. The overall malaria prevalence was 22.2% and a significant high difference in prevalence was observed in Buhigwe district (28.2%, p<0.001). The highest prevalence (30.4%, p<0.001) among villages was observed in Kigege. Age group (5-14) years was of higher risk of malaria infection compared to other groups with significant association (OR: 1.64, 95%CI:1.29 - 2.08, p<0.001). While, females had lower likelihood of being infected as compared to males. Individuals from Lundo village were nine times more likely to have malaria infection as compared to those from Magoda village (OR:9.86, 95%CI:5.65 - 17.20, p<0.001). The analysis of distribution of malaria infections identified risk areas, individuals and related factors for malaria infection. The identified risk factors for malaria infection will facilitate rational use of available malaria control interventions.

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EVALUATION OF THE ASSOCIATION BETWEEN OCCUPATION AND MALARIA PARASITE GENETIC RELATEDNESS IN CAMBODIA

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Cambodia and other countries in the Greater Mekong Subregion (GMS) have experienced a large decline in Plasmodium falciparum cases; however, achieving elimination will require targeted interventions for remaining at-risk groups. Identity-by-descent (IBD) analyses are increasingly being used to study the genetic relatedness between malaria-causing Plasmodium parasites. This study assessed the association between parasite relatedness measured by IBD and occupation (i.e., military member or farmer). We used IBD to estimate genetic relatedness between P. falciparum isolates from uncomplicated clinical malaria cases collected in two Cambodian provinces (Oddar Meanchey and Kratie) from 2014-2016. Whole genome sequencing data was generated from 160 P. falciparum isolates and variants called using an established pipeline. Pairwise IBD between isolates was estimated using hmmIBD. Multivariable regression was used to estimate the association between occupation and relatedness while adjusting for potential confounding by year and collection province. Pairwise comparisons between all isolates indicated a high average proportion of the genome (39%) shared IBD. No statistically significant association was observed between occupation and relatedness after adjustment for collection province (p=0.79, p=0.23). IBD sharing was lower between isolates from different provinces than the same province (p=<0.001), with isolates from different provinces sharing 26% of their genomes on average compared to 46% for isolates from the same province. The significant association between parasite relatedness and province, and lack of association with occupation, indicates that infections in both groups may originate from the same source in each province, suggesting that geographically targeted interventions may be appropriate for both occupation groups. This study combines genomic and traditional epidemiological approaches to gain insight into infection sources. As GMS countries near P. falciparum elimination, similar approaches can be used to identify geographic units or high-risk groups that could benefit from joint interventions.

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COMPARING COMPARTMENTAL MODELS AND STATE SPACE MODELS WITH SPATIAL DYNAMICS. A CASE STUDY OF MALARIA

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Compartmental models and state space models have long been used interchangeably to study different physical phenomena. However, there is limited understanding of the similarities and differences between them, and their limitations in relation to each other. We discuss the two types of models, compare and contrast them with malaria as a case study. A comparative analysis is done for the general forms of the two models. A compartmental model with two patches, three habitats and two strata of human population and a state space model of the same number of

patches, habitats and human strata are presented. Using similar values for the parameters, simulations for the two models are run using appropriate software and the results are compared. Data on malaria cases and mosquito populations from 2017-2019 in Uganda will also be used to validate the two models. It is noted that complexity in a compartmental model increases with heterogeneity and stratification and that a state space model easily adapts to the complexity if the modular formulation is used. It is also noted that a compartmental model can be modified into a state space model. There is room for stochasticity in state space models which would give more reliable output as compared to stochasticity in a compartmental model. A comparison of the output results from the two models is done and it is noted that they are comparable though their difference might lie in parameters such as time at risk which is present in the state space model but not explicitly in the compartmental model. Simulation time for the state space model is shorter than for the compartmental model. Therefore, in terms of increasing complexity with heterogeneity and stratifications, compartmental model becomes too complex to represent and analyze effectively while state space models can accommodate more complex phenomena if the modular formulation is used.

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A MATHEMATICAL MODEL FOR MICROSTRATIFICATION OF MALARIA INTERVENTIONS IN URBAN NIGERIA.

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Malaria remains a major global health problem, with an estimated 247 million clinical episodes and 619 thousand deaths in 2021 Approximately 92% of these incidence cases and 95% of these deaths were observed in Africa, and Nigeria constituted about 30% and 27% of the clinical episodes and deaths, respectively. Nigeria is rapidly urbanizing and without concomitant increase in amenities and resources for planning, urban areas will see a rise in slums and informal settlements with conditions that favor the proliferation of Anopheles mosquito vectors and increased human exposure to malaria vectors. The resultant heterogeneous transmission may hinder Nigeria's achievement of the Global Technical Strategy targets to reduce malaria cases and deaths by at least 90% in 2030. In collaboration with Nigeria's National Malaria Elimination Programme, University of Ibadan, and Osun State University we are developing an agent-based model using the Epidemiological MODeling software (EMOD) to inform the selection of appropriate intervention strategies for malaria control in two Nigerian cities - Kano and Ibadan metropolis. Our model incorporates data from a mixed-methods field study, currently ongoing in our study locations, and Demographic Health Surveys (DHS), intervention distribution schedules from programmatic data, and intervention effect sizes from the research literature. We captured environmental features that may correspond to sub-city heterogeneities in transmission. Each sub-city transmission archetype has the same seasonality. The seasonality is calibrated to the average monthly routine data from the Rapid Impact Assessment surveys (RIA) from 2014 -2021 and this seasonality was assumed for the three major vector species. We capture baseline transmission intensity using malaria prevalence data from DHS at regional level and the predicted Insecticide Treated Nets (ITNS) usage. The ITNS data is estimated from a spatial model to estimate the ITNs usage in each sub-city transmission archetype using the covariates associated with ITNs use.

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HIGH PREVALENCE AND RISK OF SUBPATENT PLASMODIUM FALCIPARUM INFECTIONS IN REGIONS WITH LOW TRANSMISSION INTENSITIES AND THEIR IMPLICATION FOR MALARIA ELIMINATION IN TANZANIA

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Subpatent Plasmodium falciparum infections below the limit of detection of current diagnostic methods (rapid diagnostic tests (RDTs) and microscopy) can potentially contribute to infectious reservoirs that sustain transmission and cause failure of ongoing elimination strategies. This baseline study was conducted in 14 regions of Tanzania with varying malaria transmission to determine the prevalence of and risk factors associated with subpatent P. falciparum infections. The study used 2,685 RDT-negative samples randomly selected from 18,688 dried blood spot (DBS) samples collected in 2021 at 100 health facilities (HFs) in 10 regions and four communities from four additional regions. Parasite DNA was extracted from DBS by Tween-chelex method and Pf18S gene was amplified by quantitative real-time polymerase chain reaction (qPCR). Generalized linear model was used to relate predictors to the risk of subpatent P. falciparum infections. Overall, 524 samples (19.5%) were positive by qPCR, with the positivity ranging from 6.0 to 36.7% across different regions. The median parasite density was 1,030 (IQR=318 – 5,150) copies/µL. Individuals with fever at presentation (axillary temperature ≥ 37.5 °C) had reduced risk of subpatent infections by 67% (OR=0.33, 95% CI 0.25-0.45; $p < 0.001$). Individuals sampled in community surveys had higher risk of subpatent infections than patients enrolled at HFs (OR=3.94, 95% CI 2.60 - 5.97; $p < 0.0001$). Patients from regions with low/very low transmission intensities had significantly higher risk of subpatent infections compared to those sampled from high/moderate transmission regions (OR=2.67, 95% CI 1.87-3.83; $p < 0.0001$). Age and sex did not significantly affect the risk of subpatent infections. The findings show high prevalence of subpatent infections in 14 regions of Tanzania and higher risk of such infections in low/very low transmission regions that are currently targeted for malaria elimination. Thus, more sensitive detection methods are urgently needed to identify carriers of undetectable parasites to effectively guide targeted intervention strategies to support malaria elimination by 2030.

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INCIDENCE RATES OF MALARIA, MENINGITIS AND MORTALITY IN CHILDREN UNDER FIVE YEARS OF AGE IN GHANA AND KENYA PRIOR TO THE ROLL-OUT OF THE MALARIA VACCINE

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Although advances have been made in reducing the global burden of malaria, morbidity and mortality due to the disease remain very high, especially among children less than 5 years of age in sub-Saharan Africa. In 2021, the WHO recommended widespread use of the RTS,S/AS01E malaria vaccine for children living in regions with moderate to high Plasmodium falciparum transmission. This recommendation was based on results from the ongoing Malaria Vaccine Implementation Programme (MVIP) that introduced the RTS,S/AS01E vaccine in selected areas of Ghana, Kenya and Malawi in 2019. Within MVIP areas, several studies are

being conducted by the RTS,S epidemiology group to evaluate vaccine safety, effectiveness and impact. As knowledge gaps on background disease incidence rates may hamper this evaluation, the present study (NCT02374450; EPI-MAL-002 study) was designed to assess incidence rates of malaria, meningitis, death and other health outcomes leading to hospitalisation in children less than 5 years of age enrolled before the implementation of the RTS,S/AS01E malaria vaccine. The same outcomes will be monitored and compared in the post-vaccine implementation safety and impact study (NCT03855995, EPI-MAL-003 study). Final analysis results of the EPI-MAL-002 study conducted in Ghana and Kenya during 2016–2022 are presented here. This analysis includes 23,601 children who were either followed-up through prospective cohort event monitoring (9,041 children enrolled in the 6–12 weeks and 9,854 in the 5–17 months age groups) or through hospital-based disease surveillance (4,703 children). In the 5–17 months age group, the incidence rates of meningitis and cerebral malaria, within an at-risk period of 1 year after a virtual schedule mimicking RTS,S/AS01E vaccination, were both equal to 28 (95% confidential interval [CI]: 9–65) per 100,000 person-years; the all-cause mortality rate was 643 (95% CI: 531–771) per 100,000 person-years. This is the first study to provide a broad assessment of the burden of disease in children less than 5 years of age in Ghana and Kenya including malaria, meningitis and mortality prior to the roll-out of the malaria vaccine.

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USING MORTALITY AUDITS TO IDENTIFY FACTORS INCREASING MALARIA MORTALITY IN KARAMOJA, A HIGH-BURDEN REGION OF UGANDA

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PMI Uganda Malaria Reduction Activity aims to reduce malaria morbidity and mortality in five high-burden regions. According to the Malaria Indicator Survey 2019, Karamoja has the highest prevalence at 34% compared to the national average of 9%, partly because of culture-related resistance to care seeking and high disease transmission. We describe mortality audits at selected health facilities to identify factors leading to malaria related deaths and modifiable factors. HMIS data reviews showed high mortality at six level IV health facilities and district hospitals in Karamoja (September 2022 - February 2023), of which five were selected for a provider survey and mortality audits. Data were collected on perceived and documented causes of deaths, complications, gaps in documentation and reporting, using a survey questionnaire and mortality audit checklist. Excel was used for data collection and analysis. Data were collected from 39 providers and 26 patient file reviews. Most providers were nurses (56.4%) and only 51.3% of providers had received malaria training in the past year. Providers reported “delayed care” (> one day of symptom onset), “delayed referral” (>one day of referral) and severe anemia (Hb ≤ 6 g/dL) as most frequent causes of death. The file reviews showed that 76.9% of patients were children ≤5 years, of which 50% were infants, 46.1% had complications, and 42.3% died within the first day. The median time to death from symptom onset was 6 days (IQR 3.25, 10) and median time from admission to death was 2 days (IQR 1, 3). Gaps identified at the health facility level included delayed referral, lack or delay of clinical investigation, wrong drug or dosage, incomplete patient records and unavailability of blood products for transfusion. Mortality audits are important for identifying factors that lead to high malaria mortality at health facilities. This guides capacity building and behavior change interventions. Our findings highlight the need for community sensitization to improve early care seeking and strengthening clinical practices at primary level and referral facilities through targeted mentorship and supportive supervision.

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PREVALENCE OF FALCIPARUM AND NON-FALCIPARUM MALARIA IN THE 2014-15 RWANDA DEMOGRAPHIC HEALTH SURVEY

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Malaria remains a major cause of morbidity in sub-Saharan Africa despite advances in treatment. Most malaria infections are caused by Plasmodium falciparum. However, evidence suggests that non-falciparum malaria are becoming more common as falciparum rates decline. This is important as first-line therapy for falciparum infection is ineffective against the dormant stages of Plasmodium ovale and vivax parasites. We assessed 4,597 individuals in the 2014-2015 Rwanda Demographic Health Survey (DHS) for asymptomatic falciparum and non-falciparum malaria. Using dried blood spots, (DBS) real time PCR for four species of Plasmodium parasites (falciparum, malariae, ovale, and vivax) was done. Samples (n= 2,255) were drawn from 56 clusters with high malaria prevalence (at least 15% positivity for malaria via rapid diagnostic testing). In addition, a random sample of 2,342 DBS from 401 remaining clusters in lower transmission areas were assessed. Of the 4,597 DBS, 1,233 individuals were positive for P. falciparum, 248 for P. ovale, 168 for P. malariae, and 7 for P. vivax. We are currently determining national and regional malaria prevalence estimates for each species and assessing for associations between DHS covariates and malaria infection. While P. falciparum malaria remains the most common form of malaria in Rwanda, P. ovale and P. malariae cause a significant number of asymptomatic infections. A better understanding of the distribution of P. falciparum and non-P. falciparum infection in Rwanda, as well as risk factors associated with infection, will help the national malaria control program target interventions to reach malaria elimination.

6852

UNDERSTANDING MALARIA BEHAVIORAL RISK FACTORS IN SEASONAL MIGRANT WORKERS IN SELECTED MID-HIGHLAND AND LOWLAND DISTRICTS OF NORTHWEST AMHARA REGION, ETHIOPIA

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The Ethiopia Ministry of Health is aiming for countrywide malaria elimination by 2030. However, population movement represents a challenge for the successful implementation of malaria control and elimination activities. Every year, in Amhara Region, close to 500,000 seasonal migrant workers move from the low malaria-risk highlands to the high malaria-risk western lowlands, seeking work on agricultural farms. This population movement is considered one of the key factors contributing to and maintaining malaria transmission in low-transmission areas. To inform the design of targeted intervention strategies, we conducted a qualitative study to better characterize the risk profiles of seasonal migrant workers, including movement patterns, exposure, and behaviors. Focus group discussions (FGD) and key informant interviews (KII), coupled with direct observations of the livelihood of migrant workers were conducted in both lowlands and

highlands. In total, 6 FGDs with 49 seasonal migrant workers, 24 KIIs with workers, and 18 KIIs with selected key informant stakeholders were conducted. Migrant workers typically start traveling to the lowlands around April/May and return around November/December, coinciding with the peak malaria transmission season. Participants indicated they do not usually travel to the same farm site every year and can work at up to 5 farm sites during the season. The study also found that seasonal migrant workers have high indoor and outdoor exposure to mosquitoes. At the farm sites, they often sleep in small grass shelters with large openings and reported sleeping outdoors and working at night during harvesting. Migrant workers also have limited access to health care services, mainly due to large distances to formal health facilities. Coverage of conventional vector control interventions was found to be low, and the shelters do not have sprayable surfaces, and it is difficult to hang and use nets in them. LLINs are also not useful during harvesting when they work overnight. These results highlight the need for alternative vector control and case management interventions targeted to the needs of seasonal migrant workers.

6853

COINFECTION BURDEN AND RISK FACTORS OF MALARIA AND HELMINTH INFECTIONS AMONG PREGNANT WOMEN IN TANZANIA

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Malaria and helminth co-infection is among the global health public burden. Various studies have reported malaria helminth co-infection targeting school-age children in f Tanzania. However, there is a paucity of data on malaria and helminth co-infection among pregnant women. This study investigated the co-infection burden of malaria and helminth -infections and risk factors among pregnant women in the Morogoro and Geita regions in Tanzania. A hospital-based cross-sectional study was conducted among 559 consented pregnant women from two Morogoro and Geita regions. A pretested se questionnaire was used to collect demographic data and risk factors. Malaria infection was diagnosed by light microscopy, soil-transmitted helminths (STH) were determined by formal-ether concentration followed by microscopy and Schistosomiasis was detected by filtration techniques followed by microscopy. The determination of malaria and helminth parasite intensity was done using WHO standards. The overall prevalence of malaria was 7.2%, Schistosoma mansoni (2.0%), and Schistosoma haematobium (6.3%) while STH was the most common infection at 53.5%. Overall, malaria and any helminth co-infection prevalence was 7.0%, Pf malaria and STH was 5.9%. However, the majority of malaria and helminth infections were of moderate and light intensity respectively. Multivariate analysis revealed younger pregnant women (18-30 years), having primary or no education had a higher risk of malaria infection. In addition, bed net sharing, farmers, primigravidae women, second-trimester attendants, and those lacking malaria knowledge showed similar high risk. On the other hand, unwashed hands, uncovered pit latrines, soil-eating behavior, fishing, and drinking water from wells were associated with helminth infections. This study showed that malaria and helminth co-infection in Tanzania is substantial among pregnant women. Calling for improved targeted efforts in the provision of health education on the preventive and control measures towards malaria and helminths infections among pregnant women.

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NOVEL METHODS TO ESTIMATE THE LIKELIHOOD OF MIXED-SPECIES INFECTIONS AND RELATIVE SPECIES ABUNDANCE IN MALARIA

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Previously neglected human malaria species are gaining greater importance in endemic areas striving for malaria eradication. Because of hypnozoites, Plasmodium vivax and P. ovale sp. Are more resilient than P. falciparum. Evidence of recrudescence from sequestered blood-stage parasites might also render P. malariae a resilient species. Additional challenges are posed by non-human primate transmission reservoirs of P. knowlesi that render the species difficult to control in humans. The occurrence of mixed-species infections has become more evident because of the sensitivity offered by PCR-based diagnostics. However, such infections likely remain undetected by light microscopy since P. falciparum tends to dominate concurrently infecting malaria species. Consequently, light-microscopy results in underestimates of mixed-species infections. Since PCR-based diagnostics are not always available in resource-limited settings, results from light-microscopy can be combined with PCR diagnostics to estimate the distribution of mixed-species infections and the relative abundance of malaria species. As such, we developed a novel maximum-likelihood framework to estimate (i) the distribution of mixed-species infections and (ii) their relative abundance for different sample designs. In a study design in which all P. falciparum(+) infections detected by light microscopy are subjected to PCR, it is possible to derive an explicit maximum-likelihood estimator for the desired quantities. It can be proven that the estimator is asymptotically unbiased, efficient, and consistent. Because it has an explicit form, bias correction can be straightforward. As an illustration, we apply the method to data from India and Kenya. We further discuss generalizations for a variety of sampling designs. The methodology introduced has promising statistical properties to monitor the relative abundance of human malaria species in endemic areas, particularly those aiming for malaria eradication. Importantly, the method per se is also applicable to non-human malaria.

6855

MALARIA TRANSMISSION IN GOLD MINING AREAS, A CHALLENGE TO OVERCOME IN THE BRAZILIAN AMAZON REGION

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It is widely known that mining activities lead to deforestation, an increase in Anopheles breeding sites and close contact between humans and vectors, promoting an increase in the malaria burden, as observed in the Brazilian Amazon. The state of Pará showed a 7% increase in malaria cases in 2022. Cases associated to gold mining areas increased by 7%. We collected 238 blood samples and 306 Anopheles in Jacareacanga, a municipality located in the southwest of Pará with an Annual Parasitic Index of 1,101. After informed consent, a form was applied to study participants. Thick blood smear (TBS) showed a positivity of 57%, with 77% diagnosed as Plasmodium vivax, 22% as P. falciparum and one mixed infection. Among 98 samples tested by RDT, 11.2% were positive, with parasitemias ranging from 240-1440 p/microliter. TBS revealed 11.5% of positive samples among those negatives by RDT. All P. falciparum infections were treated with ACTs, according to the Brazilian guidelines. As for treatment for P. vivax, 80% received chloroquine plus primaquine and 15.6% ACTs plus primaquine, due to the short period of time since the last malaria episode

(15-60 days), suggesting disease relapse. Asymptomatic infections were detected in 11.3% of the subjects according to TBS, all due to P. vivax. PCR and genomic analyzes are ongoing. Prophylactic measures including repellents, bed nets or any other, were reported by 44.5% of the patients and 57% of negative individuals. Regarding the place of infection, 75.4% were infected in gold mining areas, 17.3% in urban areas and 7.3% in rural areas. Mosquitoes collected indoor and outdoor were identified as An. darlingi (53.6%), An. triannulatus (27.1%), An. nuneztovari (13.4%) and other An. species (5.9%). Results highlight the impact of gold mining activities on malaria transmission not only in the mining sites, but also in the surroundings of the urban area, due to displacements between these regions. The interviews conducted with gold miners revealed poor adherence to the prescribed treatment, as well as the practice of self-medication due to illegal access to antimalarials. Increasing surveillance and health education is essential.

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PREVALENCE OF MALARIA AMONGST CHILDREN UNDER FIVE AND ASSOCIATED FACTORS IN SUB-SAHARAN AFRICA: A POOLED ANALYSIS COVERING 33 COUNTRIES, 2000 - 2022

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Morbidity and mortality due to malaria are of public health concern in Sub-Saharan Africa (SSA). Household, maternal, paternal and environmental factors have been implicated in high malaria. We determined the prevalence of malaria and associated factors amongst children under five years in SSA using data over a 12-year period. Geospatial covariate data and women 15-49 age population dataset were downloaded from the Demographic and Health Survey (DHS) and World Bank data Repository for 33 SSA countries from 2000 to 2022. The final appended and merged dataset was denormalized and sampling weights applied. Logistic regression was used to determine the association between malaria and exposure variables across household, maternal, paternal and environmental factors. The majority of data were from West Africa 53.9% (12,442/509,087) with overall malaria prevalence of 23.2%. Compared to urban areas, children living in rural areas had 1.24 times odds of malaria (aOR = 1.24, 95% CI [1.11 – 1.39]). Children born in households with at least one other wife were 1.11 times more likely to experience malaria compared to their counterparts (aOR = 1.11, 95% CI [1.03 – 1.19]). Compared with households with mothers with no mobile phones, children in households with mobile phones had 0.88 times less likelihood of experiencing malaria (aOR = 0.82, 95% CI [0.82 – 0.94]). Children born to women currently working and fathers with higher level of education were 1.23 times more likely to have malaria respectively (aOR = 1.23, 95% CI [1.15 – 1.33], aOR =1.23, 95% CI [1.05 – 1.43]). Children of mothers with higher education had 0.69 times reduced odds of malaria compared to those with mothers with no education. An episode of drought was associated with a 4-percentage point decrease in malaria prevalence (aOR=0.96, 95% CI [0.51 – 0.982]). Residence, households with more than one wife and mobile phone, mothers working status, mother and fathers' education status, and episodes of drought were associated with malaria prevalence among children under 5 in SSA. We recommend integrated approaches to malaria control considering all categories of associated factors.

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SEVERE HAEMOLYSIS DURING PRIMAQUINE RADICAL CURE OF PLASMODIUM VIVAX MALARIA: TWO SYSTEMATIC REVIEWS AND INDIVIDUAL PATIENT DATA DESCRIPTIVE ANALYSES

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Primaquine (PQ) kills Plasmodium vivax hypnozoites but can cause haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. We did two systematic reviews: the first used data from clinical trials to determine the spectrum of definitions and frequency of haematological serious adverse events (SAE) related to PQ treatment of vivax malaria. The second used data from prospective studies and case reports to describe the clinical presentation, management and outcome of 'severe' PQ-associated haemolysis necessitating hospitalisation. In the first review, SAEs were reported in 70 of 249 clinical trials. There were 34 haematological SAEs amongst 9,824 patients with vivax malaria treated with PQ, 9 of which necessitated hospitalisation or blood transfusion. Criteria used to define SAEs were diverse. In the second review, 21 of 8,487 articles screened reported 163 patients hospitalised following PQ radical cure; 79.9% (123/154) of whom were prescribed PQ at ≥0.5mg/kg/day. Overall, 101 patients were categorised as having probable or possible 'severe' PQ-associated haemolysis, 96.8% of whom were G6PD deficient (<30% activity). The first symptoms of haemolysis were mostly reported on day 2 or 3 (45.5%) and all patients were hospitalised within 7 days of PQ commencement. 57.9% (77/133) of patients had blood transfusion. Seven (6.9%) patients with probable or possible haemolysis died. Even when G6PD testing is available, enhanced monitoring for haemolysis is warranted following PQ treatment. Clinical review within the first 5 days of treatment may facilitate early detection and management of haemolysis. More robust definitions of severe PQ-associated haemolysis are required.

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TRENDS OF MALARIA PREVALENCE AND ASSOCIATED RISK FACTORS AMONG SCHOOL AGE CHILDREN IN MAINLAND TANZANIA: CROSS-SECTIONAL SURVEYS FROM 2015 - 2021

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In most countries, including Tanzania, malaria surveillance efforts categorize vulnerable populations as children under-five years and pregnant women. Moreover, as they represent approximately one-third. of the general

population and often exhibit a low uptake of insecticide treated nets; schoolchildren play an important role as a plasmodium reservoir and mostly asymptomatic though still have patent infections. Lack of appropriate strategies targeting this age group masks or slow down elimination efforts. The School Malaria Parasitaemia Survey (SMPS) implemented biennially conducted from 2015 till 2021, covering 890 public primary schools, 241,670 schoolchildren in all 184 councils in 26 regions of mainland Tanzania, was designed to provide understanding on the landscape of malaria profile for school children to guide designing locally-appropriate interventions. This work assessed malaria prevalence trends and associated risk factors in mainland Tanzania. Generalized linear modelling was conducted to determine factors associated with malaria prevalence across survey rounds and temporal trends. We found statistically significant reductions in malaria prevalence in 2017, 2019 and 2021 by 32%, 39%, and 52% respectively compared to baseline (2015). Asymptomatic malaria carriage was associated with age (p=&lt0.001) and inversely associated with elevation (p=0.001) whereby schoolchildren living in areas below 750m above sea level (asl) had a malaria prevalence of 23% (2015) which dropped to 12.3% (2021) compared those living in areas above 1750 m asl with malaria prevalence reduced from 4% (2015) to 0.4% (2021). Malaria prevalence was higher among children with a fever history (AOR=1.32, CI: 1.26-1.38, p=0.001) in 2015 and (AOR=1.65, CI=1.47-1.85, P=0.001) in 2021. Sleeping under a mosquito bed net had a protective effect across the four survey rounds in 2015, 2017, 2019, and 2021 with the AOR reduction risk estimated at 33%, 26%, 20%, and 44% respectively against children not sleeping under nets. Our results highlight the benefits of SMPS in providing more granular insight into malaria infection trends by age and region.

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MOLECULAR SPECIATION OF PLASMODIUM FROM THE TWO LARGEST POPULATION CENTERS OF CAMEROON

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Cameroon is one of 11 WHO-designated high burden to high impact countries and home to a diverse ecology described as a microcosm of sub-Saharan Africa. Although Plasmodium falciparum is the dominant circulating species, little is known about the prevalence of non-falciparum species due to the poor sensitivity of rapid diagnostic tests and microscopy in detecting minor species. We used molecular methods to speciate samples collected from six sites across the greater Douala and Yaoundé areas, the two main urban centers in Cameroon. Around Douala, samples were collected from symptomatic patients from the regional military hospital, Nylon district hospital, a private hospital (Hôpital des sœurs), and Ndogpassi district medical center, with additional sampling of community members on the rural island of Manoka. Around Yaoundé, samples were collected from symptomatic patients at Chantal Biya Foundation district hospital. All samples underwent speciation using the same, well-established nested PCR protocol. Approximately 50% of participants were women, and ages ranged from 3 months to 86 years old (mean 25 years, SD 20 years). Amongst all samples (n=831), 54.8% were positive for a Plasmodium species. Amongst the positive samples, 89.5% were P. falciparum mono-infections, 1.3% were P. malariae mono-infections, 0.7% were P. vivax mono-infections, 0.4% P. ovale were mono-infections, and 8.1% were P. falciparum mixed species infections. P. vivax positive samples (n=19) are currently being sequenced and data will be reported. These results demonstrate the circulation of four major human malaria parasites in the two most populated centers in Cameroon. All four parasites were detected among symptomatic patients at hospitals in Douala and on the island of Manoka. At a single hospital in Yaoundé, all species aside from P. ovale were detected. The presence of non-falciparum malaria, and P. vivax in particular, highlights the need to revisit current diagnostic and treatment algorithms in Cameroon in order to ensure appropriate case management and continue progress towards elimination.

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REDUCTION OF MALARIA CASE INCIDENCE FOLLOWING THE INTRODUCTION OF CLOTHIANIDIN-BASED INDOOR RESIDUAL SPRAYING IN PREVIOUSLY UNSPRAYED DISTRICTS: AN OBSERVATIONAL ANALYSIS USING HEALTH FACILITY REGISTER DATA FROM COTE D'IVOIRE, 2018-2022

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Indoor residual spraying (IRS) using neonicotinoid-based products (clothianidin and clothianidin combined with deltamethrin) was deployed for the first time in two districts of Côte d'Ivoire in 2020 and 2021 to complement standard pyrethroid insecticide-treated nets. This retrospective observational study is among the first to assess the impact of neonicotinoid-based IRS on malaria case incidence. Health facility malaria case data were abstracted from consultation registers for September 2018-April 2022 in two IRS districts and two control districts that did not receive IRS. Community health worker-reported cases confirmed by rapid diagnostic test were obtained from district reports and DHIS2. Health facilities missing registers for >3 months each year were excluded. Controlled interrupted time series models were used to estimate the effect of IRS on monthly all-ages population-adjusted confirmed malaria cases and to estimate cases averted by IRS. Models controlled for climate, transmission season, proportion of confirmed cases reported by CHWs, proportion of confirmed out of suspected cases, and non-malaria outpatient visits. The estimated mean annual malaria incidence over 24 months pre-IRS was 308.2 cases per 1,000 population in control areas, and 420.8 in IRS areas. The month after 2020 IRS deployment, incidence decreased by 26.7% (IRR=0.73, 95%CI=0.59-0.92) in IRS areas and increased by 16.1% in control areas (IRR=1.16, 95%CI=0.97-1.39). An estimated 64.1 cases per 1,000 population (95% CI=34.1-104.5) were averted in IRS areas over 12 months post-IRS. After IRS in 2021, incidence in IRS areas immediately decreased by 37.2% (IRR=0.63, 95%CI=0.47-0.84), and increased by 12.6% in control areas (IRR=1.13, 95%CI=0.89-1.42). Over 8 months post-IRS, an estimated 82.4 cases per 1,000 (95% CI=76.9-86.78) were averted in IRS areas. The difference in incidence change between IRS and control areas was significant both years (P<0.05). Neonicotinoid-based IRS appeared to substantially reduce malaria case rates following campaigns in 2020 and 2021 and remains a priority intervention of the Côte d'Ivoire National Malaria Program.

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URBAN AND PERI-URBAN MALARIA: NEW EPIDEMIOLOGICAL LANDSCAPE OF MALARIA TRANSMISSION IN VENEZUELA

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Malaria epidemic epicenter in Venezuela is the mining regions south of the Orinoco River, where illegal gold mining and associated deforestation have rapidly increased and expanded over the last decade in southern Venezuela. Recent interventions by international agencies to control this epidemic have focused their efforts on the areas of highest transmission, but local internal migration generated by mining has led to a resurgence of this disease in other urban and peri-urban areas where viable anopheles vector populations exist. We conducted a cross-sectional study with data on diagnosed malaria cases from the main sentinel site of Ciudad Bolívar between 2019-2023. Out of 1,297 patients analyzed, 1,082 (83.4%) had P. vivax, 131 (10.1%) P. falciparum, and 84 (6.5%) had mixed malaria (P. vivax/P. falciparum) infections. A total of 588 (45.3%) cases were related to illegal mining. The main non-mining malaria occupations were heads of household (n = 210, 16.2%), agriculture/livestock (n = 116, 8.9%), and workman (n = 85, 6.6%). The median age was higher in the non-mining group compared to the mining group (33 vs. 30, p = 0.006). In the mining group, there was a higher predominance of men than in the non-mining group (72.3% vs. 51.8%, p < 0.001). The median P. vivax parasitemia were significantly higher in the mining group compared to the non-mining group (3,700 vs. 3,175, p = 0.001). The probable area of infection in the non-mining group was concentrated mainly in urban and periurban parishes of Angostura del Orinoco municipality (n = 273, 41.9%), such as Marhuanta (n = 125, 19.2%). In contrast, the most frequent probable area of infection in the mining group was Sifontes municipality (n = 255, 45.4%), mainly in the Dalla Costa parish (n = 171, 30.4%). Malaria not related to illegal mining represents the majority of the cases studied, therefore, our results provide sound evidence of autochthone malaria transmission in peri-urban and urban areas in southern Venezuela. In the transition towards the elimination of malaria in the Americas, urban or peri-urban malaria can become an epidemiological scenario that is not expected but at the same time difficult to combat.

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REDUCING MALARIA CAUSED ABSENTEEISM AMONG ORPHANS AND VULNERABLE CHILDREN IN CAMEROON: A CROSS SECTIONAL STUDY AMONG TEACHERS AND CAREGIVERS

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Malaria is a major cause of morbidity and mortality in Cameroon, especially among children. It has a direct impact on efforts to improve education, protection, and socio-economic outcomes among children living with and affected by HIV, their caregivers, and families.Catholic Relief Services (CRS), along with national partners, identified malaria as a leading cause of school absenteeism in efforts to provide educational subsidies to improve educational access, progression, and completion. CRS conducted a baseline cross-sectional study from February 2022 to December 2022 to determine patterns of malaria among OVCs (orphans and vulnerable children) and its impact on school attendance and other proximal factors. The study had two concurrent arms. The first arm of the study enrolled educators and 18 schools (10 public, 5 private religious, and 3 private seculars) located in the same six health districts (catchment areas). Among the 18 schools enrolled, 41% of absenteeism in school was due to suspected malaria cases and 55% of absenteeism lasts between 3-5 days. The study found a positive association between malaria and school absenteeism. Analysis shows that there is a statistically significant relationship between malaria prevalence and school absenteeism among OVCs [OR 6.18, 95% CI 5.79-6.57]. Qualitatively, 89% of teachers witnessed cases of suspected malaria amongst pupils and 83% said it had an impact on educational performance. The second arm of the study enrolled 1,318 children among 524 OVC households and in the same six health districts to determine the proximal impact of malaria and HIV status. Among caregivers of OVCs living with HIV, 69% reported malaria-HIV coinfection worsens illness and 22% reports it affects HIV drug adherence. Adjusted incidence of malaria-caused absenteeism by OVC status will be presented. These results suggest that expansion of OVC-support agents to test for malaria will help further the education subsidies provided to OVCs and the need to and improve coordination with community health workers to provide malaria case management services within schools.

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EPIDEMIOLOGICAL CHARACTERISTICS OF MALARIA PARASITES IN SOKOTO STATE, NORTHWEST NIGERIA

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Community malaria surveys provide data on malaria epidemiology and dynamics of transmission for monitoring given interventions being deployed. This study was undertaken to determine the epidemiology of malaria in three communities of Sokoto state namely: Doruwa, Kambama and Kwargaba, Sokoto State, Nigeria. It was a cross-sectional community-based survey involving 689 participants. Malaria parasitaemia was by light microscopy using standard protocol. Participants were of the age group 5-10 years 216 (31.8%), 11-15 years were 124 in number representing 18.3% and >20 years were 227 (33.4%). Age groups 16-20 years, 63 (9.3%) were the least participants in the study. About 51 (7.55%) of participants had axillary temperature >370C while 627 (92.7) had axillary body temperature <37.50C (P=0.000). Our findings shows that malaria prevalence by microscopy was 19.7%. Overall malaria parasite geometric mean density was 988.82/µL of blood (range 16-71220) with P=0.138 based on Kruskal Wallis test. Parasite intensity stratification based on <1000, 1000-4999 and >5000 were 72(57.1%), 37(29.4%) and 17(13.5%) respectively with P=0.454 based on Pearson's Chi square. On parasites speciation, the following were enumerated: Plasmodium falciparum 103 (76.3%), P. malariae 4 (3.0%), P. ovale 4 (3.0%), P. falciparum + P. malariae 14 (10.4%), P. falciparum + P. ovale 1 (0.7%). Across the three communities, P. falciparum as the predominant species detected, 103(76.3%). Also, Gender was not statistically associated with malaria (P=0.758; 0.197) although males 62 (20.3%) had more malaria than females 53 (15.5%). Malaria is hyper-endemic in these communities requiring concerted interventions for intentional burden reduction.

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RECURRENT DE NOVO MUTATION CONTRIBUTES TO DRUG RESISTANCE EVOLUTION IN PLASMODIUM FALCIPARUM

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Effective malaria elimination requires an understanding of how resistance mutations arise, establish, and spread in parasite populations. Drug resistance in the malaria parasite Plasmodium falciparum has recurrently evolved first in Southeast Asia and South America, geographic regions with low transmission. Retrospective genetic analyses found causal mutations on multiple distinct genomic backgrounds in both these regions, suggesting that recurrent de novo mutation may drive resistance emergence. In real time, such repeated mutational events are challenging to detect and track as they evade most genomic surveillance methods. Here, we tailor a selection testing framework to the specific scenario of recurrent de novo mutation. To circumvent the high background relatedness of small, inbred parasite populations, we employ identity-by-descent analysis to define haplotype blocks, track recombination events, and identify targets of both hard and soft sweeps. Once haplotypes are defined, we identify de novo mutations shared among multiple distinct haplotypes. We apply the approach to two whole-genome data sets: recent data from over 800 P. falciparum blood-stage infections sampled from the Guiana Shield of South America and Southeast Asian parasites previously sequenced by the MalariaGEN consortium. In recent decades, both parasite populations experienced strong selection and phenotypic adaptation due to changes in drug usage, diagnostic/treatment rates, and vector habitat availability. We use previously identified resistance-associated alleles (Kelch13 C580Y and CRT C350R) as benchmarks and find additional candidates of recurrent de novo mutation in other resistance-associated genes. Overall, the results support the hypothesis that small Plasmodium populations are not mutation-limited, as the same de novo mutations appear on distinct haplotypic backgrounds. This observation should inform the methods used to monitor, track, and contain emerging drug resistance.

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MOST ABUNDANT PLASMODIUM FALCIPARUM GENE TRANSCRIPTS IN THE BLOOD OF KENYAN CHILDREN WITH ACUTE MALARIA

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Human malaria remains a leading global cause of morbidity and mortality. Severe and fatal malaria are predominantly caused by Plasmodium falciparum. As blood-stage parasites play a central role in disease severity, P. falciparum gene expression was measured in whole blood from children (3-36 months, n=60) who presented at hospital with acute malaria and varying parasite densities. Next-generation sequencing was performed at a depth of >20 million mappable reads using an Illumina NovoSeq platform and mapped to a Kenyan isolate reference genome (pfKE01) using HTSeq. This identified ~3200 distinct P. falciparum transcripts when each sample was normalized as transcripts per kilobase million. Subsequent analysis revealed that the top 15 most abundant transcripts accounted for 41.0%±18.2% (mean±SD) of the total parasite transcripts. Specifically, a small nuclear RNA (snRNA) encoded by PfKE01_110041500:snRNA, a critical component of the spliceosome, ranked the highest (22.2%±6.7%). The remaining 14 transcripts were mRNAs for P. falciparum proteins in several categories: (i) early transcribed membrane proteins (ETRAMP11.2, ETRAMP2, ETRAMP11.1, ETRAMP14, ETRAMP10, and ETRAMP5), located at the parasite-host interface, (ii) histidine-rich proteins (HRP2, HRP3, and MAHRP1), (iii) ring-infected erythrocyte surface antigen (RESA/Pf155), (iv) skeleton-binding protein 1 (SBP1), a conserved Plasmodium protein, and (v) heat shock protein 70 (HSP70) family members. SBP1 has been shown to be crucial in loading PfEMP1 onto the P. falciparum-infected erythrocyte surface, and both Pf155 and PfHSP70 were demonstrated to protect the parasites from thermal insult and facilitate survival during febrile episodes. Moreover, widely used malaria rapid diagnostic tests are designed to detect PfHRP2/PfHRP3 in patient blood samples. Studies in P. vivax suggest that ETRAMPs may be promising malaria vaccine candidates. Identification of highly expressed P. falciparum transcripts in children with acute malaria highlights potential therapeutic targets and vaccine candidates for improving clinical outcomes in the ongoing fight against malaria.

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GENETIC DIVERSITY OF PLASMODIUM VIVAX IN HIGH-RISK MALARIA AREAS IN CORDOBA, COLOMBIA

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Plasmodium vivax is the most widely distributed species of human malaria, causing significant morbidity worldwide. The genetic diversity of P. vivax populations is an important factor in the epidemiology, pathogenesis, and transmission of malaria. The Pvmsp3α gene is one of the most polymorphic genes in P. vivax, and its variability has been used to study the genetic diversity of this species. In this context, PCR-RFLP analysis of the variable region of the Pvmsp-3α gene has emerged as a useful tool to investigate the genetic diversity of natural populations of P. vivax parasites.The genetic diversity of natural populations of P. vivax parasites in areas of high malaria risk in Córdoba-Colombia was studied by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) of the variable region of the Pvmsp-3α gene. A total of 125 whole blood samples were collected on filter paper from patients with P. vivax residing in the municipalities of Tierralta and Puerto Libertador.Samples confirmed as P. vivax were subjected to PCR-RFLP for the Pvmsp-3α gene, the restriction enzymes used were Alu I and Hha I. Of the 125 samples analyzed by nested PCR for the Pvmsp-3α gene, 116 amplified successfully, confirming molecularly in these samples the single infection by P. vivax. The size of the PCR products of the Pvmsp-3α gene showed the circulation of three different genotypes, type A (1900 bp), type B (1500 bp) and type C (1100 bp), with genotype A being the most frequent (88%). 97.4% (113/116) of the samples showed single infections and 2, 6% (3/116) polyclonal infections, one by types A and C and two by types A and B. Digestion of the PCR products of the Pvmsp-3α gene with the Alu I enzyme showed 10 different restriction patterns and 9 with the Hha I enzyme. The results of the enzymatic restriction of the 113 samples analyzed revealed that 40/113 (35.3%) and 47/113 (41.6%) of these samples, showed polyclonal infections when digested with Alu I and Hha I enzyme, respectively.The Pvmsp-3α gene exhibited high polymorphism and the results suggest that this gene can be used in Colombia as an epidemiological molecular marker for P. vivax genotyping.

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GENOME-WIDE SINGLE NUCLEOTIDE POLYMORPHISM (SNP) ANALYSIS OF PLASMODIUM FALCIPARUM DRUG RESISTANCE-ASSOCIATED LOCI IN AREAS OF DIFFERENT MALARIA ENDEMICITY IN TANZANIA

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Genetic diversity of Plasmodium falciparum drives its ability to adapt environment changes, develop resistance to antimalarial drugs, and evade the host immune response; these enable the parasite to continue to persist despite massive intervention. Understanding the P. falciparum genetic diversity across populations of different malaria transmission is critical for the implementation of new strategies to eliminate malaria in Tanzania. A total of 300 samples were collected between May 2014 and January 2015 from three districts of Tanzania (Muheza – a low, and Muleba and Nachingwea – both high transmission areas) as part of the MalariaGEN Community Project. High-quality SNPs retained after quality checks were analyzed for the complexity of infections, population structure, and signatures of selection. The complexity of infections was different across the study population, ranging from 0.2 (most polygenomic) to 1.0 (monogenomic). Based on principal component and identity by state analyses, P. falciparum populations clustered into a single cluster with no significant population structure. Genome-wide analysis showed a signature of differential selection on positions of genes for drug resistance-associated loci. The highest density of selection was observed in chromosome 7 around the chloroquine resistance transporter (Pfcrt) locus in all populations. While highest density for dihydrofolate reductase (Pfdhfr) and dihydropteroate synthase (Pfdhps) loci around chromosomes 4 and 8 respectively were observed in Muheza and Muleba compared to Nachigwea. The signature of selection was also observed in the immune-related locus Pftrap around chromosome 13 of P. falciparum from Muheza and Muleba. These results suggest that drugs and immune pressure are dominant selective forces against P.falciparum in Tanzania but their effect on the parasite genome varies geographically. Thus, interventions interacting with these genome variants need to be monitored as malaria elimination strategies are implemented.

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IMPACT OF PLASMODIUM FALCIPARUM INFECTION ON DNA METHYLATION OF CIRCULATING IMMUNE CELLS

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Epigenetic modifications are known to regulate cell phenotypes during the course of infection. However, it remains largely unknown whether epigenetic modifications play a role in the host immune response in human malaria. In this study, we investigate the dynamics of genome-wide in vivo DNA methylation profiles of 66 children in Burkina Faso, West Africa, sampled longitudinally before infection, during symptomatic Plasmodium infection, and after malaria treatment (n = 189 genome-wide DNA methylation profiles). Temporal analysis of the data revealed major and statistically significant changes in the epigenetic profiles of children in response both to infection and treatment and identified differentially methylated probes and regions (FDR<0.01). The analysis revealed a widespread hypomethylation of CpGs upon infection that revert back to before infection state following malaria treatment. The significant methylation changes observed implicate divergence in core immune processes including regulation of lymphocyte, neutrophil, and myeloid leukocyte function. Integrative DNA methylation-mRNA analysis of the top most differentially methylated regions revealed a statistically significant association between transcript abundance of the master pro-inflammatory gene TNF and the methylation profiles of CpGs within the gene. These results indicate a link between hypomethylation and inflammation during the symptomatic parasitemia stage. Also, our results highlight the role methylation plays in modulating the host response to malaria infection and suggest a central role of epigenetic factors in mounting immune response in human malaria.

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MICROSATELLITE CHARACTERIZATION AND ANTIGENIC SEQUENCING OF PLASMODIUM FALCIPARUM FIELD ISOLATES FROM KENYA, PERU, AND THAILAND FOR DOWN SELECTION OF A NEW STRAIN FOR USE IN CONTROLLED HUMAN MALARIA INFECTION STUDIES

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The development of an effective malaria vaccine would be monumental in helping control and eliminate malarial infections, which are a global risk to human health. Due to the low efficacy of the current malaria vaccines, it is essential that challenge strains used during vaccine and drug trials accurately reflect the genetic diversity of Plasmodium falciparum strains in the field. Currently, only four Pf strains are being used as challenge strains during Controlled Human Malaria Infection (CHMI) studies that test vaccine and drug efficacy. To identify additional potential challenge strains for future use in CHMI studies that reflect the genetic diversity present in the field, we are receiving blood samples from subjects infected with P. falciparum from clinical sites in Peru, Kenya, and Thailand. To date, eighty-six isolates have been received from the three sites. Pf strains from these samples are in various stages of culture adaptation and many have been genetically characterized by both microsatellite analysis of twelve loci and Sanger sequencing of the antigenic genes PfCSP, PfAMA1, PfMSP1, and PfMSP2. In total thus far, forty-four different strains have been identified between all isolates, assayed via microsatellite analysis, and sequenced. All strains thus far are genetically distinct from 3D7 and 7G8, the current strains used for CHMI studies. In addition, strains appear to cluster with other previously sequenced geographically similar strains based on genetic distance matrices constructed from sequencing data obtained from NCBI and the recently released Pf7 database. These strains will ultimately be compared against new isolates, tested for drug susceptibility and gametocyte formation, optimized for infection of mosquitos, assayed for liver cell infectivity, and considered for future P. falciparum strains in CHMI trials.

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GENETIC DIVERSITY OF PLASMODIUM FALCIPARUM RETICULOCYTE BINDING HOMOLOGUE-5 (PFRH5) IN REGIONS OF DIFFERENT MALARIA TRANSMISSION IN TANZANIA

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Recently, the Plasmodium falciparum reticulocyte binding-like protein homologue family (PfRH) specifically the pfrh5 gene has been the focus of vaccine development as it is a key determinant of erythrocyte invasion. However, little is known about the extent of genetic variability of pfrh5 gene in P. falciparum isolates from areas of varying transmission intensity. This study assessed the genetic diversity of pfrh5 gene by testing the hypothesis that the pfrh5 gene locus is conserved in regions of different malaria endemicity in Tanzania. A total of 300 whole genome sequences generated from samples collected between May 2013 and January 2014 from three districts in Tanzania (160 in Muheza, 61 in Muleba and 79 in Nachingwea) were retrieved from MalariaGEN project Database. Bioinformatic tools were used to study within-host diversity, evidence of natural selection, population differentiation and structure. Results showed high within-host diversity (Fws<0.95) in Muleba (42.6%) compared to Nachingwea (39.2%) and Muheza (36.9%). Nucleotide diversity in the pfrh5 gene was high in Muleba (0.00102) compared to Muheza (0.00096) and Nachingwea (0.00049). No evidence of genetic diversity in the pfrh5 gene was observed

across all the districts (Fst mean = 0.00238). Tajma`s D analysis was done to look for signatures of selection and showed direction selection in both Muheza (-1.055) and Nachingwea (-0.676) while Muleba showed neutrality (Tjd= 0.151). More analysis is under way to map the diversity of the pfrh5 gene in all the districts. The preliminary results reveal low levels of genetic variation in the pfrh5 gene across the districts, these results correspond to the findings from previous studies conducted in 2020 in Nigeria. However, a broader investigation is required in some other parts of the country to support the potential of pursuing pfrh5 gene as a malaria vaccine antigen.

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POPULATION GENOMICS OF PLASMODIUM FALCIPARUM AND MALARIA CONTROL: IMPLICATIONS IN ABIDJAN (COTE D'IVOIRE)

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The onset of Plasmodium falciparum (P. falciparum) resistance to antimalarial drugs requires careful surveillance of African parasite population. Genomics tools are implemented to detect evolutionary changes that could impact on malaria control and elimination strategies. Here, we evaluate the genome-wide pattern of selection and sequence variation of P. falciparum populations in Abidjan, Côte d'Ivoire. The study was conducted in three localities of Abidjan from 2013 to 2014. We collected 70 blood samples following a written informed consent from patients above two years of age. After extracting P. falciparum and human DNA from isolates, we performed Whole Genome Sequencing and used population genomics approaches to investigate genetic diversity, complexity of infection and identify loci under positive directional selection. We observed an excess of rare variants in the population showing a clear mutation process in the isolates. Moderate Fst estimates (0.3) was detected for surfin, an immune invasion gene family. Seven iHS regions that had at least two SNPs with a score greater than 3.2 were identified. These regions code for genes that have been under strong directional selection. Two of these genes were the chloroquine resistance transporter (crt) on chromosome 7 and the dihydropteroate reductase (dhps) on chromosome 8. Our analyses showed a recent selective sweep in the erythrocyte membrane protein (Pfemp1). In conclusion, our analyses identified genes under selective drug pressure and balancing selection on protective immune-specific genes. These findings demonstrate the effectiveness of genomics analyses to follow malaria parasite evolution of parasite and adopt appropriate strategies to eliminate malaria in Côte d'Ivoire.

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ASSESSING TRANSMISSION DYNAMICS AND RELATEDNESS OF PLASMODIUM FALCIPARUM ON BIOKO ISLAND, EQUATORIAL GUINEA

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In 2019, the Bioko Island Malaria Elimination Project (BIMEP) conducted their annual malaria indicator survey on Bioko Island (BI), Equatorial Guinea, revealing 13.4% malaria prevalence by RDT. The challenge facing BIMEP, as BI approaches pre-elimination, is defining the sources that contribute to the persistence of malaria in the island. To this end, we are investigating transmission dynamics of Plasmodium falciparum (Pf), the predominant malaria species on BI, both within BI and between BI and continental Africa. Dried blood spot samples from participants with reported fever and a positive RDT for Pf were selected for selective whole genome amplification and sequencing (n=74). Utilizing a variety of population genetics metrics and analyses, including nucleotide diversity (π), FST, admixture and identity-by-descent (IBD), the genetic diversity and population structure of the BI parasite population were compared to continental African countries. Initial results show BI parasites cluster with, and have similar ancestral background to, samples from its geographical neighbor Cameroon. This further supports previous epidemiological evidence of malaria importation to BI via human migration, and the observation of mixing between island and continental strains, despite a geographical barrier. Next, to determine whether Pf in BI forms a panmictic population, relatedness between BI samples was measured using IBD to characterize on-island transmission dynamics. Overall, BI samples appeared mostly unrelated (average IBD = 0.003). However, stratification by urban and rural communities revealed some differentiation (FST = 0.03) and higher IBD among rural infections (average IBD = 0.008) than among urban (average IBD = 0.002) consistent with a partially structured population. If progress continues, rural communities may be amenable to elimination interventions without the fear of constant reseeding from urban environments. Further investigation using epidemiological and genetic data will be utilized to provide greater detail of BI transmission among epidemiological subgroups within the context of malaria control management.

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PLASMODIUM FALCIPARUM POPULATION STRUCTURE IN SOUTHWESTERN AFRICA, USING WHOLE GENOME SEQUENCE DATA: INITIAL GENOME-WIDE SEQUENCE DATA FROM ANGOLA

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Malaria continues to be the principal cause of morbidity and mortality in Angola, primarily due to Plasmodium falciparum (Pf) infection. Angola ranked 9th worldwide in number of malaria deaths in 2021 but the distribution of disease is remarkably heterogeneous, with provinces varying between <1% and >50% malaria prevalence. Despite malaria's heavy toll on public health in Angola, Pf genetic diversity and demography in the country remain largely unexplored. Here we aimed to characterize malaria infections in six provinces in Angola, two each in regions where malaria transmission is hyperendemic (Cabinda, Uíge), mesoendemic stable (Luanda, Cuanza Sul) and seasonal with low prevalence (Cunene, Namibe). We hypothesize that (1) multiplicity of infection is positively correlated with transmission intensity and (2) that Pf transmission among provinces conforms to a model of isolation by distance. Finally, (3) Pf genetic diversity in Angola will be contrasted with that found in neighboring countries. To address these questions, parasite DNA was isolated from 150 dried blood spots collected in 2022, and subjected to selective whole genome amplification, and sequencing in an Illumina NovaSeq 6000 platform. The sequencing data was mapped against the P. falciparum reference genome, single nucleotide polymorphisms (SNPs) were identified according to best practices, and joint SNPs calling was done together with WGS data from several hundred publicly available Pf samples from East, West and Central Africa, as well as Brazil and French Guiana. A Principal Component Analysis (PCA) done on the SNP calls revealed that Pf samples from Angola cluster with others from Central Africa. Admixture analyses are still ongoing, to determine the extent to which the ancestry of the Angolan Pf population differs from those of neighboring countries. In addition, average multiplicity of infection and overall nucleotide diversity will be estimated for each province, and

population differentiation between provinces will be estimated with Wright's fixation index (FST). To test isolation by distance, FST will be compared with geographic distance using a Mantel test.

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SEQUENCE POLYMORPHISMS IN THE PFS47 6-CYSTEINE PROTEIN IN PLASMODIUM FALCIPARUM ISOLATES FROM ANGOLA, 2019

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The survival and transmission of the Plasmodium falciparum parasite is dependent on the gene encoding the 6-cysteine protein Pfs47 (PF3D7_1346800) that plays a crucial role in the parasite avoiding the mosquito vector's immune system. Allelic variants of the Pfs47 sequence constitute haplotypes that vary globally and are adapted to evade the immune system of specific Anopheles mosquitoes found in each region. We utilized a targeted amplicon deep sequencing (TADS) protocol to evaluate the highly polymorphic Pfs47 gene for its ability to determine the geographic origin of P. falciparum. A total of 56 samples from three provinces in Angola (11 from Benguela, 14 from Lunda Sul, and 31 from Zaire) were individually sequenced and evaluated for single nucleotide polymorphisms (SNPs) in Pfs47. From these, 52 samples (11 from Benguela, 14 from Lunda Sul, and 27 from Zaire) had sufficient alignments to Pfs47 (PF3D7_1346800) and were evaluated further. There was a total of 12 haplotypes observed in Angola made up of 11 unique amino acid changes. Two haplotypes were exclusively found in Zaire, two in Lunda Sul, and one in Benguela. Major SNPs, those with a weighted allele frequency of 25% or more, were P194H, N272I, E188D, E27D, and P369H. Apart from E27D (Domain 1) and P369H (Domain 3), the other three polymorphisms occur in Domain 2 of Pfs47. Interestingly, E27D is most prevalent in Lunda Sul, E188D is most prevalent in Zaire, and N272I is more prevalent in Zaire and Benguela than in Lunda Sul. Finally, we utilized 535 publicly available consensus sequences for Pfs47 (99 from Asia, 59 from Americas, and 377 from Africa) and compared them with our Angola samples. Through hierarchical clustering, the representative haplotype for Angola is most similar to haplotypes found in Western African countries, as expected. This evaluation strengthened the observation that E27D and N272I are distinctly African SNPs. Although Pfs47 haplotypes can discern the geographic origin of P. falciparum among Africa, Asia, and the Americas, more power is needed to evaluate whether Pfs47 polymorphisms can discern parasite origin among countries or provinces/regions.

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DRUG RESISTANCE PROFILE OF PLASMODIUM FALCIPARUM IN THE COMMUNITIES OF CONDORCANQUI, AMAZONAS, PERU

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Malaria is a serious health problem in the native communities of Condorcanqui in the Amazonas region of Peru, reporting a 2.5-fold increase in the number of cases since 2019. Resistance to antimalarial drugs hampers malaria control and elimination; suspected resistance to artemisinin, chloroquine, sulfadoxine, pyrimethamine, and mefloquine in Plasmodium falciparum can be explored by analyzing polymorphisms in the PfK13, Pfcrt, Pfdhps, Pfdhfr, and Pfmdr1 genes, respectively. In this study, P. falciparum positive cases, collected during 2019 to 2022, from native communities of Condorcanqui were evaluated. Genomic DNA was isolated from fifty-one blood samples on filter paper, collected from 2019 to 2022 and species confirmation was performed by real-time PCR. Polymorphisms of PfK13, Pfcrt, Pfdhps, Pfdhfr and Pfmdr1 genes were analyzed by nested PCR followed by Sanger sequencing. Electropherograms were analyzed in Geneious Prime and then compared to the 3D7 reference sequence obtained from the NCBI database. All samples had the same genotype, carrying mutant alleles for Pfcrt (C72S and K76T), Pfdhfr (A16V, C50R, N51I and S108N/T), Pfdhps (A437G, K540E, A581G) and Pfmdr1 (Y86N and Y184F). However, no mutations were found in the PfK13 propeller domain. These results are consistent with a recent clonal expansion, due to a P. falciparum outbreak reported in the area in 2019. Continued surveillance of polymorphisms associated with antimalarial resistance is recommended to guide the formulation of rational drug policies and the mitigation of risk of P. falciparum artemisinin resistance.

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MOLECULAR EPIDEMIOLOGY OF NON-FALCIPARUM PLASMODIUM INFESTATIONS IN DIFFERENT AREAS OF THE IVORY COAST

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Malaria is a major public health problem, particularly in the tropical regions of America, Africa and Asia. Plasmodium falciparum is not only the most widespread but also the most deadly species. The share of Plasmodium infestations caused by the other species (P. ovale and P. malariae) is clearly underestimated. General objective was to determine the molecular epidemiology of plasmodial infestations due to P. malariae and P. ovale in Côte d'Ivoire. This is a cross-sectional study which took place from February to March 2021 at the Centre de Recherche et de Lutte contre le Paludisme (CRLP) of the Institut National de Santé Publique (INSP). The collection of samples took place from May 2015 to April in different malaria epidemiological facies in Côte d'Ivoire. Analysis of the collected samples was performed. In each patient, we collected blood by venipuncture at the elbow on EDTA tubes. These samples were used to make confetti on Wathman paper for the molecular diagnosis of malaria. Molecular diagnosis as well as differential diagnosis of plasmodial species using the nested PCR technique.A total of 360 samples were tested with a success rate of 72.5% (261 out of 360). The sex ratio was 0.84. The overall plasmodic index was 72.5%. The specific index was 77.4%; 1.5% and 0% for P. falciparum, P. malariae and P. ovale in mono-infestation, respectively. There was also 15% P. falciparum and P. malariae co-infestation, 3.4% P. falciparum and P. ovale co-infestation and 2.3% P. falciparum, P. malariae and P. ovale triple-infestation. After exclusion of P. falciparum monoinfestation cases, 59 samples were finally retained to evaluate the molecular epidemiology of non-falciparum Plasmodium infestations. Typing of P. ovale subspecies showed a clear predominance of P. ovale curtisi (81.2% of cases). P. falciparum remains the most prevalent malaria species in Côte d'Ivoire, but P. malariae and P. ovale are endemic at a low rate. The elimination of malaria requires a better understanding of the specific epidemiological characteristics of P. malariae and P. ovale with a particular emphasis on the identification of asymptomatic carriers.

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A MORE EFFECTIVE MULTIPLICITY OF INFECTION: INCORPORATING WITHIN-HOST RELATEDNESS AND GENOTYPING ERROR TO OBTAIN MORE ACCURATE ESTIMATES OF PLASMODIUM WITHIN-HOST DIVERSITY AND POPULATION ALLELE FREQUENCIES

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Analysis of Plasmodium genetic data is complicated by the unique biology of malaria where multiple genetically distinct strains may be present in a single infection. Naive approaches to estimating allele frequencies without accounting for the number of distinct infecting strains, known as multiplicity of infection (MOI), and genotyping error, may result in biased estimates. Undercounting strain contribution leads to overestimating and underestimating rare and common allele frequencies respectively, biasing downstream metrics that rely on these estimates. Analysis of malaria also often assumes a panmictic population, however the phenomena of co-transmission, where multiple strains within a single individual are transmitted by a single mosquito, results in highly related progeny in downstream infections. This within-host relatedness can bias estimates of MOI that assume infecting parasites are independent and complicates the concept of MOI. For example, the presence of multiple unrelated strains suggests a different epidemiological origin compared to multiple highly related strains, despite having the same MOI. To address these issues, we developed a Bayesian approach for the simultaneous estimation of individual level MOI, within host relatedness, and population allele frequencies from polyallelic data subject to genotyping error. We introduce a new concept of "effective MOI" (eMOI), a continuous metric that captures the interplay of MOI and within host relatedness. Using a high diversity amplicon sequencing panel, we are able to accurately recover eMOI as high as 12 from simulations with genotyping error, even in the absence of any within sample relatedness where eMOI = MOI. We applied our approach to previously collected data from northeastern Namibia containing 2585 samples from 29 clinics across 4 health districts genotyped at 26 microsatellite loci, revealing substantial within host relatedness (median eMOI = 1.55 (IQR: .26), median MOI = 5.16 (IQR: 3.46), median relatedness = 0.77 (IQR: .26)). Estimated MOI was lower when not allowing for relatedness (median MOI = 1.0263 (IQR: 1.40)).

6878

STRUCTURAL AND FUNCTIONAL ANNOTATION OF A UNIQUE HYPOTHETICAL PHOSPHATASE OF PLASMODIUM VIVAX

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The protozoan parasite Plasmodium vivax is one of the causative agents leading to life threatening malaria cases worldwide. Infection with P. vivax can lead to severe and fatal infections, contributing to significant global morbidity and mortality. Due to increasing drug resistance, conventional antimalarial medicines are losing their efficacy, necessitating the urgent need for alternative and more potent antimalarial medications or vaccines. Recent breakthroughs in sequencing technologies provide vital information about the parasite's entire genome to aid in the discovery of novel drugs or the development of vaccines, but much more must be uncovered due to its insufficient proteome annotation. Conserved hypothetical proteins with unknown functions pose a unique challenge in understanding the complex lifecycle of these parasites. Computational analysis provides a general prediction of biochemical function establishing a foundation for further direct experimentation. Specifically, domain identification and subsequent homology modeling allow us to develop a greater understanding of the potential roles of these proteins in signal transduction and stage-specific gene expression during intraerythrocytic development. In this study, a putative characterization of the hypothetical protein PVX_090120 evaluated its potential as a target for future chemotherapeutic strategies.

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BUZZWORTHY: NOVEL HIVE SEQUENCING TECHNOLOGY MAKES SINGLE-CELL SEQUENCING POSSIBLE FOR MALARIA FIELD ISOLATES

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While single-cell sequencing has been revolutionary for molecular biology and understanding gene expression of infectious diseases, its application to Plasmodium has been limited due to a lack of single-cell preservation options compatible with collecting Plasmodium field isolates. Until now, preservation methods for single-cell sequencing have utilized probes only designed for the human transcriptome or rely on cryopreservation which results in the loss of fragile Plasmodium life stages. Here we apply HIVE single-cell sequencing to Plasmodium parasites, a new technology that separates the sample capture and processing into two steps that can be performed at different locations. The cell capture can be completed in low-resource field settings to isolate single Plasmodium parasites in individual wells where they are preserved for transportation to a lab facility for processing and library preparation. We optimized sample preparation and processing using P. knowlesi and P. falciparum in vitro cultures to simulate capturing P. vivax and P. falciparum isolates in the field. The initial sequencing analysis shows that we recovered 1000+ cells and identified clear biomarkers for our cell clusters. More detailed analysis is ongoing and we will present how these preserved gene expression profiles compare to the publicly available Malaria Cell Atlas data in this proof-of-concept study. This new single-cell sequencing technology can transform Plasmodium research by making it possible to perform single-cell studies on field isolates. This is of particular importance for species that cannot be cultured in vitro, such as P. vivax, and for minority subpopulations often missed by bulk RNAseq. Studies will also be able to investigate gene expression profiles of individual parasites in heterogeneous populations including mixed life stages and polyclonal infections, which will lead to advancements in Plasmodium biological systems such as drug resistance and invasion.

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ASSESSING THE INTERACTION BETWEEN NATURALLY-ACQUIRED PFCSP-SPECIFIC HUMORAL IMMUNITY AND THE PROTECTIVE EFFICACY OF THE ANTI-MALARIAL MONOCLONAL ANTIBODY CIS43LS

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CIS43LS is an antimalarial monoclonal antibody that targets a conserved junctional epitope on the Plasmodium falciparum circumsporozoite protein (PfCSP). We recently reported that a single 40 mg/kg dose of CIS43LS given intravenously to adults before the 6-month malaria season in Mali provided 88.2% protective efficacy against P. falciparum infection. It is important to understand whether baseline levels of naturally acquired PfCSP-specific antibodies impact CIS43LS efficacy, and conversely, whether CIS43LS impacts the subsequent PfCSP-specific antibody

response during malaria transmission. Moreover, it is important to investigate how CIS43LS-mediated protection from blood-stage infection effects levels of pre-existing blood-stage-specific antibodies. To address this, we are measuring levels of PfCSP- and blood-stage-specific antibodies in serum collected from study participants (N=330 adults) at baseline before CIS43LS/placebo administration, 84 and 168 days later. We are performing bead-based, multiplexed analysis of various antibody isotypes (IgGl-4, IgA, IgM) specific for full length PfCSP and various components thereof (N-term, NANP repeat region, C-term, and junctional peptides) as well as the blood-stage antigens including PfMSP1. The relationship between pre-existing antibody levels and CIS43LS efficacy will be determined, and naturally acquired antibody responses to PfCSP and blood-stage antigens in those who received CIS43LS, or placebo will be compared. This analysis may provide insight into whether CIS43LS efficacy varies with background levels of PfCSP-specific humoral immunity (i.e. vary with age and malaria transmission intensity) and the extent to which naturally acquired humoral immunity to the pre-erythrocytic and erythrocytic stages of P. falciparum might be impacted by CIS43LS.

6881

THE PROTECTIVE ROLE OF MATERNALLY DERIVED ANTIBODIES AGAINST SYMPTOMATIC MALARIA IN THE FIRST YEAR OF LIFE

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While Plasmodium falciparum infection during pregnancy is common in endemic settings, there is significant uncertainty as to how transplacental malaria exposure and neonatal antibody repertoires at the time of birth affect the incidence, symptomatology, and severity of malaria infections in the first year of life. To interrogate these questions, which may provide new avenues for novel therapeutics, we enrolled a birth cohort of children from Busia, Uganda, an area with very high and perennial malaria transmission, and followed them through one year of age. Mothers were enrolled during pregnancy, and at the time of birth, cord blood samples were collected from 678 infants. Both mothers and children received all care at a study clinic, including artemisinin-based therapy for smear-positive cases of symptomatic malaria. Routine assessments were performed every four weeks, including evaluation for parasitemia by microscopy. The 678 cord blood samples were analyzed using the Luminex MAGPIX System by means of Luminex magnetic microsphere conjugation with 17 malaria antigens with subsequent staining with florescent secondary antibodies. Several antibodies measured in cord blood were associated with exposure to malaria in pregnancy, including IgG to AMA1 and Rh2. In contrast, higher cord blood IgG to EBA175 (OR 1.31, P=0.001), EBA140 (OR 1.19, P=0.006), and MSP2 (OR 1.39, P=0.006) were associated with increased odds of asymptomatic parasitemia in infancy, suggesting a role for these maternal antibodies in protection against symptomatic malaria in early life. These findings have significant implications for the development of active and passive immunization to protect infants against adverse outcomes of malaria in infancy.

6882

DENGUE AND MALARIA IMMUNE CROSSTALK: UNDERSTANDING THE IMPORTANCE OF CO-INFECTIONS IN ENDEMIC REGIONS

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40 % of the world's population lives in the tropics, areas characterized by poverty, but also by the presence of multiple pathogens. This is a special challenge for the immune system which deals with multiple infections, often at the same time. Although theoretically there is a strong geographic overlap between Malaria and Dengue Fever, there is scarce data on the interaction of these two diseases. The interruption of Malaria transmission has led to malaria-free areas in Asia and Latin America and these areas report increasing Dengue fever outbreaks over time. In contrast, sub-Saharan Africa is still a Malaria hyper-endemic area where Dengue fever incidence is largely undetermined, and there is no scientific data that can explain the widespread absence of Dengue fever outbreaks. Our study aims to understand the interaction between these two infections in samples from a pediatric cohort in Ghana. We first determine Dengue Virus incidence using a newly developed serological test for endemic areas, allowing high specificity for different Flaviviruses. We performed a phenotypical analysis of Dengue-specific T cells in the context of previous or acute Malaria infection using high content flow cytometry. This is to our knowledge the first study addressing this immunological crosstalk. Furthermore, we shed light on how the history of previous and/or concurrent infections shapes the immune response and thereby influences disease outcomes in real-life settings.

6883

T CELL RESPONSES AGAINST LIVER STAGE PLASMODIUM FALCIPARUM ANTIGENS IN UGANDAN CHILDREN EXPOSED TO MALARIA

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Experimental vaccine models show that the CD4+ T cell response against liver stage (LS) Plasmodium is critically important for immunity against reinfection. However, the identity of the relevant antigens and epitopes targeted by these cells remains largely unknown. In addition, this protection is partially abrogated by blood stage (BS) infection. CD4+ T cells feasibly play a role in this phenomenon, given their ability to regulate and polarize other effectors of immunity. We aimed to (1) identify the targets of the CD4+ immune response at the LS; and (2) analyze the size and phenotype of circulating T cell subsets with liver homing properties in infants with diverging histories of malaria exposure. To overcome the data gap on antigen expression in LS P. falciparum, we used a data mining approach to prioritize parasite genes on the basis of their stage-selective expression in other Plasmodium species. We selected 11 LS and 3 BS candidate antigens, and HLA-DRB1 binding peptides were predicted on conserved segments of their encoded proteins. Seventy-eight peptides were tested for T cell recognition using PBMC from malaria-exposed infants recruited for the PRISM study. In vitro T cell expansion revealed an IFN-γ response against sequences from all BS and at least 5 LS antigens in multiple donors. In parallel, we defined a set of phenotypic markers based on their reported relevance for liver homing and implication in protective anti-malarial T cell responses. These were combined with lineage, memory, and subset markers in a spectral flow cytometry panel, which we used to characterize circulating T cell subsets in Ugandan infants. Preliminary characterization

of specimens from the Tororo Child Cohort study showed significant differences in the populations defined by these markers within the αβ and γδ T cell compartments associated with diverging levels of malaria exposure (>35 episodes vs ≤2 episodes since recruitment). We are currently extending this characterization to infants in the PROMOTE BC1 study, who underwent intermittent or continuous chemoprevention affecting primarily BS parasites.

6884

OFF-TARGET ANTIBODY RESPONSES INDUCED BY RTS,S/AS02A/1B IN MALARIA-NAÏVE ADULTS ASSOCIATED WITH PROTECTION AGAINST CONTROLLED HUMAN MALARIA INFECTION

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The RTS,S vaccine targets the circumsporozoite protein (CSP), which coats the Plasmodium falciparum sporozoite surface. Although some studies have demonstrated an association between anti-CSP repeat region IgG antibody titers and vaccine-induced protection from RTS,S, the relationship does not seem to be linear or suggest an absolute protective threshold. New data suggests that off-target/cross-reactive antibody responses may also be associated with protection. We examined IgG responses in malaria-naïve adults vaccinated with RTS,S who were either protected (n=18) or unprotected (n=17) against controlled human malaria infection to examine the association between off-target responses and protection. Baseline and post-vaccination sera were probed on a pre-erythrocytic peptide array with representation of diverse variants of 127 proteins previously associated with vaccine-induced or naturally acquired protective immunity as 16-amino acid peptides overlapping by 15. Protected adults were seropositive for more peptide variants in regions of CLAMP, GSK3, DOC2 and MSP5 compared to unprotected adults. Protected adults also had higher reactivity than unprotected adults to peptide variants in regions of CLAMP, GSK3, DOC2, LRR9, and MSP5, with some peptides of CLAMP, GSK3, and MSP5 being targets of both increased seropositivity and reactivity. BLAST between areas of differential responses and CSP identified sequence similarities between a CLAMP peptide and the CSP central repeat region and a CLAMP peptide and a DOC2 peptide and an area of the CSP C-terminal region upstream of Th2R. We previously identified the CSP C-terminal sequence at this location as a potential epitope with higher seropositivity in the RTS,S-protected adults in this study. A different area of DOC2 had sequence similarities to the hepatitis B surface antigen. Our findings support emerging data that off-target antibody responses induced by RTS,S may be important for protection, either through direct action or as an indicator of higher quality CSP antibodies. Further work to isolate cross-reactive antibodies and examine their binding and function is warranted.

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ROLE OF MALARIA AND EPSTEIN-BARR VIRUS IN PEDIATRIC CANCER DEVELOPMENT IN MALAWIAN CHILDREN

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Endemic Burkitt Lymphoma (eBL), an aggressive B-cell non-Hodgkin lymphoma, is the most common childhood cancer in sub-Saharan Africa (SSA), with a peak occurrence at 7-years of age. Its distribution has been linked to chronic and intense holoendemic Plasmodium falciparum malaria transmission. Epstein Barr virus (EBV) is also a known cofactor for eBL development; both malaria and EBV infection explain the geographic concentration of eBL in malaria-endemic regions where EBV is ubiquitous. We wanted to investigate if children with eBL have a higher proportion of EBV infection. Additionally, among the children with an EBV infection is there a difference in EBV viral load between children with eBL and children with other malignancies. Lastly, is there an effect of sex or age on EBV viral load. Participants were part of a childhood cancer study conducted at the main hospital in Blantyre, Malawi, between July 2005 and July 2006. All 572 children aged 15 years or younger with a provisional diagnosis of cancer admitted to the pediatric oncology ward in Blantyre were recruited. Cancer diagnosis was based on clinical presentation and confirmed by histology and cytology. Only HIV-negative children were included as part of this study. EBV DNA was quantified by measuring the BALF5 gene using quantitative polymerase chain reaction (qPCR). We found a significant relationship between cancer type and EBV positivity, where children that developed eBL are more likely to have detectable levels of EBV than children with other cancers (p-value < 0.01). Of the children with detectable virus, 223 children with eBL and 141 children with other cancers, we found that children with eBL had a significantly higher EBV viral load (p-value < 0.01). Next, we wanted to determine if there was an effect of age or sex on EBV viral load, both in children that developed eBL as well as children with other cancers. When looking at the effect of age on EBV viral load we found a significant effect of age with viral load (p-value = 0.04). Together these results suggest that EBV viral load is directly correlated to eBL development furthermore, increased age is associated with increased EBV viral load.

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OPSONIC PHAGOCYTOSIS OF PLASMODIUM FALCIPARUM MEROZOITES IS ASSOCIATED WITH PROTECTION FROM CLINICAL MALARIA IN AN AREA OF LOW AND UNSTABLE MALARIA TRANSMISSION

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Immunoglobulin G (IgG) antibodies to Plasmodium falciparum (Pf) antigens are known to be important in protection from clinical malaria, but immune correlates of protection from clinical malaria are still sub-optimally characterized. Most characterization has been done in areas of moderate to high malaria transmission, but data is limited for areas of low transmission due to a need for prolonged evaluation periods. It is unclear if immune correlates of protection are identical in areas of high vs. low malaria transmissions. In areas of high malaria transmission, studies suggest that antibody-dependent cellular phagocytosis (opsonic phagocytosis, OPA) strongly correlates with protective immunity, but this has not been investigated in areas of low malaria transmission. In a highland area of low and unstable malaria transmission in western Kenya, we conducted a nested case-control study in which we collected plasma samples from 5753 individuals in 2007, and followed these individuals through 2017

for the development of clinical malaria. Individuals who developed clinical malaria were defined as cases and compared to age- and village-matched controls who did not develop clinical malaria. OPA of merozoites was higher in cases (30.9%, n=56) than controls (28.6%, n=56, p=0.051). The data suggest that the OPA of merozoites may be an immune correlate of long-term protection in low malaria transmission areas. Future studies will assess OPA of merozoites and selected Pf antigens in a larger sample of cases and controls to determine specific antigen targets for OPA and examine whether OPA is a better immune correlate of protection from clinical malaria in low malaria transmission settings than IgG, IgG1, or IgG3 antibody levels to Pf antigens

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QUANTIFYING THE EFFECT OF NUMBER OF INFECTIONS ON MALARIA IMMUNITY

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Naturally acquired immunity provides near complete protection from symptomatic falciparum malaria, yet the mechanisms underlying its development remain poorly understood. Increasing age and transmission intensity are associated with multiple measures of anti-disease and anti-parasite immunity, including lower parasite densities, lower probability of symptomatic malaria, and higher fever thresholds. It is unknown to what extent these trends can be explained by cumulative exposure versus other factors, such as parasites' genetic diversity, complexity of infection (COI), and age-dependent immunity. In this study, we aim to quantify the relationships between number of unique infections, COI, age, annual entomological inoculation rate (aEIR) and anti-disease and anti-parasite immunity. We performed amplicon sequencing of AMA1 in longitudinal blood samples from 158 individuals in birth cohorts in Uganda collected via active and passive detection. Individuals ranged from 1mo to 10yrs of age, and were enrolled in the study for 3.6 years on average. aEIRs during the study ranged from 30-1000 infectious bites per year. We successfully genotyped 889 samples, 6 samples per individual on average, representing 89% of a person's symptomatic malaria episodes. Haplotypes per sample ranged from 1-11 (avg=2). This relatively low value is consistent with frequent, symptomatic infections cleared by treatment. From genotyping, we can infer unique infections per individual and apply a mixed effects model to quantify the impact of number of infections and predictors, like COI, age, and aEIR, on measures of immunity, including probability of symptomatic malaria, parasite density, and fever threshold. Preliminary results indicate that higher aEIR and lower age are associated with higher probability of symptomatic disease as previously observed. In symptomatic infections, higher COI is associated with lower parasite densities, or fever thresholds, while, in asymptomatic infections, higher COI is associated with higher parasite density. This work provides an important foundation to future studies on the development of P. falciparum immunity.

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ITERACTIVE SUBTRACTIVE BIOPANNING OF A PLASMODIUM FALCIPARUM SEXUAL STAGE (I-III) PHAGE DISPLAY LIBRARY IDENTIFIES A POTENTIAL TARGET OF ANTI-GAMETOCYTE IMMUNE RESPONSES

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Decades of malaria research have identified highly promising vaccine candidate antigens capable of eliciting protective immune responses at multiple malaria life-cycle stages. These include antigens such as PfCSP (pre-erythrocytic stage), PfRh5 (blood-stage), and Pfs230 (classical transmission-blocking activity in the mosquito mid-gut). Additional antigens however are likely to be discovered to augment combinatorial vaccines that target multiple life cycle stages. Gametocytes, the asexual form of the parasite responsible for transmission from human to mosquito vector, may also allow opportunities for intervention. To identify sexual stage antigens capable of eliciting by gametocyte controlling immune responses, we have performed a whole proteome differential screen of a Plasmodium falciparum phage display constructed from early stage gametocytes (Stages I-III). Employing an iterative subtractive bio-panning approach in conjunction with plasma previously collected from a western Kenya treatment-reinfection study (n=143), we performed out initial screen with highly matched pools (n=10/each) of resistant plasma (low gametocytemia[RP]) and susceptible plasma (high gametocytemia [SP]), matched for a host of variables including asexual parasitemia, age, Hgb, % HgbAS trait, exposure, etc. to identify 12 clones uniquely recognized by RP but not SP. Next, we performed a whole cohort validation to determine whether or not antibody titers to each antigen measured 2 weeks post treatment but prior to reinfection in all members of the cohort, predicted gametocyte indices over the 18 weeks of follow-up. In multivariate linear regression and generalized estimating equation models, antibody titers were significantly inversely correlated with gametocytemia ($P \leq 0.04$), in numerous outcomes. In silico analysis of this predicted large 300kD protein, identified a Plasmepsin IX cleavage site, indicating a potential rhoptry organelle secreted protein. In conclusion, we have a identified a novel antigen, potentially capable of eliciting gametocyte controlling immune responses.

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CYTOMEGALOVIRUS VECTOR PROLONGS LIVE MALARIA VACCINE IMMUNITY THROUGH INNATE AND ADAPTIVE MECHANISMS

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Immunity to Plasmodium infection or vaccination is known to decay. In mouse models, this decay correlates with loss of parasite-specific T cells, not antibody. Whole live parasite vaccines, such as "infection and drug cure", protect. However, sterile protection from live P. chabaudi vaccination lasts less than 200 days. Persistent infection itself protects, and generates both effector (Teff,) and effector memory T cells (Tem). Both CD4+ Teff and Tem contribute to protection, as we recently showed for Plasmodium infection. Cytomegalovirus (CMV) is a promising chronic vaccine vector that can induce sustained T cell responses. CMV vectors contribute to protection against SIV, tuberculosis and liver-stage malaria through CD8 T cells. As CMV promotes Tem and Teff, we tested murine CMV encoding P. chabaudi MSP-1 epitope B5 (MCMV-B5), as a booster to prolong live vaccine-induced protection from P. chabaudi infection. The

MCMV vector alone had adjuvant properties, contributing non-specifically through prolonged stimulation of IFN-γ to improved protection from P. chabaudi infection. In vivo neutralization of IFN-γ, but not IL-12 and IL-18, late in MCMV infection, led to complete loss of the adjuvant effect induced by the MCMV vector prolonging protection from P. chabaudi challenge. Interestingly, the MCMV booster prolonged protection from heterologous infection beyond day 200. The MCMV-B5 booster increased B5 TCR Tg T cell survival and drove a highly-differentiated Tem phenotype. MCMV booster increased dendritic cell numbers, and led to increased IL-12 production upon Plasmodium challenge, suggesting innate priming. In addition, anti-IFN-γ pre-treatment reduced the polyclonal Teff response to challenge, suggesting a role for improved antigen presentation. B5 epitope expression, not IFN-γ, was responsible for maintenance of B5 Tem numbers and Th1 cytokines. Our findings suggest that an MCMV vectored boost can prolong protection through the effects of IFN-γ, and could be used to promote specific T cell responses.

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VΔ2+ ΓΔ T CELL CHROMATIN ACCESSIBILITY AND IMMUNE FUNCTION ASSOCIATES WITH PRIOR MALARIA INCIDENCE

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Repeated malaria infection results in children in malaria-endemic regions gaining the ability to tolerate parasitemia without symptoms. One mechanism driving immune tolerance and the shift towards asymptomatic parasitemia is the attenuation of cytotoxic, pro-inflammatory responses by innate immune cells. Aiming to better understand the processes underlying changes in Vδ2+ γδ T cell function, we analyzed Vδ2+ T cells isolated from children (n=20) enrolled in longitudinal cohorts in Tororo, Uganda, by paired ATAC-Seq and RNA-Seq. By using multiple samples from the same children, including before and after a district-wide insecticide campaign that dramatically reduced malaria transmission, we could assess differential chromatin accessibility and transcription associating with year, prior incidence of clinical malaria, or exposure to infected mosquitoes. We identified differential sites enriched for genes involved with immune signaling (e.g. IL-19, CD8, CXCR6, STAT1) and regulation (e.g. BCL2, KLRC1, HAVCR2, TIGIT). Footprinting analysis further identified distinct transcription factor activities associating with malaria incidence. Experiments using CRISPR knock outs to confirm the role of target genes in modulating Vδ2+ T cell function are in progress. In parallel, we established in vitro stimulation assays to simulate the in vivo context; results support both cell-intrinsic and -extrinsic mechanisms contributing to reduced Vδ2+ T cell responsivity following malaria exposure. All together, this work provides needed insight into mechanisms driving incomplete acquisition of natural antimalarial immunity and could be applied to novel therapeutics targeting innate immune responses.

6891

ELEVATED LEVELS OF CEREBROSPINAL FLUID NEURON-SPECIFIC ENOLASE ARE ASSOCIATED WITH LONG-TERM NEUROLOGIC AND COGNITIVE IMPAIRMENT IN CHILDREN WITH CEREBRAL MALARIA

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Cerebrospinal fluid neuron-specific enolase (CSF NSE) is a known biomarker of adult and pediatric neurologic disorders, including stroke and encephalopathy. In severe malaria, one study with a small sample size has investigated CSF NSE in adults and none in children. We evaluated admission CSF NSE levels in 144 children, 1.5-12 years of age with cerebral malaria (CM), and examined associations with blood-brain barrier (BBB) disruption measured using CSF to plasma albumin index, and neurologic deficits (ND) and cognitive impairment (NCI) tested at discharge, 6, 12, and 24-months follow-up. Mean (SD) CSF NSE levels in children with CM (5.01 (7.67) ng/mL) were significantly higher than CSF NSE levels in children in two cohorts of children without neurologic symptoms (1.52 (1.01) and 2.12 (0.30) ng/mL, N=37 and 32, P<0.001 for both comparisons). CSF NSE levels were elevated in children with CM and BBB impairment (n=39, median 4.22 ng/mL [95% CI 2.16, 5.47]) compared to 103 children with CM and no BBB impairment (median 2.19 [95% CI 1.43, 4.40], P=0.002). Children with CM and persistent ND at 12 and 24-month follow-up had elevated admission CSF NSE compared to children with CM and no persistent ND (all P≤0.04). The predictive value of admission CSF NSE for ND increased over time with AUC of 0.59, 0.70, 0.77, and 0.86, at discharge, 6, 12, and 24-months. CSF NSE levels were also associated with worse z-scores for working memory over 24 months follow-up in children who were <5 years of age at CM episode and at follow-up cognitive testing (β [95% CI] -0.26 [-0.47, -0.06], P=0.01), and with worse z-scores for overall cognitive impairment over 24 months follow-up in children who were <5 years of age at CM episode but ≥5 years at follow-up testing (β [95% CI] -1.13 [-1.93, -0.32], P=0.007). Elevated levels of the neuronal injury marker CSF NSE at admission are associated with persistent neurologic and cognitive impairment in pediatric CM.

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ELEVATED RENIN PREDICTS MORTALITY IN CHILDREN WITH SEVERE MALARIA

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Renin has been identified as a biomarker of acute kidney injury (AKI) in critical illness. In the present study, we assessed plasma renin levels in children with severe malaria (SM) from a two-site prospective cohort study and their association with inpatient mortality and endothelial and immune activation. Plasma renin was measured in enrollment samples from 594 Ugandan children with SM and 120 age-matched community children using Luminex bead assay. Community children renin levels were used to establish a population reference with the 99th percentile as the cut-off for elevated renin. The mean age of children was 2.1 years and 44.3% were female. Children with SM had substantially higher renin levels than community children, with 26.9% of children having elevated renin. Children with elevated renin had a mortality rate of 8.9%, corresponding to a 5.4-fold increased odds (95% CI, 2.8 - 10.4, p<0.0001) of mortality compared to children without elevated renin. 62.8% of children that died had elevated renin (p<0.0001). Furthermore, 117 children (19.7%) had severe (stage 2/3) AKI. Among the 10.9% of children that had both elevated renin and severe AKI, there was a 10-fold increase in mortality (29.2%) compared to when neither condition was present (2.9%). Clinical complications associated with elevated renin included signs of poor tissue perfusion (acidosis) and kidney injury (severe AKI, elevated BUN, blackwater fever). To further delineate the role of renin in malaria pathogenesis, we evaluated multiple pathways of organ injury as well as endothelial and immune activation. As elevated

renin was strongly associated with severe AKI, we stratified models by AKI to evaluate renin-specific pathways. Children that had elevated renin without severe AKI showed evidence of endothelial activation and an increase in selected markers of kidney injury and hemolysis. In conclusion, renin is elevated in children with SM and strongly associated with mortality, particularly when it occurs concurrently with AKI. Additional studies are needed to understand whether interventions targeting renin could be beneficial in severe malaria.

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ASSOCIATION OF XANTHINE OXIDASE LEVELS AND DEVELOPMENT OF SEVERE MALARIAL ANEMIA

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Malaria is a potentially fatal infectious disease caused by Plasmodium parasites, with most casualties occurring in children under the age of 5 infected with P. falciparum. P. falciparum infection can manifest with a variety of different complications, one of which is severe malarial anemia (SMA). SMA is caused primarily by the loss of uninfected red blood cells (RBCs). Although the mechanisms underlying the loss of uninfected RBCs during Plasmodium infection are not yet fully understood, oxidative stress has been proposed as a potential contributor to SMA. To further investigate the contribution of oxidative stress to the development of this complication, we quantified the levels of xanthine oxidase (XO), an oxidative enzyme that is upregulated during malaria, in serum samples from a cohort of 552 Ugandan children with severe P. falciparum malaria. We found that patients with SMA had significantly higher levels of XO activity in circulation, compared to patients with non-SMA severe malaria. Moreover, we observed a significant negative correlation between XO levels and RBC hemoglobin, suggesting a potential role for this enzyme in the development of SMA. XO levels did not correlate with serum levels of immune complexes or anti-phosphatidylserine antibodies, two factors that contribute to SMA. This suggests that XO may contribute to the development of this complication independently of these previously established mechanisms. In future experiments we will further clarify the role of XO in the development of SMA using a murine model of malarial anemia, where mice will be treated with allopurinol, an inhibitor of this enzyme. Lastly, we also observed that XO is associated with other severe manifestations of malaria including acidosis and kidney injury, among others. Since patients with severe malaria can present with multiple complications, and inhibitors of XO are affordable and already approved for use in humans, corroborating the role of XO as a causative agent for SMA and other malarial complications may facilitate the use of XO inhibitors as a potential novel treatment for these life-threatening complications.

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LONGITUDINAL CLONAL PARASITE DYNAMICS FOLLOWING ARTEMETHER-LUMEFANTRINE TREATMENT FOR MALARIA IN HIV-INFECTED AND HIV-UNINFECTED CHILDREN IN UGANDA

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Sub-Saharan Africa has seen continent-wide shifts in susceptibility patterns to artemisinin-based combination therapy (ACT) partner drugs and now faces emerging artemisinin resistance. High transmission settings require consideration of post-treatment parasite dynamics and the role of waning drug exposure and multiclonal infections in the selection and spread of resistance. In the context of a 42-day study of 3 versus 5-day artemether-lumefantrine (AL), we used 18S and SBP1 RT-PCR alongside amplicon-sequencing (amp-seq) to distinguish post-treatment clonal dynamics. Weekly samples were analyzed from 76 HIV-infected and 227 HIV-uninfected Ugandan children in a high-transmission setting. 18S RT-PCR revealed a dramatic submicroscopic parasite burden after AL, with nearly 70-75% of children having detectable 18S RNA throughout 42-day follow-up. The ring-stage marker, SBP1, was notably positive in 10% and 17% of HIV-uninfected children at 7 and 14 days post-treatment, respectively. We performed amp-seq of cpmp, cpp, and csp to distinguish and quantify parasite clones at a relative abundance of 0.1%. Clone diversity was high, with a multiplicity of infection (MOI) of 4.3 prior to AL treatment that notably increased upon recurrent parasitemia (day 28 MOI 5.2). Our dataset revealed a pattern of clonal persistence following therapy with ring-stages detectable for up to two weeks after AL. Finally, stratification by HIV status demonstrated that the prevalence and density of ring-stage parasites was significantly lower over the course of follow-up in HIV-infected children, which we attribute to daily trimethoprim-sulfamethoxazole prophylaxis. Our next step will be to assess the relationship between clonal persistence/re-infection and lumefantrine levels, available from this same cohort. Our data represents the first use of amp-seq paired with molecular parasite density and drug exposure data to study longitudinal post-treatment clonal dynamics and represents the largest and longest follow-up of ring-stage specific RNA following AL in Africa. Such novel data are critical as we strive to extend the useful therapeutic life of ACTs.

6895

INVESTIGATING MICROBIOME AND TIGHT JUNCTION INTEGRITY IN THE GUT DURING PLASMODIUM KNOWLESI INFECTION IN MACAQUES

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Gastrointestinal illness is one of the more common manifestations of infection with Plasmodium falciparum and P. knowlesi. The involvement of the gut during malaria and how it enhances the severity of the disease is key to understanding overall malaria pathogenesis, yet uncertainty exists regarding these mechanisms. Previous work in murine models has demonstrated that inflammation in the gut during malaria is associated with disruptions to the microbiome and gut barrier integrity. Limited information exists, however, in terms of whether similar phenomena occur in human and non-human primates. Recent work by our group has demonstrated elevated levels of mucosal microbes in rectal swabs collected from rhesus macaques at the acute phase of malaria infection with P. cynomolgi. To validate that this finding also occurs in a model that exhibits sequestration in

the gut tissue and pathology of the gastrointestinal system, we performed a follow-up study using P. knowlesi, which exhibits cytoadherence through the expression of the SICAvar gene family and is known to cause gut pathology. To investigate whether similar microbiome changes were seen in this context, we performed shotgun metagenomics of rectal swabs from macaques infected with P. knowlesi. Here, we detected an enrichment of mucosal microbes, specifically Helicobacter macacae, during the acute phase of the P. knowlesi infection compared to pre-infection. This result mirrored that which was seen in our P. cynomolgi study. To further investigate the gut, we performed immunohistochemistry on colon tissue from these same animals and labeled tight junction proteins Claudin-5 and Occludin, which regulate intercellular permeability in the gut epithelium. These studies revealed reduced expression of tight junction proteins in colon samples collected from the acute phase of the infection, suggesting that there may also be a reduction in gut barrier integrity alongside the disruption of the gut microbiome. The study adds to a broader goal to comprehend the mechanisms underlying gastrointestinal pathology and the role of gut microbiota in malaria pathogenesis.

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THE SEVERE MALARIA TRIUMVIRATE: AN INVESTIGATION OF ABO BLOOD GROUP, ROSETTE FORMATION, AND PFEMP1 TYPE

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Malaria kills approximately 430,000 people every year, mostly children under 5 years old in sub-Saharan Africa. Many of these lethal cases are due to cerebral malaria (CM), a condition caused by Plasmodium falciparum and characterized by cerebral inflammation, blood-brain barrier (BBB) breakdown, brain swelling and death. The exact mechanisms that lead to CM are unknown. Rosetting is a phenomenon occurring in malaria infections in which an infected red blood cell (RBC) is surrounded by non-infected RBCs, bound by surface ligands. Rosetting has been associated in previous studies with CM severity. ABO blood group may also be related to CM development with non-O blood group patients being more likely to develop cerebral malaria, although studies have been contradictory on this topic. Further, previous studies have shown an association between non-O blood groups and rosetting. Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP-1) variants have binding domains specific to rosetting phenotypes. PfEMP-1 is an important virulence factor in P. falciparum encoded by around 60 different var genes. Some of these var genes are potentially critical in CM development and in rosetting. To our knowledge, relationships between all three of these potential factors in CM development (var genes, ABO blood type group, and rosette formation) have not been investigated. In this work, malaria patient blood samples from a clinic in Blantyre, Malawi were analyzed via rt-qPCR to detect var genes (especially those associated with rosetting) and correlate these with blood type and CM status. We hope this study will better elucidate the relationship between ABO blood group, rosette formation, and cerebral malaria development.

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DEDUCING THE EFFECT OF VARIABLE OXYGEN CONCENTRATIONS ON PLASMODIUM FALCIPARUM GROWTH

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Elucidating within-host infection dynamics is crucial to figuring out the underpinnings of how malaria infections progress. Understanding the role of bodily oxygen concentrations on Plasmodium parasite multiplication rate (PMR) may provide more insights into this progression. Over the course of its life cycle, Plasmodium falciparum cytoadheres to the endothelial lining of the capillaries within various organs in the body that have differing oxygen concentrations. The effect of this difference in oxygen on the parasite's growth is not well understood and previous modeling work generally does not consider variable oxygen levels. We tested two different oxygen concentrations (1% and 13%) and monitored parasite growth for three complete cycles of development within human red blood cells. This was carried out with considerations for variabilities in blood from different donors. Our data supports a significantly higher parasitemia in cultures grown in 1% oxygen compared to those grown at 13% oxygen. In order to improve understanding of the parasite dynamics in vitro, we constructed a stage-structured mathematical model composed of a series of ordinary differential equations (ODEs) incorporating empirically determined parameters such as PMR. Assuming prolonged exposure to differing oxygen concentrations, we found parasitemia peaked later in our simulations before crashing in 13% oxygen. As the quantity of red blood cells is known to undergo a shift within-host due to bone marrow production and splenic elimination, we extend the model to include red blood cell production and elimination to make predictions about in vivo parasite population level response. Better understanding of the effect of differing oxygen concentrations on parasite growth and development could lead to the improvement of understanding of chronic malaria infections and the mechanisms mediating them.

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PREDISPOSING FACTORS RELATED TO THE PVMSP3ALFA GENE AND THE CYTOKINE RESPONSE IN VIVAX MALARIA.

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The purpose of this study was to determine Pvmsp3alfa gene genotypes and cytokine responses as predisposing factors for malaria complicated by Plasmodium vivax. Sixty-one whole blood samples were collected on filter paper and plasma from patients with P. vivax. Two groups of individuals were evaluated, patients admitted to hospital with some sign of complication, and the control group of patients with acute malaria, who did not present any sign of complication. From the sample on filter paper, DNA extraction was performed using chelex100, later a nested PCR was applied to amplify the Pvmsp3alfa gene. The PCR-RFLP technique of the variable region of the Pvmsp3alfa gene was implemented. Samples confirmed as P. vivax underwent enzymatic digestion with Alu I and Hha I. The cytokines plasma concentration (IFNγ, IL10, IL1β, IL2, IL4, IL5, IL6, IL8 and TNFα) was performed by Luminex (multiplex ELISA). The patients show anemia (100%), thrombocytopenia (90%), 20.6% respiratory dysfunction (20.6%) and renal dysfunction (3.4%). It was discovered that there are significant differences, for the variables, parasitemia and hemoglobin between the two groups. There are significant differences for the cytokines IL8 ($p=0.025$), TNFα ($p=0.04$) and ILβ1 ($p=0.03$), with alpha <0.05, between patients with CM and the control group. The size of the PCR products of the Pvmsp3alfa gene shows two different genotypes: type A (1900 bp), type B (1500 bp). Digestion of the PCR products of thePvmsp3alfa gene with the enzyme Alu I produced ten restriction patterns, while the enzyme Hha I produced nine in patients with complicated malaria (CM). The haplotype with the highest frequency in complicated patients was PA1 and significant differences were found in IL10, IL6 and GM-CSF between the group that presented the PA1 haplotype and the patients that appeared with other haplotypes. In conclusion, the parasite density seems to be an important factor to stimulate the production of TNFα and the PA1 haplotype of the Pvmsp3alfa gene and the TNFα, IL1β and IL2 molecules, may be predisposing factors for complications during malaria due to P. vivax.

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HOST-DERIVED LIPIDS SHAPE PLASMODIUM FALCIPARUM DEVELOPMENT AND PATHOGENICITY: AN INTEGRATIVE MULTI-OMICS ANALYSIS IN MALARIA-INFECTED CHILDREN

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Although fatty acid-based lipids are crucial for regulating Plasmodium falciparum parasite maturation, replication, and sexual commitment during the intraerythrocytic developmental stage, our current understanding of the interplay between lipid metabolism and infection in vivo is limited. Here we apply an integrative multi-omics approach combining high-resolution analysis of complex human serum lipids (999 complex lipid molecules) and host-parasite co-transcriptomics (12,375 host and 1,923 parasite transcripts) to document for the first time lipid metabolism and transcriptomic perturbations in 100 malarial children from Burkina Faso sampled before and after Plasmodium falciparum natural infection (n = 200) and assessed their impact on parasite development and disease progression. Our results provide a detailed in vivo blueprint of infection-triggered lipidomic changes and identify sub-classes of polyunsaturated phospholipids and triglycerides associated with parasitemia. Integrative lipidomic-transcriptomic analysis identified parasite gene expression changes in core parasite lipid remodeling and biosynthesis pathways that are activated by host-derived lipids. We experimentally validate the crucial role of these phospholipid subclasses in supporting the parasite's asexual and sexual development in vitro. These findings expand our understanding of the role of polyunsaturated fatty acid and phospholipid metabolism in P. falciparum parasite pathogenesis and transmission biology. Furthermore, our identification of specific gene-lipid networks offers potential therapeutic targets for future antimalarial interventions and control strategies.

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PROFILE OF ENDOTHELIAL BIOMARKERS (ANGIOPOEITIN-1 AND ANGIOPOIETIN- 2) IN PATIENTS WITH UNCOMPLICATED MALARIA IN LAGOS

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Malaria related mortality is associated with significant of host endothelial activation such as host angiogenic factors such as angiopoietin-1 (Ang-1) and angiopoietin -2 (Ang-2). This study profiles the levels of plasma Ang-1 and Ang-2 which are critical regulators of endothelial activation and integrity with some haematological parameters such as total white blood cell counts (WBC), haemoglobin level (Hb), packed cell volume (PCV), and malaria parasite density in uncomplicated Plasmodium falciparum malaria patients. This study was conducted in four hospital sites: Ijede, Imota, Bayeku and Ori-okuta in Ikorodu Local Government Area, Lagos, Nigeria. A total of 83 participants with the age ranged from 2 years - 79 years; the mean age was 22.6±16.3 years. The study population comprised 49 uncomplicated malaria patients and 34 non-malaria patients. Plasma levels of Ang-1 and Ang-2 of the study participants were measured using an enzyme-linked immunoassay. The haematological parameters were determined using the WHO standard. Pearson correlation was used to evaluate the correlation between plasma levels of each biomarker in malaria patients. A p-value of < 0.05 was considered significant. There was no significance difference observed in PCV, Hb and WBC parameters but there was a significance difference ($p < 0.001$ and $p < 0.05$) observed in the levels of Ang-1 and Ang-2 in malaria positive patients when compared with non- malaria patients. A significant decrease was seen between the Ang-1 levels of uncomplicated malaria, and non-malaria patients; however, significant increase was seen in Ang-2 levels between uncomplicated malaria and non-malaria patients ($p<0.05$). The ratio of Ang-2: Ang-1 showed a significant increase ($p =0.001$) between malaria positive patients and non-malaria patients. Endothelial activation of angiopoietins may be involved in the pathogenesis of malaria. This study suggests that Ang-1 and Ang-2 may be used as biomarkers to determine the severity of malaria infection.

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THE ROLE OF PSYCHOSOCIAL FACTORS IN NET USE IN KENYA: FINDINGS FROM THE KENYA MALARIA BEHAVIOR SURVEY

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Research shows that psychosocial factors can influence net use, yet, their role has rarely been studied in Kenya. Kenya's Division of National Malaria Program (DNMP) and Breakthrough ACTION Kenya conducted the Malaria Behavior Survey in 2022 in 8 malaria-endemic counties. Interviews were conducted in 1,456 households and included information on 7,573 household members, 4,196 mosquito nets, 1,787 women, and 466 of their male partners. Key outcomes included insecticide treated net (ITN) access (one ITN per two household members), ITN use the night before the survey among those with access, and consistent self-reported daily use of nets among those in households with at least one net (consistent use). 88% of household members had access to an ITN, yet only 80% with access reported sleeping under an ITN the night before the survey. Most (89%) respondents reported that they consistently use a net. Multivariable logistic regression models were fit to examine the socio-demographic and psychosocial factors associated with consistent net use. Perceived confidence to use a net (Adjusted odds ratio (AOR): 6.6, 95% confidence interval (CI): 4.8-9.2), favorable attitudes towards net use (AOR: 2.2, 95% CI: 1.6-3.0) net care (AOR: 1.6, 95% CI: 1.2-2.1), and weekly radio listenership (AOR: 1.5, 95% CI: 1.1-2.2) were positively associated with consistent net use. Respondents aged 20 years and above had 2 to 3 times increased odds of consistent net use compared to those aged 15-19. Those in households with at least one net per 2 household members also had significantly increased odds of reporting consistent net use (AOR: 3.3, 95% CI:2.1-5.1). Common unfavorable attitudes towards ITNs included perceptions that insecticide smell disrupts sleep (41%); net care is a tedious task (36%); purchased ITNs are more effective than free ITNs (31%); and dislike of sleeping under an ITN during warm weather (29%). The results highlight Kenya's high net use rate and suggest that increasing access to ITNs, promoting favorable attitudes towards ITN use and care, boosting confidence in one's ability to use ITNs, and radio programming targeting adolescents may increase and sustain it.

6902

A FIVE-ARM TRIAL COMPARING ARTESUNATE-AMODIAQUINE AND ARTEMETHER-LUMEFANTRINE-AMODIAQUINE WITH OR WITHOUT SINGLE-DOSE PRIMAQUINE TO REDUCE PLASMODIUM FALCIPARUM TRANSMISSION IN MALI

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Artemisinin Combination Therapies (ACT) are the first-line treatment for uncomplicated Plasmodium falciparum malaria. ACTs rapidly clear asexual P. falciparum parasites, responsible for clinical symptoms, but have limited activity against mature gametocytes, which are the only life stages capable of transmitting to mosquitoes. To reduce P. falciparum transmission, the World Health Organisation recommends the addition of a single low dose of primaquine (0.25 mg/kg), a potent and fast-acting gametocytocidal drug, to ACT. Although Artesunate-Amodiaquine (ASAQ) is a commonly used ACT, limited available data suggest poor activity against gametocytes and the added benefit of SLD PQ in combination with ASAQ remains unknown and Artemether-Lumefantrine (AL) showed more gametocyte clearance and transmission reduction efficacy compared to Dihydroartemisinin-Piperaquine (DP). Recently, triple artemisinin-based combination therapies (TACT) such as Artemether-Lumefantrine plus Amodiaquine (ALAQ) have been proposed to delay the emergence of drug resistance and to provide efficacious treatment for multi-drug resistance P. falciparum infections. To determine transmission reducing efficacy of ASAQ with and without SLD PQ and AL with and without Amodiaquine (AQ) and Primaquine (PQ), we conducted a five arm, single-blind, randomized controlled trial in Ouelessebougou, Mali. Participants aged 10-50 years with asymptomatic P falciparum malaria with gametocytes detected by blood smear were randomised in a 1:1:1:1:1 ratio, to receive either ASAQ, ASAQ-PQ, AL, ALAQ or ALAQ-PQ. The primary efficacy endpoint, analysed in all infected patients with at least one infectivity measure before and after treatment, was median within person percent change in mosquito infection rate in infectious individuals from baseline to day 2 post treatment, assessed by membrane feeding. The recruitment is completed, and data cleaning is ongoing. Full results on the safety and malaria transmission blocking effect of these combinations will be presented.

6903

A QUASI-EXPERIMENTAL STUDY TO ESTIMATE EFFECTIVENESS OF SEASONAL MALARIA CHEMOPREVENTION IN AWEIL SOUTH COUNTY IN NORTHERN BAHR EL GHAZAL, SOUTH SUDAN

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Seasonal malaria chemoprevention (SMC) is an effective intervention to prevent malaria in children, in locations where transmission is seasonal. Due to sulfadoxine-pyrimethamine (SP) resistance concerns in East and Southern Africa (ESA), SMC was implemented in the Sahel region of West and Central Africa. Growing evidence suggest that SMC with SP and amodiaquine retain high level of effectiveness in ESA despite these concerns. This study aims to generate evidence on effectiveness of SMC when delivered under programmatic conditions in an area with an unknown antimalarial drug resistance in the Northern-Bahr-el-Ghazal. Five SMC cycles were delivered in Aweil South between July and November 2022. We conducted a non-randomised quasi-experimental study comparing intervention county with control county. Data were obtained from repeated cross-sectional household surveys of caregiver's children aged 3–59 months using cluster sampling. Wave1 survey took place in both counties before SMC implementation; Waves2 and 3 took place after cycles2 and 4. Difference-in-differences analysis was performed by fitting logistic regression models with interactions between county and wave. Estimates of effect of SMC expressed as odds ratios (OR) with 95% confidence intervals (CIs). A total of 2,760 children sampled in study across three survey waves in both study counties. Children in the intervention arm had 70% lower odds of caregiver-reported fever compared to those in control-arm during one-month period prior to Wave2 (OR:0.30, 95%CI:0.12–0.70, p=0.003) and 47% reduction in Wave3 (OR:0.63, 95%CI:0.22–1.59, p=0.306) after controlling for baseline difference between counties in Wave1. Odds of caregiver-reported RDT-confirmed malaria were 82% lower in previous one-month period prior to Wave2 (OR:0.18, 95% CI: 0.07–0.49, p=0.001) and Wave3 (OR:0.18, 95%CI:0.06–0.54, p=0.003). These results indicate that SMC is an effective intervention for malaria prevention in children in Northern-Bahr-el-Gazhal. More research is necessary for a better understanding of the role of drug resistance in determining SMC effectiveness and scalability in region.

6904

DIGITAL TRANSFORMATION IN HEALTH: GUINEAN EXPERIENCE OF USING A NATIVE ANDROID APPLICATION COUPLED WITH DHIS2 IN THE 2022 NATIONAL ITN DISTRIBUTION CAMPAIGN

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From 2013 to 2019, Guinea carried out three ITN distribution campaigns using paper-based data collection systems. Based on lessons learned from the 2021 digitalization of Guinea's seasonal malaria chemoprevention campaign, the 2022 ITN campaign was digitalized. This abstract describes the technological approach used for the digitalized ITN campaign and key challenges encountered. The digitalization was based on a customized Android application "MILDA 2" designed by HISP WCA to collect individual data centralized in DHIS2. The application was installed on 7785 tablets, which were managed by a Mobile Device Management (MDM) system. A national server and a cloud-based system were configured to host the data. The first step in the digitalization process involved development of the designer's guide and the integration of the micro-planning tree into DHIS2. The campaign data was collected by scanning the QR code of a physical coupon provided to the households, followed by completing electronic and physical coupons. An Excel database was used for comparative analyses. A back-scan of unrecognized coupons was performed to improve the completeness of the data. MDM protection limited tablet losses to 0.04%. The completeness of the enumeration data in DHIS2 was 95% for the population, 95% for households and 90% for the ITNs, compared to the physical count data. For distribution, 70% of households were covered and 75% for ITNs. The advantages of digitalization included shorter data collection period, data availability for multiple programs and higher data quality. The major difficulties were the instability of the application, the server and the poor network/internet coverage. The digitalization of the ITN distribution campaign in Guinea has been a hopeful experience for the digital transformation of the health sector.

6905

PLASMODIUM FALCIPARUM MALARIA INFECTION AND ANEMIA PREVALENCE IN UNDER FIVE YEAR OLD CHILDREN RECEIVING SEASONAL CHEMOPREVENTION IN A VILLAGE OF TANGHIN WOOBDO BURKINA FASO

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In Burkina Faso, children under 5 years of age account for 72% of malaria deaths. Seasonal malaria chemoprevention (SMC) is a strategy to prevent malaria in children under 5 years old. Its expected benefits are to prevent approximatively 75% of malaria episodes and probably reduce the incidence of moderate to severe anemia. This study aimed to assess hemoglobin rate and Plasmodium falciparum infection prevalence after large-scale SMC implementation in one village of Sabou health district.The study was conducted in Sabou Health District where malaria is hyperendemic and seasonal. SMC was delivered as sulfadoxine-pyriméthamine plus amodiaquine (SP-AQ) at monthly intervals from July to October 2020 to 182 children. Five cross-sectional surveys were conducted at baseline, before each SMC and endline which place 2 months after SMC. During each survey, malaria parasitemia and anemia were assessed. We noticed a significant increasing prevalence of Plasmodium falciparum infection across the different rounds of SMC. Malaria infection varied from 14.28% [IC95%: 9.15-19.41] at baseline to 29.23% [22.35-36.12]) during the pic of transmission, and 17.85% [IC95%:12.00-23.70] at the endline survey. Parasite density showed the same trend with 3199.459 P.f trophozoites/µl [IC95%: 1171.890 – 8735.068] at baseline and 4726.601 P.f trophozoites/µl [95%IC: 2038.318-10960.390] at endline. The prevalence of moderate anemia (Hb<8g/dl) was similar at baseline and endline (59.30% versus 53.05%; p = 0.24) and the hemoglobin rate of subjects was respectively 9.76 g/dl and 9.67g/dl (p=0.54).SMC did not bring a gain on hemoglobin levels in children. P. falciparum infection prevalence and parasite density were similar before and after the SMC; this should be probably due to drug pressure on children's immunity. Additional assessment of SMC's data in large sample across country and immunological analyses could contribute to highlight SMC benefits on the fight against malaria.

6906

INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY WITH MEFLOQUINE MAY REDUCE NEVIRAPINE LEVELS AMONG HIV-INFECTED WOMEN

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Sub-Saharan Africa is the region with the highest burden of malaria and HIV worldwide, being pregnant women the most vulnerable populations. Mefloquine (MQ) for intermittent preventive treatment (IPTp) of malaria in pregnancy has shown to significantly reduce malaria-related adverse maternal outcomes. However, while safe and effective in HIV-uninfected pregnant women, results from a randomized placebo-controlled trial assessing the safety and efficacy of IPTp-MQ among HIV-infected pregnant women showed that MQ recipients had a two-fold increased risk of HIV mother-to-child transmission (MTCT) compared to the control group. In this analysis we aimed to determine the antiretroviral (ARV) drug levels among a sub-sample of pregnant women participating in the aforementioned trial by treatment arm. ARV drug levels were determined in venous and cord blood samples of 249 pregnant women enrolled from 2010 to 2012 in Manhiça, Southern Mozambique. No significant differences in the maternal and fetal levels of nevirapine (NVP), lamivudine (3TC) and zidovudine (AZT) were found across groups. However, maternal levels of NVP tended to be decreased in MQ recipients compared to the placebo one among the subset of women transmitting the HIV to their infants (344.64 [558.99] vs 926.4 [619.67], p=0.054). Our findings suggest potential pharmacological interactions between MQ and NVP that warrant caution in the administration of antimalarial drugs to HIV-infected women on ARV treatment.

6907

CONTRIBUTION OF ACCESS IN THE IMPROVEMENT OF IPTP3 COVERAGE AMONG PREGNANT WOMEN IN MADAGASCAR, 2019 - 2022

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Madagascar has adopted intermittent preventive treatment during pregnancy (IPTp) using sulfadoxine-pyrimethamine (SP) in its national strategic plans for malaria control since 2013, with a national target of >50% for coverage with at least three doses of IPTp (IPTp3). The USAID-funded ACCESS program has supported the Ministry of Public Health since 2020 to implement a series of interventions focusing on peripheral health facilities with low or non-reported IPTp3 coverage, including targeted supervision focused on SP availability, data quality monitoring, and respectful care to increase service uptake. Using routine data extracted from the District Health Information Software II platform, we compared IPTp3 coverage (number of IPTp3 doses / number of first antenatal care visits) between Jan-Dec 2019 (before start of interventions) and Jan-Dec 2022 (after implementation) in 1,551 public facilities in the 59 districts implementing the ACCESS-supported IPTp strategy and 1,305 facilities in the 45 non-ACCESS-supported districts. In 2019, IPTp3 coverage was 22% (145,094/668,327) nationally; coverage was 17% (59,574/347,562) in ACCESS-supported districts and 27% (85,520/320,765) in non-supported districts. In 2022, IPTp3 coverage was 51% (340,669/671,191) nationally: 56% (216,388/388,148) in the districts supported by ACCESS—meeting the national target—and 44% (124,281/283,043) in the districts not supported by ACCESS. This represents an increase of 39 percentage points of IPTp3 coverage in ACCESS-supported districts between 2019 and 2022, compared to a 17-percentage-point increase in IPTp3 coverage in non-supported districts, suggesting that the intervention package was successful in improving IPTp3 coverage and expanding this model could further improve coverage. A difference-in-differences analysis controlling for potential confounders is recommended to provide further evidence for the effectiveness of ACCESS's interventions.

6908

COMBINING SMC ACTIVITIES WITH CATCH-UP IMMUNIZATION AND COMMUNITY MALARIA CASE MANAGEMENT IN GUINEA

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Since 2021 the National Malaria Control Program and the Expanded Program on Immunization, supported by their partners, have collaborated in six districts to combine seasonal malaria chemoprevention (CPS) and immunization activities. The objective of this study was to share the innovative measures and results achieved during the seasonal malaria chemoprevention campaign, with a focus on improving vaccination coverage and malaria case management in the community. A descriptive study was conducted between October 3 and 11, 2022, during the fourth round of the SMC campaign in 10 health districts of Guinea. The preparatory phase consisted of organizing meetings, identifying strategies and needs, and designing tools. The implementation phase included distributing SMC drugs, identifying children and women to be caught up, providing immunization, and treating all confirmed malaria cases in the community. The final phase involved synthesizing achievements, results sharing, and drawing lessons learned. In the implementation phase of the SMC campaign, for a target of 522 698 children, the administrative coverage of the fourth round was 95% (92-98%). For catch-up immunization, 23,817 EPI cards were identified at the health center level, and 18,474 children were located and immunized in the community by SMC distribution agents, i.e., 78% coverage. For pregnant women, 4,651 ANC cards were identified at the health center level, and 3,899 pregnant women were located and caught up by agents, for a coverage of 83%. The agents tested 3,172 suspected malaria cases in the community and treated 1,542 RDT-confirmed malaria cases. In conclusion, the mutualization of SMC activities with catch-up immunization has contributed to improving immunization coverage and reduced malaria cases in the community level. The next step should be to replicate in all the 17 eligible districts for SMC in Guinea.

6909

THE IMPORTANCE OF QUANTIFICATION TO OPTIMIZE RESOURCE MOBILIZATION FOR A CONTINUOUS SUPPLY OF ANTIMALARIAL COMMODITIES IN MADAGASCAR

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Correct quantification of needs is important for resource mobilization to ensure availability of antimalarial commodities. Since 2019, the USAID IMPACT program in Madagascar supports the Ministry of Public Health (MOPH) to improve the process of quantifying medicines and supplies to test and treat malaria. The country had few experts to conduct accurate forecasting and supply planning, limited financial resources to procure forecasted quantities and lack of visibility and coordination on procurement of commodities from multiple funding sources. In 2018, IMPACT provided technical assistance to a Procurement Supply Management (PSM) Committee led by the National Malaria Program (NMP). Since 2019, IMPACT provided training and coaching to PSM committee members on data collection and adjustment methods, forecasting and supply planning and the use of quantification tools, mainly the supply plan tool PipeLine to enable them to analyze data and correctly project needs. From 2019 to 2021, 42 quantification staff were trained: 13 from NMP, 14 from MOPH, 4 from SALAMA (central medical store), and 11 stakeholders. Quantification exercises were conducted annually with semester reviews to adjust the needs and mobilize financial resources to fill gaps. The quantification process contributed to increased mobilization of financial resources, dedicated to procuring malaria medicines and supplies to cover 81% of needs forecasted for 2021 ($8,092,744) and 100% for 2022 ($6,419,125) through sources of funding including the PMI, the Global Fund, UNICEF and the Malagasy government. Madagascar experienced no central-level stock outs of antimalarials and diagnostic tests in 2021 and 2022 despite the national and global logistics disruptions due to COVID-19. In July 2022, stock levels at SALAMA were sufficient to meet quarterly needs forecasted by the 114 districts of Madagascar with a maximum stock level of 6 months. Improvement of the central quantification process has contributed to improving the country's supply of antimalarial commodities. Other components of the supply chain remain to be strengthened for better availability of health commodities.

6910

PSYCHOSOCIAL FACTORS ASSOCIATED WITH INTENTIONS FOR SEEKING EARLY ANTENATAL CARE (ANC) DURING A FUTURE PREGNANCY: FINDINGS FROM THE KENYA MALARIA BEHAVIOR SURVEY

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Despite recent gains, only 38% of pregnant women in the malaria-endemic Lake region of Western Kenya received all three doses of intermittent preventive treatment during pregnancy (IPTp) according to the 2022 Kenya Demographic Health Survey. Given the association between antenatal care (ANC) and IPTp uptake, there is a need to understand the psychosocial factors associated with ANC intentions to inform future malaria programming. Kenya's Division of National Malaria Program (DNMP) and Breakthrough ACTION Kenya fielded the Malaria Behavior Survey in 2022 and interviewed 1,787 women of reproductive age from 1,456 households. Psychosocial factors, including attitudes towards seeking ANC and IPTp, were assessed based on agreement to a series of statements. Responses were scored and summed into factor-specific scales. Bivariate and multivariable logistic regression models examined socio-demographic, psychosocial, and structural factors associated with ANC intentions among women of reproductive age. Among women who had a child in the last two years who also intended to have more children, 70% intended to attend ANC early, 90% intended to attend 4 or more ANC visits, and 24% intended to attend 8 or more ANC visits in their next pregnancy. Attendance at ANC visits was significantly and positively associated with uptake of one, two, and three or more IPTp doses ($p<0.01$). In the final adjusted logistic regression model, respondents with favorable attitudes towards seeking ANC as well as favorable attitudes toward IPTp had significantly increased odds of early ANC intentions in their future pregnancy (Adjusted odd ratios (AOR): 3.7; $p<0.001$). Having seen or heard a malaria message in the last six months was also significantly associated with 1.9 higher odds of early ANC intentions (AOR: 1.9; $p<0.05$). The findings highlight the need for better understanding of the drivers of favorable attitudes towards ANC and IPTp to inform the design of social and behavior change activities to improve women's intentions to seek ANC early during their next pregnancy and ultimately, their receipt of IPTp.

6911

IMPACT OF COMMUNITY-BASED PROMOTION OR FOCUSED MALARIA IN PREGNANCY TRAINING FOR HEALTH PROVIDER ON THE COVERAGE OF INTERMITTENT PREVENTIVE TREATMENT IN PREGNANCY IN SAN, MALI

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Malaria in pregnancy (MiP) is associated with poor maternal and newborn outcomes. The World Health Organization recommends all women in their second and third of their pregnancy receive intermittent preventive treatment during pregnancy using sulfadoxine-pyrimethamine (IPTp-SP). In Mali, IPTp-SP is delivered through antenatal care (ANC) visits for eight ANC contacts. However, infrequent, late or non-attendance at ANC has been associated with less IPTp-SP uptake. Between April 2020 and September 2022, we conducted a cluster randomized trial in 30 community health centers in San, Mali, to assess whether community-based promotion of IPTp or MiP focused training and supervision for ANC health workers could increase IPTp uptake. Intervention arm 1 (IA1) is a community-based promotion campaign to improve women's awareness of and demand for at least three doses of IPTp-SP (IPTp3), while intervention arm 2 (IA2) consists of enhanced MiP focused training and supervision for health workers in ANC clinics. In the third (control) arm (CA), the current standard training and IPTp implementation strategy were maintained. The intervention impact was assessed using data collected from a baseline household survey, conducted in February-March 2020 prior to the study, and an endline survey in September 2022. Differences between proportions of women with IPTp3+ were tested using the chi2 test. A total of 2,195 women were interviewed at baseline. Overall, about 40.4% (37.9%-42.9%) received IPTp-SP at baseline; coverage was similar among treatment arms (41.2% in IA1, 36.9% in IA2, and 42.4% in the control arm) (p=0.213). At endline, among 1,464 women interviewed, IPTp3 coverage increased in both intervention arms, to 51.1% in IA1 and 50.0% in IA2, while coverage in the control arm declined slightly to 41.8%, representing an increase of 9.8% in IA1 (p=0.02) and 13.1% (p=0.001) in IA2. Both interventions significantly improved IPTp-SP uptake, although coverage remains lower than the national target. Rolling out MiP focused training more widely could help Mali to achieve national IPTp3 coverage targets.

6912

NEW TREATMENT REGIMEN OF SEASONAL MALARIA CHEMOPREVENTION A PROMISING ALTERNATIVE TO DISRUPT PLASMODIUM OF TRANSMISSION IN THE FIELD

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Seasonal malaria chemoprevention (SMC) intervention is based on antimalarial treatment for a target population to cure any asymptomatic infection and preventing new infections over a period of time. In some endemic countries, the SMC focuses on under 5 years old children for 5 months in the year with satisfactory outcomes when compared to no interventions. However, this target population is currently reinfected few weeks post intervention as some important reservoirs remain unperturbed. Asymptomatic Plasmodium carriage is important in children up to 15 years, and no large-scale collective curative action is carried out in children aged 5 to 15 years, making them the indefectible reservoirs of parasite. Also, malaria infection remains higher after the last SMC treatment leaving numerous asymptomatic carriers who remain infected during the dry season and ensure parasite transmission at the next wet season when the vectors become abundant. However, SMC effectiveness could be optimized with lasting synergistic effects if it was implemented integrating the major epidemiological variables such as human reservoirs and the temporal variations of the vector density. We investigated the potential additional benefits of SMC implemented taking account some parameters. In a pilot study, standard regimen SMC has been implemented but targeting up to 10 years old children and covering 6 months period with an observed versus unobserved regimen in 2 villages. In a sample of about 800 children (5-10 years old), the SMC efficacy for the Plasmodium infection was significantly lower during the peak raining season (about 10%) compared to this observed at the end of the wet season (70%). This finding correlated with the vector abundance, highlighting the important role of infectious mosquitoes which continuously reinfects the children after the protection period. Importantly, the negative individuals after last treatment remained uninfected until dry season. The next step of investigations focuses on follow up of this group to provide more information about the potential long-term impact of the new regimen SMC on the incidence of malaria infection.

6913

MULTI-LEVEL AND EVIDENCE-BASED ADVOCACY SUPPORTED INCREASED UPTAKE OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA AMONG PREGNANT WOMEN OF CROSS RIVER STATE, NIGERIA

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Sulphadoxine-Pyrimethamine (SP) is an affordable, effective drug used for intermittent preventive treatment of malaria in pregnancy (IPTp) yet remains largely unavailable. In Cross River State, Nigeria, 75% and 33% of pregnant women received two and three doses of IPTp respectively from October 2020 to November 2021, well below the national target of 80%. The U.S. President's Malaria Initiative for States (PMI-S) project adopted systems advocacy to foster action from community to state government actors to commit to SP procurement across health facilities. PMI-S convened multi-sectoral and multilevel stakeholders to develop evidence-based advocacy briefs highlighting the major issue of SP unavailability. The briefs were data-based, pre-tested and adapted to suit stakeholders with decision-making power. They were used as tools to streamline advocacy activities which commenced in November 2021. The advocacy briefs were given to malaria actors at the state, community, and health facility level to ensure adequate supply of SP and support for malaria interventions in Cross River. Data from the National Health Management Information System was analyzed to assess the impact of the advocacy activities and found that they helped increase donation of SP, commitments by chairmen of Local Government Areas, ownership of procurement and management of SP by health facility

managers, and Ward Development Committee donations of SPs. In fact, IPTp 2 coverage was over 80% by August 2022, meeting its target and 37% for IPTp3, closing the gap to target. These findings show that tested, tailored and multi-level advocacy lead to successful resource mobilization and support preventive treatment of malaria in pregnancy.

6914

COMPARISON OF DIARY-REPORTED BEDNET USE ACTIVITIES AND ACCELEROMETER-BASED BEDNET DATA FROM COTE D'IVOIRE

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Malaria has not declined as expected in some countries despite the wide-scale distribution of long-lasting insecticide treated bednets (LLINs). One explanation could be overestimated LLIN use or the timing of use may not correspond with the timing of vector exposure. Questionnaires about LLIN use may be unreliable as measures of LLIN use, since they are prone to recall and social desirability bias, and only give a snapshot of LLIN use the previous night thus missing any temporal variation. Electronic monitors of LLINs use can provide hourly objective measurements of whether an LLIN is in use or not. This study is an early analysis of households enrolled in an observational study using electronic monitors of LLIN use in the peri-urban town of Tiassale, Cote d'Ivoire. In this analysis, 4 households were followed for 10 nights each in February 2023 (40 nights of monitoring). Accelerometer-based LLIN monitors were attached to one bednet in the household and inhabitants were asked to keep a diary of the times during the night that the LLIN was unfurled, folded up and whenever anyone entered or exited the LLIN. On average, the households reported unfurling the net for sleep at 2150 in the evening and folding up the net at 634 in the morning, with an average of 1.7 net entries (SD: 1.4) and 1.81 exits per night (SD: 1.4). Overall agreement between a previously developed machine learning algorithm for classifying LLIN activities based on accelerometer data and the participant diaries was 80.0% (116/145). This varied by LLIN activity: net put down (82.5%), net put up (79.5%), entry into net (79.5%) and exit from net (77.8%). This analysis suggests that accelerometer-based monitors of LLIN use have good agreement with reported use and may be a useful tool for monitoring LLIN use in malaria endemic settings over time.

6915

ESTIMATING THE IMPACT OF LLIN USE PATTERNS ON ANOPHELES MOSQUITO EXPOSURE AMONG SCHOOL-AGED CHILDREN IN UGANDA

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School-aged children (SAC) in Africa have high prevalence of malaria, yet they are often the least likely to use long-lasting insecticide treated bednets (LLINs). Existing interventions to improve LLIN use in this age group include school-based education and universal distribution programs. Although low use has been attributed to a lack of access, little is known about LLIN use patterns in SAC who have access to LLINs. SmartNet is a validated tool for electronically measuring LLIN use over time. The aim of this study is to characterize LLIN use patterns among SAC and estimate the impact on malaria exposure. Data was collected from 99 individuals living in 20 households in the Tororo District of Uganda from May to October 2019. Time in and out of bed were measured by self-report. Mosquito burden was measured with CDC light traps every two weeks, and hourly distribution of mosquito exposure throughout the night was calculated using human landing catches in nearby houses. SAC were defined as children 5 to 15 years old. Compared with other ages, SAC were less likely to use their LLIN at all overnight (OR 0.42, p = 0.014) and used LLINs for 1.1 fewer hours per night (p = 0.001). Without any LLIN use, SAC were exposed to an average of 2.48 mosquitoes per night. Based on SmartNet data, measured LLIN use would prevent 69.7% of exposures to an average of 0.75 per night. If all SAC unfurled LLINs by 7 PM, 98.7% of exposures could have been prevented, 87.9% if unfurled by 8 PM, and 71.7% if unfurled by 9 PM. This study shows that mere access to LLINs may be insufficient to decrease mosquito exposure in SAC, and provides insight into what temporal use patterns, including earlier LLIN coverage, may be the most effective in preventing exposure.

6916

IMPACT EVALUATION OF SEASONAL MALARIA CHEMOPREVENTION THROUGH ANALYSIS OF LARGE, AGGREGATED ROUTINE COVERAGE SURVEYS IN NIGERIA, BURKINA FASO, CHAD, TOGO AND MOZAMBIQUE (2020-2022)

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Previous studies on seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine (SP) and amodiaquine (AQ) suggest it is highly effective in reducing risk of Plasmodium falciparum malaria infections among eligible children in areas with seasonal transmission. As SMC has expanded geographically and monitoring surveys established, there is growing potential for aggregated datasets based on routine surveys to address new research questions which may previously have been technically infeasible using Health Management Information Systems data or financially infeasible as primary research. Malaria Consortium has built a harmonized dataset including all end-of-round annual SMC coverage surveys since 2020 with data on children, their caregivers and households. These surveys were representative of SMC target populations and conducted by independent contractors. Using these data we conducted an analysis on 47,345 eligible children aged 3-59 months in five countries to test the association between receipt of SMC (SPAQ on Day 1) in the penultimate cycle of each SMC round and caregiver-reported rapid diagnostic test (RDT) confirmed malaria cases in the subsequent month. We then tested associations between numbers of doses of SP and AQ received and RDT-confirmed malaria in 21,589 children in Nigeria. We fitted random-effects logistic regression models adjusted for child, caregiver and household variables including net use. The results showed that receipt of SMC was significantly associated with 30% lower odds of RDT-confirmed malaria (OR: 0.70, 95% CI: 0.65-0.76, p<0.001). In Nigeria, compared with those who had not received any dose of SMC medicines, there were lower odds of RDT-confirmed malaria among children who received Day 1 SPAQ only (OR: 0.61, 95% CI: 0.35-1.07, p=0.088), Day 1 SPAQ plus one AQ dose (OR: 0.45, 95% CI: 0.31-0.66, p<0.001), and Day 1 SPAQ and both AQ doses (OR: 0.53, 95% CI: 0.47-0.60, p<0.001). The results imply full adherence to the dosing regimen is needed to ensure SMC's full effectiveness. Next steps will involve a case-control analysis using propensity score matching, and addressing new research questions.

6917

COVERAGE OF INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN INFANTS AFTER FOUR YEARS OF IMPLEMENTATION IN SIERRA LEONE.

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Intermittent Preventive Treatment of malaria in infants (IPTi) is a malaria control strategy consisting of the administration of an antimalarial drug alongside routine immunizations. So far, this is being implemented nation-wide in Sierra Leone only. IPTi has been renamed as Perennial Malaria Chemoprevention -PMC-, accounting for its recently recommended expansion into the second year of life. Before starting a pilot implementation on PMC, the currently implemented strategy and malaria prevalence were assessed in young children in selected areas of Sierra Leone. A cross-sectional, community-based, multi-stage cluster household survey was conducted from November to December 2021 in selected districts of the Northern and northwestern provinces of Sierra Leone among 10- 23 months old children, whose caretakers gave written informed consent to participate in the survey. Coverage of IPTi and malaria prevalence -assessed with rapid diagnostic tests-, were calculated using percentages and 95% confidence intervals weighted for the sampling design and adjusted for non-response within clusters. A total of 720 children were recruited. Coverage of 3 IPTi doses was 50.57% (368/707; 95% CI 45.38 – 55.75), while prevalence of malaria infection was 28.19% (95% CI 24.81 – 31.84). Most children had received IPTi1 (80.26%, 574/707; 95% CI 75.30 – 84.44), and IPTi2 (80.09%, 577/707; 95% CI 76.30 – 83.40) and over half of the children also received IPTi3 (57.72%, 420/707; 95% CI 53.20 – 62.11). The uptake of each IPTi dose was lower than that of the vaccines administered at the same timepoint at all contacts. In Sierra Leone, half of the children received the three recommended doses of IPTi indicating an increase in its uptake compared to previous data of just a third of children receiving the intervention. However, efforts need to be made in improving IPTi coverage, especially in the planned expansion of the strategy into the second year of life following recent WHO guidelines.

6918

ARTEMETHER-LUMEFANTRINE AS A CHEMOPROPHYLACTIC TREATMENT OF MALARIA

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Antimalarial chemoprophylaxis for high risk groups in endemic areas of Southeast Asia has the potential to reduce malaria transmission and accelerate elimination. However, the optimal choice of medication and dosing for many potential candidates is not clear. In Southeast Asia, the high prevalence of artemisinin and multidrug resistant Plasmodium falciparum limits the choice of drugs suitable for chemoprophylaxis. Artemether-lumefantrine is one of the six WHO-recommended artemisinin-based combination therapies (ACTs) for treatment of uncomplicated P. falciparum and P. vivax malaria, but is not widely used for prophylactic purposes. As artemether-lumefantrine has not been used previously for prophylaxis, a pharmacometric modelling and simulation approach was used to determine the optimal dosing schedule. Population pharmacokinetic-pharmacodynamic modelling and simulation was used to evaluate different dosing scenarios. Lumefantrine exposures were evaluated for different dosing schedules; (1) a full 3-day treatment course of 480 mg lumefantrine given once a month, (2) a full 3-day treatment course of 480 mg lumefantrine given twice a month, (3) a loading dose of a full 3-day treatment course of 480 mg lumefantrine followed by 480 mg lumefantrine QD given once a week, and (4) a loading dose of a full 3-day treatment course of 480 mg lumefantrine followed by 480 mg lumefantrine BID given once a week. A full 3-day treatment course given twice a month, and twice daily treatment given once a week, resulted in trough concentrations consistently above the therapeutic threshold of 200 ng/mL. However, the most favorable exposure profile, and arguably most practical dosing scenario was an initial 3-day full treatment course followed by twice daily dosing given once a week for the duration of chemoprevention. This dosing was consequently evaluated in a prospective clinical trial in Cambodia and showed excellent safety and protective efficacy.

6919

USING MODELING TO ASSESS THE OPERATIONAL AND EPIDEMIOLOGICAL FACTORS AFFECTING EFFECTIVENESS OF PRAGMATIC PERENNIAL CHEMOPREVENTION IN OSUN STATE, SOUTHERN NIGERIA

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Perennial malaria chemoprevention (PMC) is recommended for children living in areas with high and persistent transmission, but it has not yet been widely implemented. Recent recommendations encourage countries to adapt PMC to their local contexts, taking both epidemiological and operational factors into account. However, there are no clear guidelines on how to do this, and it is unclear what the tradeoffs might be, as epidemiological and operational needs do not always align. Compared to delivery via the Expanded program of immunization (EPI) to specific ages of the child, a pragmatic approach to delivery might involve offering additional chemoprevention at every health visit. Through individual-based mathematical modeling, we compare the pragmatic PMC to the EPI-based-only delivery schedule in children under the age of two years. We evaluate epidemiological and operational factors that might influence PMC performance, including malaria transmission and exposure, distance to health facilities and health care seeking, as well as coverage, probability of missing doses, and timeliness of doses. We calibrated our model to an ongoing PMC pilot implementation study site (Osun State, Southern Nigeria), using data from the pilot study and demographic household surveys. With the pragmatic delivery schedule, children received on average twice as many doses as with the EPI-based schedule alone, for a maximum of seven EPI touchpoints. Under ideal conditions (target coverage of 80%, constant care-seeking rates, and no delays), the protective efficacy increased by 25 percentage points. Under operational conditions, the pragmatic delivery approach remained more impactful but varied depending on the different factors affecting coverage. Intervention modeling that disentangles coverage can be used to identify how to customize PMC strategies within countries by assessing the trade-off between epidemiological and operational factors.

6920

MODELLING THE PUBLIC HEALTH IMPACT OF PERENNIAL MALARIA CHEMOPREVENTION: CURRENT GUIDELINES AND A PROPOSED AGE-EXPANSION

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Updated guidelines for perennial malaria chemoprevention (PMC) extended the coverage from infants to children to up to 24 months, with a flexible contextual dosing schedule, and without the need for sulphadoxine-pyrimethamine (SP)-sensitive parasite genotype based implementation. While decade-long evidence propelled a revival of this underutilized intervention, the WHO also highlights the need for further research, including: evidence of public health impact beyond 15 months of age, expansion to children over 24 months, and assessing if total public health impact outweighs any post-intervention delayed malaria effect. To address these gaps, we applied a validated individual-based model of malaria integrated with pharmacological models of drug impact (OpenMalaria). Current and age-expanded regimens (for children up to 36 months) were modeled by administering seven and nine doses of SP, across a range of transmission and healthcare settings, against partially SP-resistant (prevalent quadruple mutations in Pfdhfr and Pfdhps genes) and fully SP-sensitive parasites. General trends of intervention cost-effectiveness was projected to inform implementation decisions. Consistent with systematic reviews, both current and age-expanded regimens had modest but important public health impact (in settings of 5-67% PfPR2-10: median protective effectiveness over the first three years of life of 14.9% and 17.2% against clinical and 8.1% and 9.7% against severe cases against partially SP-resistant parasites, or to 20.8% and 24.2% against clinical and 9.7% and 13.2% against severe cases in fully SP-sensitive settings). Total program benefits outweighed any risk of rebound delayed malaria in children under five. An age-expanded PMC regimen protects more children with high risk of severe malaria, and may counterbalance modest reductions in impact from drug resistance. Robust healthcare system additionally supports mitigating the small risk of delayed malaria. Our economic analysis confirms both PMC regimens implemented via existing EPI delivery platforms are likely to be cost-effective in the recommended transmission levels.

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HARNESSING COMMUNITY HEALTH WORKERS TO IMPROVE PERENNIAL MALARIA CHEMOPREVENTION UPTAKE IN CAMEROON: INSIGHTS FROM THE PLUS PROJECT

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Several factors limit access to malaria control services in Cameroon, such as low health seeking behaviors among beneficiaries, limited access to quality care, and data quality issues. Community health workers (CHWs) have proven effective in addressing some of these issues, linking their community to the health system as a first point of contact. CHWs are recruited through a process involving communities, decentralized territorial authorities, health area leaders, and traditional leaders, among others, and are enlisted in Cameroon's Integrated National Strategy for the implementation of activities under community guidelines. Launched in 2021, the Plus Project supports countries to adapt, implement, and evaluate models of perennial malaria chemoprevention (PMC) using sulfadoxine-pyrimethamine (SP). In Cameroon, the NMCP adopted a five-contact model of PMC in late 2021 and requested the Plus Project to implement an eight-contact model in select districts, increasing the number of doses by adding contacts at 12, 18, and 24 months, and by offering community delivery of SP for PMC starting at six months of age. To date, 275 CHWs from four health districts have been trained and supervised by civil society organizations (CSOs), aligning with the current system of CHW supervision and management. The CHWs sensitize the population on PMC and encourage them to visit their health facility to receive SP for PMC at predefined contact points alongside routine vaccines and vitamin A. The data from CHW-led PMC activities were integrated into the national tools, which have been modified to include the community-based indicators of PMC. These data are reviewed during a monthly data validation meeting chaired by each health area chief before the paper-based record is uploaded into the online HMIS database. As CHW data is currently combined with data from the corresponding health facility, the Plus Project will receive additional reports of doses of SP for PMC delivered by CHWs and track how CHWs contribute to the delivery of this key intervention. Community delivery of SP for PMC is starting in March 2022, with initial data expected in May 2022.

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ADOPTION OF A PERENNIAL MALARIA CHEMOPREVENTION (PMC) STRATEGY IN BENIN: A CO-DESIGN PROCESS

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In 2021, the Plus Project was initiated to generate data on the impact, effectiveness, and cost-effectiveness of perennial malaria chemoprevention (PMC) in Benin, among other countries, to support the widespread adoption of PMC to children under two. As a new strategy, key steps were taken to ensure the successful implementation of PMC in Benin and promote the sustainable integration of PMC into the existing health system. A co-design process was used to engage partners, stakeholders and governing bodies during the PMC development process. This included two multi-day strategic workshops with partners at national and subnational levels and the project team to 1) discuss barriers to Benin's adoption of PMC, 2) determine target geographic areas for implementation, 3) outline the target population and PMC dosing schedule, and 4) identify existing supervision, M&E, and other relevant systems to leverage and integrate with PMC. The workshops included presentations, group work, consensus-building activities, and final decision-making, resulting in key project design elements, including the identification of the target population, implementation areas, and plans for PMC integration with the national HMIS. Participants agreed on an eight-contact model to administer doses of sulfadoxine-pyrimethamine (SP) to children through leveraging the existing immunization schedule, vitamin A and routine visits to health facilities. Participants selected three health zones in the North, Center and South for implementation (Bembérekè-Sinendé, Zogbodomè-Bohicon-Zakpota, Klouékanmè-Toviklin- Lalo), based on an agreed inclusion criteria (weighted for: 1) malaria incidence and mortality in children under five, 2) vaccination coverage, and 3) population under two years) and exclusion criteria (areas where seasonal malaria chemoprevention is already implemented). This process facilitated participatory decision-making, fostered stakeholder engagement, and enabled collaboration among many partners and governing bodies. Lessons learned during the co-design process can be used to guide future country implementation and scale-up of PMC.

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DESIGNING COMMUNITY ENGAGEMENT ACTIVITIES USING A HUMAN CENTERED APPROACH TO PROMOTE PERENNIAL MALARIA CHEMOPREVENTION ADOPTION: THE PLUS PROJECT EXPERIENCE IN BENIN, CAMEROON, COTE D'IVOIRE, AND MOZAMBIQUE

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Perennial malaria chemoprevention (PMC), the updated WHO recommendation replacing intermittent preventive treatment for malaria in infants (IPTi), is shown to reduce clinical malaria by 30% and anemia by 21% in children under two. Given these results, the Plus Project is supporting governments to implement different PMC models in four countries: Benin, Cameroon, Côte d'Ivoire, and Mozambique. The target population for PMC delivery includes children under two, who receive up to eight doses of sulfadoxine-pyrimethamine (SP) during routine visits for immunizations and vitamin A. While vaccination coverage in project countries is high, low attendance at vaccination appointments after the first year of life and inconsistent vitamin A supply at clinics can hinder the effectiveness of this new intervention. To promote consistent attendance and timely PMC delivery, a human-centered community engagement (CE) approach was developed for the Plus Project. CE activities were designed to build Empathy, gather Insights about potential barriers and facilitators to PMC uptake, and develop Prototypes (EIP) for activities and messages. Key to this strategy, the plan was created to ensure that caregivers, community health workers, providers, and community leaders are the drivers of this change. To implement this approach, project teams and NMCP collaborators were invited to a Training of Trainers (TOT) to build capacity on the EIP tools, which included journey mapping, outlining trusted communication networks, and creating target group archetypes. Following the TOT, attendees organized a CE workshop where they conducted EIP activities in a selected district for each country. Insights gathered during these workshops allowed the project team to understand the facilitators and barriers to the uptake of PMC in each country, which will be used to tailor the CE plan to the needs and requests of the community. Through continued use of a human-centered CE approach, additional materials and activities will be implemented throughout implementation to promote improved attendance at vaccination clinics for PMC and other necessary child health services.

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KNOWLEDGE, ATTITUDES, PRACTICES AND ACCEPTABILITY OF DIGITAL PAYMENT BY OPERATORS OF THE INDOOR SPRAYING CAMPAIGN AGAINST MALARIA IN THE HEALTH DISTRICT OF KOUMPENTOUM (SENEGAL)

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Digitization of payments could improve worker welfare, patient welfare, and health system performance. The objective of this study was to identify factors associated with the acceptability of digital health payments by indoor malaria spray campaign operators. This is a descriptive and analytical cross-sectional study. Data were collected from operators in the 2022 domestic spray campaign. Collection took place from January 16 to January 28, 2023. We had studied the knowledge, attitudes, practices, and acceptability of digital health payment. Multiple logistic regression was used to identify factors associated with acceptability. Acceptability was 86.16% for the following reasons: perception of safety (68.55%), speed (55.35%), anonymity (46.54%) and time saving (42.14%). 88.31% of the cases were considered very good or good. The reasons for refusal were high shipping/transfer costs (100%), unavailability of service (59.09%), lack of network (54.55%) and handling errors (54.55%). In the multiple logistic regression, favoring digital payment in general (ORa = 8.21 [1.39-49.03]; p = 0.02), favoring digital payment in healthcare (ORa = 8.41 [2.02-34.93]; p = 0.0034), lack of experience using the service (ORa = 21.59 [3.92-118.68]; p = 0.0004), and satisfaction during use (ORa = 37.19 [5.99-230.81]; p = 0.0001) were predictive of acceptability of digital payment in healthcare. In conclusion, the digitization of health care payments is a challenge. It should be factored into health campaigns to improve outcomes, but telephone and internet expansion, co-payment reduction, and claims management must be improved.

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IMPLEMENTATION OF PHASE 1 OF PERENNIAL MALARIA CHEMOPREVENTION (PMC) IN CHILDREN UNDER TWO YEARS OF AGE IN ABENGOUROU, CÔTE D'IVOIRE

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Malaria is the leading cause of morbidity in children under five in Côte d'Ivoire, responsible for 65% of deaths in 2020 with an incidence of 440 (per 1000 people at risk). According to WHO guidelines, perennial malaria chemoprevention (PMC), which consists of administering a full course of antimalarial treatment at predefined intervals to infants or young children, is recommended to prevent disease in areas of moderate to high malaria transmission. With support from the Project Plus, Côte d'Ivoire began implementing PMC for children under two years of age in one health district in November 2022. Health centers providing routine immunizations (n=39/42) were included in the PMC activities. The PMC model adapted to Côte d'Ivoire provides up to 5 doses of sulfadoxine-pyrimethamine (SP) to children during routine immunizations (DPT2, DPT3, RR1, and RR2) and vitamin A supplementation at 18 months. Monitoring of implementation is essential to assess progress and detect unforeseen challenges. Key performance indicators for the provision of PMC are based on routine health system data and include the number of doses of SP administered, the number of children experiencing side effects after administration, and the availability of SP. A new supervision module was created to measure provider adherence to PMC protocols, routine monitoring, and data quality processes, with data captured during routine supervision visits. As of February 2023, 9966 doses of SP had been distributed, including 8526 doses of SP1, 1421 doses of SP2, and 19 doses of SP3. No sites reported a shortage of SP and no side effects were documented. All 39 sites were visited by supervisors who found that 100% of the providers were trained and complied with the pediatric SP dosing and DOT strategy. The supervisors' scores are being recorded and will be used to track changes in the quality of primary care delivery over time. The results of this first phase of implementation will be used as documentation for Côte d'Ivoire on the sustainability of preventative care and for the revision of national malaria prevention guidelines.

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ACCEPTABILITY AND IMPLEMENTATION COST OF THE INTERMITTENT PREVENTIVE TREATMENT FOR MALARIA IN SCHOOLCHILDREN IN MODERATE AND HIGH ENDEMIC AREAS, NORTH-EASTERN TANZANIA

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Intermittent preventive treatment of malaria in school children (IPTsc) is currently recommended by the world health organisation (WHO) to be implemented in moderate and high endemic areas. However, its wider adoption will depend on acceptability to key stakeholders such as parents, teachers, malaria programs and also the implementation cost. A qualitative research was conducted, following a clinical trial (NCT03640403, N=1566) and an implementation research (NCT04245033, N>73000) assessing the effectiveness of IPTsc in schoolchildren of high endemic areas of Tanga region, north east of Tanzania. We aimed to understand the acceptability, experiences and adoption of IPTsc among parents, schoolchildren, teachers and program leaders on IPTsc using the RE-AIM framework. We also assessed the implementation cost in a real life operational setting including possible synergies with other school health intervention programs. About 108 focused group discussions were conducted (46 to parents and 62 to school children distributed equally by gender). We also conducted 64 in-depth interviews with teachers, community health workers(CHWs) and district and national malaria program officials. Themes obtained included, key factors of intervention acceptability, these included appreciated disease burden and the observed benefits following IPTsc intervention. To most schoolchildren, their acceptability to IPTsc program was positive with a noticeable decline in malaria episodes during the study period. Schoolchildren and parents also accepted the IPTsc delivery approach through their teachers. They described some adverse events following drug administration as mild and tolerable. Program officials and school teachers expressed positively on means for sustainability of the IPTsc programme, readiness for change and overcoming identified barriers to adoption. The average IPTsc delivery cost per round per child was 0.4 USD excluding drug procurement. IPTsc was widely acceptable among communities in the moderate and endemic areas and can be implemented at a minimal cost with a substantial high impact, making it a cost saving intervention.

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IMPROVING CLIENT SATISFACTION AND COMPETENCE OF HEALTH PROVIDERS IN TANZANIA

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The World Health Organization recommends that continuous quality improvement tools include assessments of readiness, clinical performance, and client satisfaction. Many assessments concentrate on health care worker (HCW) capacity and attitude to improve quality of care and not client feedback. Tanzania's Malaria Services and Data Quality Improvement (MSDQI) assessment covers readiness, observational supervisory visits, and patient exit interviews at outpatient departments (OPDs) and antenatal care clinics (ANCs). Following completion of MSDQI assessments, supervisors provide feedback to HCWs. MSDQI performance indicators categorize average scores ≥75% as good performance. The National Malaria Control Program with support from PMI Impact Malaria Project analyzed data on observed competence of clinical services for malaria performed by HCWs and client satisfaction in Lindi, Mtwara, and Katavi regions from MSDQI assessments conducted in 2021 and repeated in 2022 for the same OPDs in 518 facilities and for the same ANCs in 512 facilities. Each exit interview for client satisfaction assessed the time clients spent at the facility, services received, interaction with HCWs, and overall satisfaction with the services provided. Between MSDQI assessments in 2021 and 2022, the proportion of facilities with good performance in overall competence of HCWs in OPDs significantly improved from 60% to 75% ($p<0.0001$) and client satisfaction increased from 81% to 85% though the increase was not statistically significant ($p=0.144$). In ANCs, competence of HCWs significantly improved from 74% to 85% ($p=0.003$), as did client satisfaction from 89% to 93% though not statistically significant ($p=0.146$). Assessment of patient counseling that included when to return to the facility, danger signs, and use of medicine significantly improved from 56% to 67% ($p<0.0001$) at OPDs and 89% to 90% at ANCs though not statistically significant ($p=0.552$). HCW competency improved during the assessment period which may be related to the MSDQI assessment and feedback process. Client satisfaction remained high.

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MECHANISMS FOR MANAGEMENT MISSINGNESS OF DATA IN THE HEALTH MANAGEMENT SYSTEM A CASE OF UGANDA MALARIA CONTROL PROGRAM

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In many clinical trials or time series setting, data are collected longitudinally over time. The researcher collecting hierarchical data is frequently confronted with incompleteness. Since the processes governing missingness are often outside the investigator's control, no matter how well the experiment or study has been designed, careful attention is needed when analyzing such data. In such studies, missingness, in particular dropout or non-reporting, is an often-encountered phenomenon. In this study we examine missingness in a longitudinal District Health Information systems (DHIS2). The DHIS is an online system used for data management and analysis purposes, health program monitoring and evaluation, facility registries and services. Particularly in this, study utilizes the malaria control program indicators to demonstrate how to manage missing data in informing policies at Ministry of Health Uganda. A number of methods have been or are being developed and tested to be integrated into the Uganda National Malaria Control Division's routine reporting system. We discuss commonly used but often problematic simple methods such as complete case analysis and last observation carried forward and contrast them to a number of viable candidates for a standard analysis, like direct likelihood, multiple imputation and versions of generalized estimating equations. Finally, we conclude with sensitivity analysis to crosscheck the proposed methods. The commonly used methods rest on strong assumptions, including missing completely at random for complete cases and unchanging profile after dropout for last observation carried forward. Such assumptions are too strong to generally hold. Multiple imputation gives a good and more plausible way of imputing missing values other than just using last

observation carried forward despite its computational complexity. Lastly the selection and pattern mixture models will provide flexible modelling for the outcome and missingness processes at the same time they will be used for sensitivity analysis.

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SYNERGY BETWEEN FACILITY AND COMMUNITY-BASED SURVEILLANCE IN THE MALARIA VACCINE PILOT EVALUATION IN GHANA: BEST PRACTICES, CHALLENGES AND LESSONS LEARNT

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To assess the programmatic feasibility of administering the recommended four doses, impact on mortality and its safety in the context of routine use. The WHO recommended the RTSS vaccine be piloted in countries with moderate to high malaria transmission. Ghana, Kenya and Malawi are participating in the pilot. A combination of facility and community-based surveillance approaches were used to estimate the effect of the vaccine on all-cause mortality, and malaria and gender-specific effects in children aged 5 to 39 months. A cluster randomized design with evenly split implementing and comparator clusters was deployed. The surveillance recorded all under-five deaths and conducted verbal autopsies on them. Vaccination status was determined for each diseased child to enable assess the risk of mortality. A series of engagement meetings were held with stakeholders as part of preparations. At the household, caregivers of the diseased children granted consent for verbal autopsy interview. Community key informants identified all deaths and reported same to verbal autopsy (VA) coordinators who were full-time workers of the health system. All VAs were conducted electronically using WHO 2016 VA instrument. Regional coordinators supervised the work and conducted quality control including re-interviewing randomly generated VAs each month. Overall, about 7361 community volunteers, 132 district verbal autopsy coordinators, 12 regional coordinators, project managers and mortality leads were the personnel involved. As at December 2022, a total of about 7732 deaths were documented with approximately 98% VAs conducted with about 0.6% consent refusals and about 90% cause of death assigned. Documented vaccine records including maternal recalls was over 90%. This presentation highlights the successes, innovations, best practices, challenges, and lessons learnt in this approach.

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PREDICTION OF RESISTANCE PIPERAQUINE BASED ON ATYPIC PIPERAQUINE CHEMOSENSITIVITY ISOTOPIC DATA

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Surveillance of antimalarial efficacy is important for the control and elimination of malaria worldwide. Tools have been developed to study this parameter in vitro. Among them, the isotopic susceptibility assay is acknowledged as a gold standard method to evaluate the in vitro drug susceptibility of Plasmodium falciparum strains. However, for the antimalarial drug piperaquine (PPQ), susceptibility inquiries often produce incomplete inhibition curves for resistant isolates even at high concentration. This makes phenotypic interpretation difficult and compels researchers to perform other assays deemed more reliable. Nowadays, survival assay represents the most robust method to identify PPQ-resistant isolates. However, this method is time consuming. Besides, the large amount of data obtained with the isotopic one would benefit from being analyzable. In this study, results obtained on 95 isolates collected in an endemic area with PPQ resistance were analyzed in parallel through standard isotopic susceptibility assays and piperaquine survival assays. The growth parameters resulting from the isotopic method were then exploited in order to define a predictive approach assessing the in vitro resistance status of an isolate against PPQ. Using lumefantrine (LU) drug-response data as reference, isolate growth ratios under PPQ vs LU were evaluated and used to classified the isolates. We observed a correlation between survival rate and growth ratio PPQmax/LUmax allowing the selection of a growth ratio threshold of 2.8 beyond which resistance to PPQ is strongly suspected. This alternate way to exploit previously stated “uninterpretable data” from isotopic susceptibility assay during longitudinal surveillance allows the prediction of piperaquine resistance phenotype with 75.8% (72/95) of accuracy.

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UNITED STATES OF AMERICA DOMESTIC MALARIA DRUG RESISTANCE SURVEILLANCE USING TARGETED AMPLICON DEEP SEQUENCING (TADS), 2018-2021

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Plasmodium infection and malaria continue to persist worldwide; therefore, global efforts towards control and elimination remains exigent. Some of these efforts include utilizing novel therapeutics and fortifying comprehensive surveillance programs. Despite having eliminated malaria in the mid-1950s, the United States (US) continues to track and support national efforts for public health surveillance of imported malaria cases. The objective of this surveillance activity is to characterize drug resistance mutation profiles of imported malaria cases in the US using molecular methods. For this purpose, we used the previously established targeted amplicon deep sequencing (TADS) and associated bioinformatics pipeline Malaria Resistance Surveillance (MaRS) to genotype molecular markers of drug-resistance in six full-length P. falciparum (Pf) genes (Pfcrt, Pfmdr1, Pfk13, Pfdhps, Pfdhfr and PfcytB) to identify known single nucleotide polymorphisms (SNPs) associated with drug resistance. Data from 1209 imported malaria specimens reported to the Centers for Disease Control and Prevention, in collaboration with the New York State Department of Health Wadsworth Center, from 2018-2021 are presented. We found that 1077 specimens (89%) were positive for Pf. Mutations in the Pfdhfr gene (pyrimethamine-resistance) were observed in 88% of specimens while mutations in the Pfdhps gene (sulfadoxine-resistance) were present in 81% of specimens. Additionally, mutations in both Pfmdr1 (chloroquine-resistance) and Pfcrt (chloroquine-resistance) genes were detected in 60% and 30% of specimens, respectively. Next, mutations in PfcytB gene (atovaquone-proguanil-resistance) were present in 0.1% of specimens. Furthermore, we found 0.9% of specimens carried previously reported mutations in the Pfk13 gene; however, these SNPs are not associated with artemisinin-resistance. Overall, our data summarize drug resistance markers among specimens from patients with imported malaria and provides information about molecular resistance to eventually aid with treatment guidelines for travelers and patients in the US.

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DIGITALIZATION OF MALARIA CAMPAIGNS IN NIGERIA: IMPACT, CHALLENGES, KEY FACTORS FOR CONSIDERATION AND OPPORTUNITIES

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Malaria remains a major public health issue in Sub-Saharan Africa, with Nigeria contributing 27% of global burden. Among other interventions, malaria campaigns (Insecticide Treated Net (ITN) & Seasonal Malaria Chemoprevention (SMC)) remain proven impactful strategies to reduce malaria burden. In 2018, National Malaria Elimination Programme (NMEP) and supporting partners introduced digitalization as part of efforts to improve malaria campaign activities. While some progress has been made, challenges remain. This work aimed to document progress made with malaria campaign digitalization in Nigeria, challenges and opportunities for improvement. A mix of qualitative & quantitative approaches were utilized to collect relevant information including in-depth key informant interviews, focus group discussions using a structured questionnaire guide and an interviewer-administered survey tool from campaign implementers at national and sub-national levels. Digitalization of malaria campaigns occurred in 27 of 36+1 states with support from 4 donors with no clear plans to scale. Deployment of digital tools for malaria campaigns has enhanced payment of campaign staff and improved visibility during implementation at the sub-national level through real-time monitoring. There are 5 tools deployed for malaria campaign processes. The utilized digital tools are not linked with the National Malaria Data Repository limiting opportunities for decision making. While there are functional platforms for coordination of malaria campaign digitalization, there is no common agenda guiding digitalization efforts. Moreover, efforts are partner-driven and there is no government-led team set up to sustain the digitalization effort. Nigeria has made remarkable progress in its malaria campaign digitalization efforts with over 50% of States in the country digitizing at least one of its malaria campaigns. However, coordination gaps still exist. We recommended that NMEP develop a policy document to guide digitalization efforts across all stakeholders and also set up a digital technology unit to coordinate digitalization efforts by stakeholders.

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A ROBUST MALARIA DATA INTEGRATED, STORAGE AND ANALYTICAL SYSTEM CRITICAL FOR ENHANCING SURVEILLANCE

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The Zambia National Malaria Elimination Programme (NMEP) has adopted Surveillance, Monitoring, Evaluation and Operations Research as a core intervention in its subnational elimination and control efforts. It is therefore, important to have a comprehensive and integrated malaria information system that collates all programmatic data into one platform. However, the ministry has three systems that aggregate malaria data without allowing for data linkage. The Health Management Information System (HMIS) for service and disease data, electronic Logistic Management Information System (eLMIS) for commodity data and the Malaria Rapid Reporting System (MRRS) for community level data. In 2019, the NMEP and Zenysis with support from the Global Fund undertook an assessment of the ability of the information system to respond to programme needs. The first step involved conducting interviews with the NMEP and other key stakeholders on the data needs of the programme. The second step involved an assessment of the eLMIS, HMIS and MRRS. The findings reviewed that the three systems were related and all vital for malaria programming but not integrated. It was also difficult to link malaria disease burden to malaria service and malaria commodity data without resorting to manual data manipulations. The coverage of these systems was at different organization unit level. The eLMIS and the HMIS did not capture community level data. On the other hand, the MRRS collected community level data but was at 67% coverage. To that effect, the NMEP implemented a platform that would house malaria data from the three systems. The Platform collated data from these systems using an Application Programming Interface. Through this, the programme is able to link disease burden with availability of malaria commodities and interventions coverage bringing about efficiency and effectiveness in malaria Programming. There is therefore, need to roll out the eLMIS to community level and integrate the HMIS and MRRS. This will facilitate a seamless flow of data from the community to the national level, and ensure that all stakeholders have access to timely and accurate malaria information.

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MALARIAGEN AMPLICON TOOLKIT: A GENOMIC SURVEILLANCE TOOL TO SUPPORT MALARIA CONTROL AND ELIMINATION

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National malaria control programmes, NMCP, need to maximise the impact of their interventions. To achieve this, monitoring emerging drug and insecticide resistance is essential for informed decision making. Our objective is to accelerate genomic data production at scale by providing a public health, research and capacity-building framework to accommodate the growing and changing needs for parasite surveillance data in malaria endemic regions, and putting the power of data generation into the hands of subject matter experts in malaria endemic countries. By generating genomic data closer to the public health decision makers, national priorities can be incorporated at every stage from sampling frameworks to data analysis - revolutionising the delivery of translational research to policymakers. We developed the MalariaGEN Amplicon Toolkit for targeted monitoring of known markers of interest in malaria parasites. Originally implemented at the Wellcome Sanger Institute, this low cost technology platform is now additionally being implemented in 6 countries across Africa and South East Asia and supporting national genomic surveillance of malaria response in 13 countries. By utilising the same platform, these data can be brought together for comparison analysis across borders and around outbreaks, prioritising the needs of public health over research outputs. Translating protocols and tools for multi-laboratory implementation greatly enhances the potential temporal spatial coverage of genomic surveillance, facilitates data interoperability and amplifies the power of the data produced for public health benefit.

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STANDARDISATION OF LABORATORY PROTOCOLS AND MULTINATIONAL IMPLEMENTATION TO ESTABLISH GENOMIC SURVEILLANCE CAPACITY IN MALARIA ENDEMIC COUNTRIES

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With the emergence of resistance to control measures, National malaria control programmes need effective tools to monitor and plan effective interventions in the face of increasing drug and insecticide resistance. The Amplicon Toolkit has been developed to meet the needs of genomic surveillance of malaria, targeting genes associated with P. falciparum drug resistance. Implementation and ongoing support accompany protocols and tools at every stage from laboratory to data integration and interpretation. As the implementation of genomic surveillance protocols for routine surveillance operations is particularly dependent on standardised methodology, we worked with teams in laboratories in West Africa and South East Asia, to adapt protocols capable of being implemented in multiple geographical locations. Through harmonisation of genomic surveillance protocols for drug resistance in P. falciparum, and using bespoke end-to-end laboratory implementation plans encompassing establishing workflows, procurement support and tailored laboratory training, we have supported four laboratories in Ghana, The Gambia, Indonesia and Vietnam, in establishing genomic surveillance capacity and thereby establishing inter-laboratory reproducibility. The protocols and training programmes developed, can now be deployed in other laboratories who wish to establish genomic surveillance capabilities. Additionally, leveraging on these previous achievements in capacity building, we aim to establish regional sequencing hubs that will provide National Malaria Control Programmes and Public Health Institutions with timely, actionable genomic surveillance data. Through establishing a Surveillance Hub Training programme, developing logistical processes and strengthening cross-border partnerships, we aim to provide proof of concept of public health impact and an operational model that will lead to multilateral investment in more comprehensive regional surveillance frameworks for malaria which can also be adapted for the surveillance of other endemic diseases.

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EMPOWERING HEALTH DISTRICTS IN SUSTAINING HIGH-QUALITY MALARIA CASE MANAGEMENT AND DIAGNOSTIC SERVICES PER NATIONAL GUIDELINES IN EQUATORIAL GUINEA

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Malaria diagnosis and treatment have been cornerstones of controlling transmission on Bioko Island for the past 20 years. Accessible, high-quality health services are essential for managing uncomplicated and severe malaria cases, enhancing malaria detection, and preventing malaria in high-risk groups including pregnant women. However, health districts face various challenges, including inadequate training, insufficient resources, and a lack of effective monitoring systems. We present a package of interventions that aim to enhance service delivery on Bioko Island in line with national case management guidelines and the operationalization of the district level health system by the Ministry of Health and Social Welfare of Equatorial Guinea. High-standard training manuals for clinical management and diagnosis of malaria, outreach training and supportive supervision (OTSS) manuals and checklists, state-of-the-art training materials, and job aids were developed. Real-time operational dashboards were designed to render OTSS indicators. The District Health Information System (DHIS2) software was customized and deployed to follow key indicators on malaria case management and diagnostic practices. This monitoring and evaluation system will be used for decision-making and adaptive management, from providing evidence for resource allocation to deciding on training and supervision priorities. A cohort of trainers in each district of Bioko Island will be identified and trained in case management and diagnostic guidelines, and supervision practices. Trainers will be evaluated over time on their effectiveness and use of data to adapt their efforts and optimize their support to the health districts. The comparison of indicators before and after implementation of this package will allow to assess changes in case management practices and adherence to guidelines within health districts on Bioko Island, while identifying challenges and areas for further improvement, providing insights into the effectiveness of the training materials and supportive supervision systems.

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MONITORING, MENTORING AND MOTIVATION VISITS TO COMMUNITY HEALTH WORKERS AS A MECHANISM TO SUSTAIN HIGH QUALITY OF CARE IN MALARIA COMMUNITY CASE MANAGEMENT: A CASE OF FOUR HIGH MALARIA BURDEN PROVINCES IN ZAMBIA

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Since 2011, 20,448 community health workers (CHWs) have been deployed in Zambia to provide basic malaria diagnostic and treatment services in their respective communities. Of these, 5,765 work in the four President's Malaria Initiative (PMI) PAMO Plus-supported provinces of Eastern, Luapula, Muchinga, and Northern. In 2020, the National Malaria Elimination Programme (NMEP) introduced monitoring, mentoring, and motivation (MMM) as an approach to sustain clinical quality of care (cQoC) and data quality among CHWs. MMM includes observing CHWs' clinical skills in testing with a rapid diagnostic test (RDT) and administering the appropriate treatment. This case study describes the MMM process and its importance to sustaining and measuring cQoC at the community level. Twice in 2022, CHWs met at their health facility where district and health facility mentors directly observed the CHWs consulting a suspected malaria patient. Mentors assessed six key variables and provided immediate feedback. Data were collected using Open Data Kit and analyzed in STATA and a score was assigned to each variable. In 2022, 2,033 CHWs with more than a year's experience participated in MMM. The results show that CHWs' case management skills are generally high. Overall, 96% of the CHWs scored above 80% (the minimum acceptable score). Of the 2,033 CHWs, 94% identified danger signs correctly, 97% made the correct decision to treat locally or refer patients to a health facility, 96% dispensed the correct treatment, and 95% administered RDTs correctly. The findings of this study indicate that MMM is a promising approach for providing individualized mentorship to improve and maintain high cQoC among CHWs. It also serves to alert mentors should CHW skills decrease, allowing for immediate action to be taken. The 2022 baseline data will be used to monitor cQoC over time.

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THE POTENTIAL OF SATELLITE-DERIVED BUILDING POLYGONS DATA AS A PROXY TO ON-THE-GROUND HOUSEHOLD MAPPING TO PROVIDE DENOMINATOR FOR PUBLIC HEALTH INTERVENTIONS: A PILOT STUDY IN BATA DISTRICT, EQUATORIAL GUINEA

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To optimize the implementation of public health interventions at the household level, it is necessary to have accurate denominators. Ideally, programs should have recourse to a household database to facilitate

planning, coordination, implementation, and monitoring of activities. The gold standard is a household mapping system that not only provides a complete list of locations but also allows spatial decision making. Such a system, however, can be very expensive and laborious as it requires geo-locating houses in the field. Satellite imagery promises alternative resources for mapping buildings and generating household denominators. Here, the recently released Open Buildings (OB) data set from Google was tested in Equatorial Guinea (EG). Three communities were randomly selected in Bata district, in mainland EG, to assess the sensitivity (recall) and positive predictive value (precision) of OB against household mapping on the ground. According to OB, a total of 1,174 buildings were identified in the three communities, which were then verified in the field. OB identifies buildings without any distinction of type and three levels of uncertainty of being a building. Field teams were deployed in these communities and could classify each building according to use (i.e. household, business, government offices and other use). They also identified any households not present in the 1,174 polygons. Hence, true positives were considered polygons mapped in OB and verified in the field as households. False positives were those polygons mapped in OB but identified in the field as either buildings for use other than household or polygons that did not correspond to a building in the field. False negatives were households identified in the field that did not have a corresponding polygon in OB. These data will help evaluate OB as a source of household denominators for public health interventions. Equatorial Guinea's political will to promote public health programs nationwide makes this crucial. Satellite-derived building polygons as a surrogate for household mapping could save resources, improve intervention planning, and scale.

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GENETIC ANALYSIS OF MALARIA IN PALAWAN, PHILIPPINES REVEALS HIGHLY MONOCLONAL INFECTIONS IN HIGH TRANSMISSION AREA

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The Global incidence of Malaria has decreased in the last 2 decades, but eradication still remains a challenge in many areas. Over 90% of malaria cases occur in the Palawan region of the Philippines. Genetic data can help guide elimination strategies by highlighting sources of infection and key transmission routes. Following an enhanced surveillance approach in Palawan, Philippines using rolling cross-sectional surveys, we combined genetic data with household coordinates to characterize the genetic diversity and transmission dynamics of malaria parasites in the Palawan study site. We successfully genotyped 247 dried blood samples, collected during the years 2016-2018 using a panel of 217 targeted amplicons, specific for P. falciparum. Targets covered areas of drug and diagnostic resistance and regions of high parasite diversity. From the resulting genetic data we estimated Effective COI (eCOI) and allele frequencies using an MCMC based approach, and intersample pairwise relatedness using a probabilistic model (Dcifer). Calculated mean eCOI for each individual sampled was 1.03, with an interquartile range (IQR) of 0.308. The data suggests that the majority of the infections are monoclonal with 90 samples deemed as polyclonal infections having mean eCOIs >1.1. Our analysis showed that 148 samples had some relatedness to other infections (r >0.6), forming one large cluster (comprising 30 infections) and several smaller clusters. Further analysis will be able to infer specific transmission networks within these clusters. Our clusters were not regionally defined suggesting that any intervention will need to be administered on a larger scale and not local. Overall our investigation of genetic data coupled with corresponding geographic data displays promising methodology in infection mapping and transmission analysis of malaria in the Philippines.

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BENCHMARKING COMMUNITY CASE MANAGEMENT WORKFORCE NEEDS AND MALARIA COMMODITY DEMAND ACROSS SUB-SAHARAN AFRICA USING GEOSPATIAL OPTIMIZATION

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Community health workers (CHWs) provide essential access to malaria treatment in many parts of Africa, especially for populations in hard-to-reach areas with limited access to health facilities. CHWs need to be geographically located so they are within walking distance of populations in need, with manageable workloads based on the population density and disease burden in their catchment area. In this study, we estimate the number of CHWs needed in each second administrative unit across 31countries in sub-Saharan Africa based on population density and travel time. Numerical optimization was used to determine the optimal number (and location) of CHWs needed to ensure all populations were within a two-hour walk of a CHW while limiting to a feasible service population size. A modeled malaria incidence surface was used to translate burden into estimated CHW workload, based on expected rapid diagnostic tests (RDTs) per month, to inform feasibility and commodity needs for integrated community case management (iCCM). We also conducted a prioritization exercise using public health facility data to identify the most underserved populations to inform CHW expansion. Our results estimated around 215,000 CHWs would be required to achieve saturation of coverage within two hours of walking travel time, of which about 102,000 (47.7%) would be required for populations greater than 5 km from a health facility. There was a wide range of expected RDTs conducted in a typical month (54.8, IQR: 32.2 - 66), which increased substantially during the peak transmission season (163.7, IQR: 90.5 - 218.5), highlighting the need for context-specific targets for coverage populations per CHW. These estimates provide a benchmark for measuring progress toward universal healthcare coverage goals and a methodological framework for developing country-specific estimates and designing optimal iCCM strategies. By improving access to care for hard-to-reach populations, scaling up CHW programs could have a substantial impact on achieving universal health coverage and the Sustainable Development Goals by 2030.

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SUBNATIONAL TAILORING AND TARGETING OF ANTI-MALARIA INTERVENTIONS IN ETHIOPIA

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Ethiopia has shown steady progress in reducing malaria morbidity and mortality, following a major scale-up of malaria control interventions and an extensive deployment of health extension workers at lower administrative units. Despite these gains, the country is facing a malaria upsurge recently, and there remain many areas still reporting high incidence, including along the western borders where large numbers of seasonal workers migrate annually. Diverse climatic factors, insecticide resistance, and lack of appropriate control interventions targeting migrant workers are among additional complicating factors. In this study, we developed a sub-national tailoring (SNT) process, and classified woredas based on

their parasite incidence, level of seasonality, level of insecticide resistance, and the presence of seasonal migrant workers to inform the targeting of appropriate control interventions. We then used a malaria transmission model to estimate the impact of scenarios including the use of seasonal malaria chemoprevention (SMC) among children under five, Piperonyl Butoxide (PBO) nets in areas with high insecticide resistance, and targeted mass drug administration (tMDA) among migrant workers, with a business-as-usual scenario assuming continuation of the current control interventions, while accounting for seasonal movement between high and low transmission woredas. Results show the largest effect of SMC among resident under-five children in the high transmission areas, while PBO nets had the largest effect among the resident population in targeted low and moderate transmission areas. A combination of tMDA for migrant workers at destination and PBO nets in moderate and low-risk source woredas is estimated to yield the highest reduction in annual clinical incidence. With a model-based SNT leading to an effective mix of targeted interventions, Ethiopia can further reduce malaria transmission and continue progressing toward its elimination goal.

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COMBAT LAO PDR: FEASIBILITY AND EFFECTIVENESS OF COMMUNITY-BASED ACTIVE CASE DETECTION AND TREATMENT

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Lao PDR has achieved dramatic success in reducing its malaria burden by implementing robust intervention coverage and surveillance. One current strategy is the 1-3-7 approach to case investigation and reactive case detection (RACD) targeting neighboring households. We conducted a pragmatic randomized controlled trial to evaluate the operational feasibility and effectiveness of enhanced RACD with HS-RDTs against the passive case detection standard of care (SOC). Thirty-two health centers were randomized to conduct RACD or SOC from September 2020-August 2021. RACD was conducted in index households and five neighboring households, with all enrolled receiving a standard RDT and HS-RDT and providing dried blood spots (DBS) for PCR analysis. RACD response coverage was 91% of index cases (n=225 followed-up, with 3,254 individuals in 498 households enrolled. RACD testing coverage was 88.2% of eligible individuals, with fifteen secondary Plasmodium vivax (Pv) infections detected by standard RDT, yielding a household test positivity rate (HTPR) of 0.5%. Together, 91.7% of index and RACD cases detected by RDT were Pv versus 8.3% P. falciparum (Pf). Results from PCR analysis for 2,718 household samples yielded a HTPR of 3.7%. Whereas PCR for index cases found a similar 91.0% Pv distribution among positive samples, household members detected through RACD were positive for Pv (63%), Pf (5%), P. malarie (28%) and P. knowlesi (14%) in mono or co-infections. Mono-infection with Pm or Pk accounted for 30% of all PCR positives, with Pk detected in multiple health centers. Results suggested that RACD is feasible in Lao PDR but is not an optimal use of resources given low sensitivity of standard field diagnostics. Data analysis is ongoing as PCR results were completed in March 2023. This trial yielded valuable data on the utility of RACD in Lao PDR, as well as on speciation and potential health risks to the population after Pv and Pf cases decline from novel malaria infections including Pk that are currently not detected by RDT.

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A PROGRAM EVALUATION OF COMMUNITY HEALTH WORKER-LED REACTIVE CASE DETECTION AND ITS IMPACT ON MALARIA MORBIDITY AND MORTALITY IN ZAMBIA

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Reactive case detection (RACD) is conducted by programs globally as a malaria surveillance and elimination strategy, but there is limited evidence of its impact. In addition to improving case detection, RACD may clear asymptomatic infections from the population and reduce time-to-treatment, preventing cases from progressing to severe disease or death. In Zambia, community health worker (CHW)-led RACD has been scaled up since 2013 as part of community case management. This retrospective analysis used routine DHIS2 surveillance data to characterize RACD implementation from 2015 through 2022 and assess RACD impact on malaria hospital admissions and deaths from 2017 through 2021 using multilevel regression modeling. From 2015 through 2022, 12,453 CHWs conducted 4,210,166 reactive tests, identifying an additional 1,201,748 cases. RACD was conducted intensively in low transmission areas like Southern Province and inconsistently or infrequently in higher burden areas. On average, CHWs who performed RACD conducted 4 index case follow-ups per month and 8 tests per follow-up. RACD intensity increased from 2015, peaking at 0.40 reactive tests per passively detected case nationally in 2019. However, by 2022, testing decreased to 0.11 reactive tests per case. Higher passive case counts were associated with both a lower likelihood of follow-up and fewer tests per follow-up conducted. At the district level, each additional reactive test per passively detected case was associated with 7% and 4% reductions in the monthly rate of under-5 and all-age malaria hospitalizations, respectively (under-5: IRR = 0.93, 95% CI = 0.88-0.99; all-age: 0.96, 0.92-1.01), and 8% and 13% reductions in under-5 and all-age malaria deaths (IRR = 0.9, 95% CI = 79-1.08; IRR = 0.87, 95% CI = 0.77-0.99), after controlling for vegetation, rainfall, temperature, month, year, urbanicity, incidence, malaria care provider density, and mass drug administration, bed net, and indoor residual spraying coverage. These reductions were modest in comparison with those associated with malaria care provider density, highlighting the greater importance of increasing access to care.

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DOCUMENTING THE EVIDENCE OF ROUTINE DATA QUALITY AUDITS ON MALARIA DATA REPORTING ACCURACY IN ZAMBIA, 2015-2021

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Routine data quality audits (DQAs) are implemented by country malaria programs to assess and improve data reporting accuracy, but they can be resource intensive, and their impact on accuracy over time is rarely documented. We evaluated accuracy in health facilities (HFs) reporting into Zambia's weekly malaria rapid reporting system using DQA datasets from 2015-2021. In Southern and Western provinces, DQAs began in 2015 in 155 HFs and expanded to 645 HFs across 33 districts by 2021. HFs were audited 1 to 7 times during the study period. Accuracy was measured using the weighted average percentage error (WAPE), and accuracy strata were defined as high (≥ 85%), medium (≥70-<85%), and low (< 70%). Three data elements were analyzed: outpatient department (OPD) attendance, rapid diagnostic test (RDT)-tested cases, and RDT-positive cases; the mean of the three data element median accuracies determined overall accuracy. Except for RDT-positive cases, median accuracy increased from 2015 to

2021: 80% to 91% for total OPD attendance, 74% to 89% for RDT-tested cases, 88% to 87% for RDT-positive cases, and 76% to 88% for overall. The percentage of HFs reporting with high accuracy increased 20-30 percentage points for total OPD attendance, RDT-tested cases, and overall, but no change for RDT-positive cases. Analysis of accuracy and number of DQA visits showed: at first DQA visit, reporting accuracy was mainly concentrated in the high (42%) and low (34%) accuracy strata; for HFs that received 6-7 DQAs (n=40), over 70% were in the high accuracy strata and 10% in the low accuracy strata. There was no correlation between HF size and overall accuracy ($r = -0.1$, $p<0.05$), and there were no temporally significant differences in accuracy among HF types. These results are robust evidence that routine DQAs have had a positive impact on reporting accuracy in Zambia. Other factors to be explored are malaria incidence, staff turnover, length of period audited, district level trends, and availability of other data quality improvement interventions, which will further support the development of recommendations to improve DQA practices in Zambia.

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LOST TIME, LOST LIVES: INVESTIGATING DETERMINANTS OF DELAYED MALARIA TREATMENT IN SUB-SAHARAN AFRICA'S CHILDREN

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Early malaria diagnosis and treatment are critical to prevent death and reduce disease transmission. Evidence from the literature shows that delayed treatment increases the odds of disease progression to severe malaria and/or death, affects drug effectiveness, increases the chance of onward transmission, and could lead to drug resistance. This study analyzed data extracted from demographic health surveys conducted between 2005 - 2022 consisting of about 600,000 sub-Saharan African children treated with antimalarials. We used hierarchical Bayesian modelling frameworks to model the spatio-temporal proportion of children who delayed receiving antimalarial treatment and the associated factors. The study further compared the magnitude of the delayed treatment between the 24-hour and 48 hours policy recommendations, deriving region and country estimates by child age, household wealth, urbanicity and endemicity. During the 18 years period, the study found that delayed treatment was a significant problem in sub-Saharan Africa, with over a quarter of children receiving treatment late. No significant difference was observed between very young (under 2 years) and older children; households in rural areas and those with low wealth are not performing well. However, the gap between rural and urban households is closing over time. Very little improvement was observed in areas with high transmission. Primary contributing factors to the delays included household size, wealth quintile, PfPR malaria risk, residence (rural or urban), illness severity, child's age, gender, seasonality, maternal age, and education.

The findings suggest a need to invest in improving effective malaria case management, particularly early diagnosis and prompt treatment, especially for the most vulnerable and hard-to-reach populations and in high transmission areas. This is a vital component of malaria control and elimination strategies. The study findings could be used to assist in creating more effective strategies to combat malaria and help reduce malaria mortality among children in sub-Saharan Africa.

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ENGAGING HUMAN-CENTRED DESIGN TO UNDERSTAND HUMAN BEHAVIOURS AND MALARIA CONTROL IN HIGHLY ENDEMIC AREAS IN MALAWI.

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Transmission of malaria is a dynamic process that requires a thorough understanding of the complex relationship between human, vector, parasite, environmental and social dynamics. Indoor and outdoor activities, physical movement of the local population and their understanding of the malaria disease dynamics profoundly impact malaria outcomes. Currently, the human dynamics that influence malaria disease transmission are well-established, yet relatively few studies have included human behaviour when investigating exposure to malaria vectors. We illuminated how everyday activities and malaria dynamics are understood in the local human behaviour context, with the population actively involved and given ownership throughout the study process. Using purposive sampling, 80 participants took part in human-centred design activities, 8 focus group discussions, 9 key informant interviews and 9 participatory rural appraisal activities (problem ranking, village mapping, seasonal and day calendars) to illustrate diverse spaces and experiences contributing to residual malaria transmission in two vector surveillance sentinel sites, in Salima District, Malawi. Thematic analysis identified how adolescents and adults representing different communities communicate, interact, empathize and stimulate local people's involvement in malaria control. Human behaviors, lifestyles, daily, weekly and monthly activities of the community members are important determinants of malaria transmission. Distinctive male and female adolescents in/out of school) and adults perspectives show the different ways communities see what malaria, including intervention programmes, are today. The human-centred design identified and empathized challenges related to human-mosquito behaviours and contextual particularities influencing transmission, practices, including sustainable solutions meeting their malaria needs and lifestyles. Inclusive approaches to understanding human behaviours and malaria control are key to improving malaria outcomes for priority populations.

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IMPLEMENTING GENOMIC SURVEILLANCE FOR MALARIA IN GHANA: OPPORTUNITIES AND CHALLENGES

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Malaria remains a significant public health problem in sub-Saharan Africa despite intensified malaria control efforts. Malaria control programs have historically relied on surveillance measures like parasite counts, entomologicalinoculation rates, incidence rates and self-reported travel history. While these metrics provide some idea of malaria transmission dynamics, they are less sensitive in areas of declining transmission intensity. They also provide limited information on parasite diversity and mechanisms of adaptation to environmental and interventional pressures. Next generation sequencing (NGS) has revolutionized genomic research by allowing scientists to understand complex biological systems at a greater depth. This has created new opportunities to study and understand the genomic landscape of malaria control and ultimately generate actionable data that could inform NMCPs to develop more effective and sustainable malaria control and elimination strategies. Unlike traditional genotyping methods, NGSprovides a more refined and sensitive high throughput, cost-effective and scalable means of surveillance. Building on existing infrastructure and expertise, this project aimed to establish a genomic surveillance hub in Ghana to perform targeted deep amplicon sequencing of malaria parasites. Using this approach, we can assess the distribution of variants associated with drug resistance both at patient and population level enabling the efficient tracking of novel variants as well as known drug resistant loci. Implementing such a system in a low resource setting, however, comes with significantchallenges. Some of these challenges include slow reagent supply chain, inflated reagents costs, lack of local technical support, poor retention of trained staff and insufficient core NGS and bioinformatic infrastructure. Here, we present our experience with

finding solutions to these challenges with input from continental and global partners as a critical step for providing genomic surveillance for malaria and other infectious pathogens in west Africa.

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PRIORITIZATION OF PLASMODIUM FALCIPARUM ANTIGENS ASSOCIATED WITH REDUCED RISK OF MALARIA DURING PREGNANCY

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Plasmodium falciparum infection during pregnancy leads to substantial maternal and infant morbidity and mortality. Such infection may result to placental malaria when infected erythrocytes adhere to the placenta via parasite-derived ligands. Despite the risk of infection being similar for women of all gravidities, the risk of poor birth outcomes is increased in primigravida due to lack of protective antibodies against placental malaria parasites. Thus, understanding how specific P. falciparum proteins interact with host's immune system during first and subsequent pregnancies provides insights on immunopathology of malaria and guide vaccine target prioritization. In this study, we assessed human antibody reactivity to 698 P. falciparum recombinant proteins from different protein groups among Kenyan primigravida and multigravida women (n=53). We observed high immunoreactivity across the protein families with the number of antigens identified increasing with gravidity. This was consistent with existing literature where repeated exposure to malaria reduces adverse pregnancy outcomes due to increased levels of antibodies. Principal component analysis revealed that the first six components accounted for 53.5% of the total variation within the dataset with antibodies against P. falciparum PfEMP1; CIDR and DBL domains contributing 83% of the total variation to the first component. In addition, PfEMP1 CIDRγ5 (PF3D7_0937800), PF3D7_1036500 (uncharacterized protein) and PF3D7_0707300 (rhoptry-associated membrane antigen) were selected by primary and sensitivity analysis as the proteins significantly associated with gravida; a key indicator of immunity against pregnancy malaria. While all five VAR2CSA domains were immunoreactive with seroprevalence of 42-62%, and correlated with the selected proteins which suggests co-acquisition, none significantly associated with gravidity. Although further work on the significance of the selected antigens will be required, these approaches may provide insights for targets that could be prioritized for vaccine development to reduce risks associated with malaria in pregnancy.

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EFFICACY OF R21/MATRIX-M™ IS MAINTAINED IN A PHASE IIB TRIAL IN CHILDREN IN BURKINA FASO OVER FOUR MALARIA SEASONS

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Progress in the fight against malaria has plateaued. Without rapid action, there is a risk of seeing a resurgence of disease. A safe, inexpensive, highly efficacious vaccine, that can be rapidly produced at large-scale is required. We have previously reported vaccine efficacy (VE) of 75% with seasonal administration of four doses of R21/Matrix-M™ (R21/MM), over 36 months, in a phase IIb randomized controlled trial in Burkinabe children. In June 2022, participants in this trial were further randomized to receive a 6th dose (third booster vaccination). This enabled evaluation of efficacy with one, two or three boosters administered annually prior to the malaria season. Over 42 months of follow up, in participants who received R21 with the high dose of Matrix-M™ adjuvant (50µg), VE for time to first malaria episode was 71% [57-80], 64% [47-75] and 69% [54-79] in the four, five and six dose groups respectively. VE against multiple malaria episodes was similar: 66% [56-74] in the four-dose group, 61% [49-70] with five doses and 67% [57-75] with six doses. R21/MM has been well-tolerated with no safety concerns. There have been no vaccine-related SAEs during this trial. Data over the full four-year follow up will be presented. These results have informed the design of the phase III trial of R21/MM and supported regulatory licensure applications. Importantly, maintained high efficacy over four malaria seasons with only four doses is demonstrated, with no concerns to date of rebound in those who have not received repeated booster doses of the malaria vaccine. These data show that the R21/MM vaccine could significantly reducing malaria cases and deaths in children living in malaria endemic areas by inducing well maintained protective immunity.

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STRUCTURE-BASED DESIGN OF A STRAIN-TRANSCENDING SINGLE-COMPONENT AMA1-RON2L MALARIA VACCINE

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Apical membrane antigen 1 (AMA1) is a key blood-stage malaria vaccine candidate and target of neutralizing antibodies. AMA1 binds to a loop in rhoptry neck protein 2 (RON2L) to form the moving junction during merozoite invasion of erythrocytes. Previous study suggests that immunization with an AMA1-RON2L complex achieves higher growth inhibitory activity than AMA1 alone and protects mice against a lethal Plasmodium yoelii challenge. We designed three single-component AMA1-RON2L immunogens, one structure-based design (SBD1) and two insertion fusions that retain the structure of the two-component AMA1-RON2L complex. We investigated all three immunogens through a combination of structural biology and biophysics tools, and parasite neutralization. All immunogens showed improved production yields and thermostability relative to AMA1 alone. The designed immunogens elicit similar antibody titers with high neutralization activity compared to AMA1-RON2L complex, yet these antibodies do not block RON2L binding to AMA1. Among three designed single-component immunogens, SBD1 immunogen stands out for its ability to induce significantly potent neutralizing antibody responses against diverse strains of Plasmodium falciparum better than AMA1 or AMA1-RON2L complex vaccination. This indicates that the SBD1 immunogen successfully directs the neutralizing antibody responses to epitopes in AMA1 that are independent of the RON2L binding site, and these non-blocking antibodies provide potent strain-transcending protection. This work underscores the importance of neutralization mechanisms for AMA1 that are independent of RON2 blockade. This stable single-component SBD1 immunogen that elicits high strain-transcending neutralizing activity may contribute to developing the next generation of AMA1-based malaria vaccines.

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EVALUATION OF THE SAFETY AND IMMUNOGENICITY OF A SINGLE- VERSUS TWO-VIAL PRESENTATION OF R21/ MATRIX-MTM IN CHILDREN IN MALI

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A two-vial presentation of R21/Matrix-MTM malaria vaccine (one vial of R21 and one vial of Matrix-MTM mixed before administration) has been used in the Phase 2 and Phase 3 trials assessing this vaccine. A single-vial ready-to-use vaccine formulation has been developed to facilitate widespread deployment of this highly efficacious vaccine following approvals. Our study aimed to assess the safety and immunogenicity of the single-vial ready-to-use formulation of this vaccine compared with the two-vial formulation in children. The design was a double-blind, randomized controlled trial. Children aged 5 -36 months were randomised 1:1 to receive the single or two- vial presentation of R21/Matrix-MTM at 0, 1 and 2 months between May and July 2022. Analysis by an independent unblinded statistician indicated that the frequency of the solicited and unsolicited adverse events was similar between the two arms. There were no serious adverse events related to vaccination. NANP specific IgG antibodies were also similar in titre between the two groups of children who received the single or two- vial formulation of the vaccine at one month post third vaccination. The new single- vial formulation of R21/Matrix-MTM malaria vaccine was safe and immunogenic in children in malaria endemic areas. Further evaluation of the single- vial formulation when given as a booster dose is ongoing.

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A SYSTEMATIC REVIEW OF PLASMODIUM FALCIPARUM CIRCUMSPOROZOITE PROTEIN BASED VACCINE CANDIDATES: IMPACT OF ANTIGEN, DOSE AND ADJUVANT ON PROTECTIVE EFFICACY AGAINST CONTROLLED HUMAN MALARIA INFECTION CHALLENGE

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Circumsporozoite Protein (CSP), abundantly present on the surface of the pre-erythrocytic sporozoite stage of the Plasmodium falciparum malaria parasite, represents an attractive target for protective intervention. CSP forms the basis of the two most advanced malaria vaccines RTS,S/AS01 and R21/Matrix-M. In addition to these two frontline vaccines, dozens of CSP based vaccine candidates have been developed based on a range of antigen delivery platforms. Candidates have been paired with an array of adjuvants, but many candidates only tested against CHMI challenge in the context of a single adjuvant based on pre-clinical data despite the lack of a defined correlates of protection. We present data from a systematic review of available literature regarding the protective efficacy against Controlled Human Malaria Infection (CHMI) challenge induced by viral vectored, soluble peptide(s), recombinant protein(s), DNA and particle-based CSP vaccine candidates across 35+ years. This report provides a comparative analysis of protective efficacy with particular focus on the apparent impact of different categories of adjuvant and antigen delivery modality that can guide the future design and development of vaccines targeting this antigen.

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GENETIC DIVERSITY & NATURAL SELECTION OF A MALARIA VACCINE CANDIDATE GENE IN THE ETHIOPIAN PLASMODIUM VIVAX POPULATION

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The burden of Plasmodium vivax in Ethiopia is amongst the highest in the world. However, P. vivax diversity, particularly that associated with antigens, such as P.vivax merozoite surface protein 3α (PvMSPα), has rarely been studied in Ethiopia. In the present study the genetic polymorphism in the defined target was assessed by examining genes encoding two blocks of this antigen locus. Finger prick blood samples spotted onto filter papers were collected from microscopically and Rapid Diagnostic Test (RDT) confirmed malaria patients attending health facilities in the study areas. DNA was extracted by ChelexSaponin extraction method, the genomic DNA was used for confirmation of P. vivax infection by targeting the 18S rRNA gene. Positive samples were subsequently evaluated by polymerase chain reaction-restriction fragment length polymorphism (PCRRFLP) for identification and assessment of the genetic polymorphism of the MSP3α gene. Further single clone infections were then analyzed using Sanger sequencing. Three size variants were amplified from the 50 isolates, Type A, B and C with frequencies of 82.97%, 12.7% and 4.2% respectively. Further details of diversity were attained by Hha I RFLP, with 11 alleles and 12% multiple clone infections. The sequence analysis showed that size polymorphisms were results of insertions and deletions in the block I component of the gene, which also had higher nucleotide diversity (π) (0.10565) than the block II (0.014). The relatively conserved block II was evolving under positive selection, but a select region that encodes a predicted B cell epitope in these blocks is under balancing selection (Tajima's D 2.64 (P>0.05), Fu and Li s F 1.7621 (P>0.05); furthermore, a peak diversity was recorded at this site (π=0.65) with low inter-population FST estimates. The conserved nature of PvMSP3α block II makes it an ideal vaccine candidate. However, future vaccine design strategies targeting PvMSP3α block II. In contrast the polymorphic nature of PvMSP3α block I make it more suited for use as a rapid genotyping tool.

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SAFETY OF THE MALARIA VACCINE CANDIDATE R21/ MATRIX-MTMWHEN CO-ADMINISTERED WITH EPI VACCINES FOR MEASLES-RUBELLA AND YELLOW FEVER AT 9 MONTHS OF AGE IN MALIAN CHILDREN

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Malaria remains one of the main causes of mortality in children in Sub-Saharan Africa. Progress in reducing malaria incidence has stalled in recent years, which highlights the need for a safe and highly effective vaccine to prevent malaria in this population. R21/Matrix-MTM has shown high efficacy in a phase 2b trial in Burkina Faso (77% at 1 year after the third dose) and it is currently being assessed in a phase 3 trial in four African countries. R21/ Matrix-MTM has proven to be safe and well tolerated. For the successful deployment of R21/Matrix-MTM, it is necessary to assess the safety of the co-administration of R21/Matrix-M with EPI vaccines, specifically with those administered at 9 months of age in most Sub-Saharan African countries. These are measles-rubella (MR) and yellow fever (YF) vaccines. To assess

the safety of this co-administration we have recruited 350 children that were aged 6-7 months at the time of enrolment. They were randomized 3:3:1 to three different groups. Children in group 1 (n=150) received 3 doses of R21/Matrix-MTM one month apart, and MR and the YF vaccines at the same time as the third dose. Participants in group 2 (n=150) received only MR and YF vaccines at 9 months of age and participants in group 3 (n=50) received 3 doses of R21/Matrix-MTM one month apart, and the EPI vaccines one month after the 3rd dose. We collected safety data for solicited adverse events for 7 days after each vaccination and unsolicited adverse events for 28 days after each vaccination. Serious adverse events are collected for the whole duration of the trial. The co-administration of R21/Matrix-MTM with the MR and YF vaccines was well tolerated and the adverse events observed were similar to the adverse events observed when R21/Matrix-M™ is administered alone. Most of the solicited and unsolicited adverse events were mild or moderate, and short-lived. The only serious adverse event reported to date was assessed as not related to the vaccine. These data support the co-administration of R21/Matrix-MTM with EPI vaccines at 9 months of age, which has positive logistic and economic implications for vaccine delivery.

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MACHINE LEARNING FOR PLASMODIUM FALCIPARUM REVERSE VACCINOLOGY

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Malaria vaccine development has been hampered by extensive antigenic variation and complex life stages of Plasmodium species. To date, malaria vaccine development has focused on a small number of antigens identified prior to availability of the P. falciparum genome. To leverage available P. falciparum systems data, we have implemented a machine learning-based reverse vaccinology approach to predict potential new malaria vaccine candidate antigens. We assembled and analyzed P. falciparum proteomic, structural, functional, immunological, genomic, and transcriptomic data, and trained models to predict potential antigens. We addressed the issue of incomplete antigen labeling using a positive-unlabeled learning algorithm to model the properties of the known antigens and the remaining proteins. We prioritized candidate antigens using models selected for their performance on reference antigens with different genetic diversity and quantified important protein properties associated with top candidates. The top candidates were clustered into three groups based on their similarities of the properties analyzed by the models. Overall, 85% of group 1 candidates were erythrocyte membrane proteins (PfEMP1s), and 36% and 26% of candidates in groups 2 and 3, respectively, were conserved proteins with unknown function. To inform future vaccine development, candidate antigens in the three groups were further characterized by gene essentiality, gene ontology, and single-cell gene expression in various life stages. A portion of candidate antigen genes in groups 2 and 3 were found to be expressed across all life stages, suggesting they may be attractive targets for potential malaria vaccines. Next steps include expression of candidate antigens and testing their ability to elicit functional immune responses in an animal model. Beyond malaria, our approach provides a framework for identifying and prioritizing vaccine antigen candidates for a broad range of disease pathogens.

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BIOPHYSICAL CHARACTERIZATION OF NOVEL HUMAN MONOCLONAL ANTIBODIES TARGETING PLASMODIUM VIVAX APICAL MEMBRANE ANTIGEN 1

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Plasmodium vivax (Pv) control efforts have lagged compared to Plasmodium falciparum (Pf) due to Pv's easy transmissibility and latent stage, making new therapeutics important. Receptor-ligand interactions required for parasite invasion of host reticulocytes, such as Apical Membrane Antigen 1 (AMA1), are potential targets for monoclonal antibody therapy or vaccines. Here we characterized a panel of 13 human monoclonal antibodies (humAbs) recognizing PvAMA1 isolated from B cells obtained from a Pv-exposed individual. We hypothesize humAbs biophysical properties will help identify those with the best growth/invasion inhibition potential. Using surface plasmon resonance biosensor (SPR), anti-PvAMA1 humAbs were immobilized on a chip and PvAMA1 was passed over at increasing concentrations to determine equilibrium dissociation constants (KD). HumAbs were competed against each other to identify overlapping epitopes. Avidity index (AI) to PvAMA1 was measured using a chaotropic agent 1.5M NH4SCN compared to PBS. Anti-PvAMA1 humAbs were tested for cross-reactivity with Pf, P. knowlsei, and Toxoplasma gondii using ELISAs. Sequence similarities to PvAMA1 are PkAMA1>PfAMA1 >TgAMA1 (85%>60%>30% identity). KDs range between 3.05e-8 to 1.07e-9 M. AIs ranged between 0.0% to 52.9%. SPR competition results, analyzed with KD and AI, identify humAbs 816817, 826827, and 832833 as having the strongest interactions with PvAMA1 and recognize unique epitopes, with 826827 and 832833 have the highest AIs. Remaining humAbs compete with other epitopes and present with lower affinities. Five/13 humAbs recognize PkAMA1, 1/13 to PfAMA1, and 0/13 to TgAMA1. One humAb recognized 3/5 versions of parasite AMA1. Results supporting this approach identify 826827 and 816817 as showing the best invasion inhibition potential using Pk and Pv clinical isolates in vitro with an IC50 of ~ 300 nM and limited invasion inhibition of Pf. The preliminary in vitro results complement the biophysical characteristics seen using SPR and ELISA and suggest screening new humAbs by biophysical properties will help to identify the best candidates for functional studies.

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COMPARISON OF JUNCTIONAL, MINOR REPEAT, AND MAJOR REPEAT-FOCUSED CIRCUMSPOROZOITE VACCINES USING THE TOBACCO MOSAIC VIRUS EPITOPE DISPLAY PLATFORM

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The RTS,S vaccine construct contains three distinct antigenic regions: the immunodominant major repeats of Plasmodium falciparum circumsporozoite protein (CSP), the C-terminal region of CSP, and the non-malarial Hepatitis B surface antigen (HBsAg) fusion partner. Vaccination with RTS,S/AS01 in humans elicits high levels of anti-repeat region antibodies,

but also induces significant bystander antibodies to HBsAg. Protection studies in murine malaria challenge models have suggested that anti-C-terminus antibodies may not directly neutralize sporozoite invasion. Despite these facts, no variations in the core RTS,S antigen structure have been proposed in over 30 years of its development. The current availability of several highly protective anti-CSP antibody epitope structures allow for rationally guided protein engineering approaches to improve the longevity, cost, and breadth of protection elicited by CSP vaccines. To explore this potential, we have proposed next-generation CSP vaccines to immune-focus humoral responses to elicit antibodies only to the most protective epitopes. Variations of the major repeat region epitope (NPNA) targeted by mAb 317 were displayed on an exposed loop of the Tobacco Mosaic Virus (TMV) capsid. The reactivities of inhibitory mAbs to different proposed TMV antigens were determined and vaccines with the major repeat epitopes were found to be highly immunogenic and efficacious against transgenic parasite challenge in mice. The junctional repeat (DPNA) epitope of CSP targeted by mAb CIS43 was also displayed on TMV, but in the mouse model these antigens were not as efficacious as the major repeat vaccines. We are currently testing the protective effect of minor repeat (NPNV) epitopes that are targeted by the highly potent mAb L9. Results of various vaccine design cycles using the TMV platform will be summarized. Vaccine down-selection studies will form the basis for cGMP manufacture and evaluation of a TMV-based vaccine in humans.

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IMMUNOGENICITY OF A PLASMODIUM VIVAX CIRCUMSPOROZOITE PROTEIN NANOPARTICLE VACCINE

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The circumsporozoite protein (CSP) is the most abundant molecule on the surface of Plasmodium sporozoites and is considered a leading pre-erythrocytic stage vaccine candidate. CSP is essential for sporozoite traversal of Kupffer cells and entry into the liver parenchyma. Anti-CSP antibodies can prevent sporozoite migration and infection of hepatocytes. Most of the protection observed with CSP vaccines is associated with the immunodominant central repeat region. This is a major challenge for developing a broadly neutralizing strain transcending CSP-based vaccine. This study aims at exploring different P. vivax CSP sub-domains for induction of broadly neutralizing antibodies. We evaluated nanoparticle vaccine (NPV) formulations for co-delivery of different CSP subdomain antigens and adjuvants to target lymphoid tissues and immune cells. The CSP NPV was created by flash nanoprecipitation (FNP) fabricated as biodegradable poly(lactic-co-glycolic acid) (PLGA) particles of uniform small size (<100-nm). Immunogenicity was evaluated in mice immunized with recombinant CSP full length (CSPFL), N-terminal (CSPNT) or C-terminal (CSPCT) domains, formulated with CpG-1018 as adjuvant and surface conjugated to PLGA NPs. The antigen formulation with CpG-1018 induced high titer antibodies to the respective rCSP antigens, which recognize the native antigen on the sporozoite. All antigens are targets of natural acquired immunity. Ongoing studies are evaluating antibodies elicited by the CSP NPV to inhibit liver stage development of Plasmodium berghei transgenic parasites expressing different PvCSP parasite strains. Data obtained from this study will determine the suitability of FNP-produced PLGA NPs as a delivery system for a CSP vaccine compared to traditional subunit vaccine formulations.

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COMPARABILITY OF THE STANDARD MEMBRANE FEEDING ASSAY ACROSS DIFFERENT VACCINE STUDIES, STUDY SITES, AND TIME

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The Standard Membrane Feeding Assay (SMFA) is utilized widely to assess the efficacy of malaria transmission blocking vaccines (TBV). The assay is performed by feeding cultured P. falciparum gametocyte parasites to Anopheles mosquitoes in the presence of test sera and measuring the resulting midgut oocyst infections against a naïve control. The activity of vaccine-induced antibodies to prevent mosquito infection can be expressed as both transmission reducing activity (TRA) where the percent reduction in oocyst count per mosquito against the naïve control is calculated and transmission blocking activity (TBA) where the percent reduction in infection prevalence against the naïve control is calculated. Here we assemble data from the comparator arms of several recent TBV studies (Pfs230D1-EPA and Pfs25-EPA in alhydrogel, Pfs230D1-EPA in AS01 in adults, Pfs230D1-EPA in AS01 in a community setting and Pfs230D1-EPA in Matrix M) to assess the variability in the baseline/control values of SMFAs performed on individuals residing in malaria endemic areas. TRA and TBA data for each study were assembled along with attributes of sites, demographics of study population, and month and year of study in order to examine these control data to determine what differences in the baseline data exist. A total of 574 samples from 209 participants were analyzed using Generalized Estimating Equation (GEE) models fitted with offsets for the number of samples each individual contributed to the analysis. Results of individual variability, within study and cross study variability will be contrasted for both TRA and TBA.

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BUILDING A NEXT-GENERATION PRIME-AND-TRAP PRE-ERYTHROCYTIC MALARIA VACCINE

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Highly effective malaria vaccines are needed to accelerate malaria elimination. Pre-erythrocytic (PE) vaccines that eliminate Plasmodium liver stages also abolish the blood stage and completely prevent onward transmission. “Prime-and-Trap” vaccination is a potent PE vaccine strategy that achieves sterile protection against P. yoelii (Py) challenge by inducing high frequency, parasite-specific, liver resident memory CD8+ T (Trm) cells. In its first generation, prime-and-trap consisted of plasmid DNA encoding the Py circumsporozoite protein (PyCSP) delivered by gene gun followed by a trapping dose of Py radiation-attenuated sporozoites (RAS). Here, a trapping dose of PyCSP plasmid DNA delivered by hydrodynamic transfection (HDT) replaced RAS and induced PyCSP-specific CD8+ liver Trm cells that achieved sterile protection against Py sporozoite challenge. Liver Trm cell frequency was reduced in HDT dose de-escalation studies, but antigen-specific complete protection was maintained in such studies to HDT trapping doses as low as 5 ng of plasmid DNA. HDT is a useful experimental tool but cannot be translated into non-human primates or humans. Instead, liver-targeted DNA lipid nanoparticles (LNPs) were developed to provide a safe and effective trapping vaccine. Liver-specific LNPs showing high transfection efficiencies were tested as trapping vaccines and generated PyCSP-specific CD8+ liver Trms but elicited less protection against Py sporozoite challenge than HDT and RAS. LNPs were modified by inclusion of a glycolipid adjuvant and results of those studies will be presented. Methods to adapt these LNPs to needle-free administration are also being developed. This next-generation prime-and-trap vaccine strategy may offer important features that could be harnessed to advance a highly effective and durable PE vaccine for malaria.

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EXPLORING IMMUNITY INDUCED BY PLASMODIUM FALCIPARUM CIRCUMSPOROZOITE, PRE-ERYTHROCYTIC VACCINE CANDIDATE, FMP014/ALFQ

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Malaria vaccine candidate FMP014/ALFQ is a Plasmodium falciparum Circumsporozite Protein (CSP) that displays (NANP)6 repeats and the alpha-TSR C-terminus on a self-assembling protein nanoparticle (SAPN) and is formulated with Army Liposomal Formulation containing QS-21 (ALFQ) adjuvant. SAPN nanoparticle substructure is such that the amino and carboxyl termini of the integrated amino acid sequences locate on the SAPN surface. SAPNs can be used to produce a wide range of different antigens and have been shown to successfully produce antibodies. We present the immunological findings of the first such recombinant nanoparticle vaccine from a single center, open-label Phase I clinical trial of intramuscularly administered FMP014/ALFQ for safety and immunogenicity. In this study, five subjects were administered a low dose, 20 µg FMP014 in 0.5 mL ALFQ and five were administered a high dose, 40 µg and 1mL adjuvant, at each vaccination on a 0-, 1-, and 2-month schedule. All doses were well tolerated with an acceptable safety profile. Serological findings revealed that FMP014/ALFQ recipients developed robust CSP antibody responses recognizing both structural elements, (NANP)6 repeat and the alpha-TSR C-terminal substructure displayed on the SAPN molecule surface. Exploratory analyses of fine specificities of responses measuring both antibody isotype and opsonophagocytic activity relative to potential functional immunity suggest a positive bias toward the lower dose vaccination group. These findings suggest that the SAPN vaccine approach is suitable as a particulate repetitive antigen display system.

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MATERNAL ENVIRONMENTAL ENTERIC DYSFUNCTION AND MATERNAL MALNUTRITION: EFFECT ON MATERNAL AND INFANT MICROBIOTA AND MOTHER-INFANT TRANSFER OF DYSBIOSIS IN CENTRAL-AFRICA

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Background : Environmental enteric dysfunction (EED) is an enigmatic disease of the small intestine intimately associated with undernutrition. EDD alterations include a disruption of the epithelial intestinal barrier, alterations in the number and height of intestinal villi, chronic inflammatory infiltrates and impaired absorption. Although notable progress has been made in deciphering the etiopathology of EED in children, evidence lacks on how maternal EED and maternal malnutrition have an impact on maternal and infant microbiota and its association with the developement of gut dysbiosis and EED in infants. Methods : We followed a cohort of 48 mothers and their 50 infants from birth until 6 months of life in Bangui (Central-African Republic). We performed metagenomic analyses of maternal stool and vaginal microbiota at delivery, in parallel to lab cultures. We analyzed oral and stool microbiota at birth, and at 1, 4, 11, 18, and 25 weeks, as well as breastmilk microbiota (starting at 1 week). We collected complete socio-economic and clinical data, anthropometric measures and 24-hour recalls and food-consumption questionnaires for diet assessment at each visit. Results : At delivery, 16 of the 46 (34.8%) women with a blood test were undernourished (albumin plasma levels <35g/l). Their stool microbiota at delivery was significantly associated with the infant undernourishment status at birth (P value of the Permanova = 0.02). The vaginal microbiota also differed significantly depending on the mother and infant undernourishment status at birth (P value = 0.04). The composition of the infant stool microbiota until 6 months also differed depending on the maternal undernourishment status and milk-type (P value = 0.02). Maternal undernourishment had a significant effect on breastmilk microbiota until 6 months type (P value = 0.003). Conclusion : The impact of maternal undernourishment on infants' stool microbiota and breastmilk microbiota confirms the importance of maternal nutrition and breastmilk microbiota for the infant gut colonization, and suggests that breastmilk might be involved in the possible transmissible nature of dysbiosis.

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ANTIMICROBIAL RESISTANCE IN E. COLI ISOLATED FROM DIARRHEAL STOOLS IN CHILDREN AGED 0-3 YEARS AT THE YIRIMADIO COMMUNITY HEALTH CENTER, MALI

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Diarrheal diseases constitute a serious public health problem, particularly in developing countries, because of their association with high morbidity and mortality in children under five years of age. Most strains of Escherichia coli live harmlessly in the intestines and rarely cause disease in healthy individuals. Nevertheless, a number of pathogenic strains can cause diarrhea diseases. Self-medication and overuse of antibiotics due to the scarcity of complementary diagnostic systems can lead to the development of multi-resistant bacteria causing diarrhea. The objective of this work was to identify the E. coli responsible for diarrhea in children aged 0 to 3 years and to characterize their sensitivity to a panel of antibiotics used in Mali. This study involved 538 children seen in in outpatient visits at the Yirimadio community health center and diagnosed with diarrhea. Yirimadio is a peripheral district area of Bamako the capital city of Mali. Stool samples were collected and analyzed by stool culture and antibiotic susceptibility was determined by the disk diffusion method on agar medium. An isolation rate of 31.6% was found. Amoxicillin and cotrimoxazole were the most resistant antibiotics, 94.1% and 92.9% respectively. For multi drug resistance, 89.4% of our strains were simultaneously resistant to two families of antibiotics, 68.2% were cephalosporinases and 40% ESBL. This study showed that E. coli is the most frequent bacteria involved in diarrhea in children under 3 years of age in Yirimadio, which are resistant to amoxicillin and co-trimoxazole, two antibiotics commonly prescribed in this setting.

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COMPARATIVE EVALUATION OF ANTIMICROBIAL SUSCEPTIBILITY OF SHIGELLA ISOLATES AMONG CHILDREN <5 YEARS IN RURAL KENYA PRE AND POST ROTAVIRUS VACCINE INTRODUCTION

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Vaccines are an effective strategy to minimize antimicrobial resistance (AMR). We aimed to evaluate Shigella antimicrobial susceptibility pre and post rotavirus vaccine introduction among children <5 years with moderate-to-severe diarrhea (MSD) in western Kenya. We used data from the Kenyan site of the Global Enteric Multicenter Study (GEMS;2008-2012) and the Vaccine Impact on Diarrhea in Africa (VIDA; 2015-2018). GEMS and VIDA were prospective, health center and community-based case-control studies which enrolled children aged <5 years with moderate-to-severe diarrhea, defined as ≥3 loose stools in the previous 24 hours with ≥1 of the following: sunken eyes, poor skin turgor, dysentery, intravenous rehydration, or hospitalization within 7 days of diarrhea onset. Stools collected at enrollment were tested for Shigella using standard culture

methods. Antimicrobial susceptibility was determined by Kirby Bauer disk diffusion. We compared AMR pre (2008-2012) and post (2015-2018) rotavirus vaccine introduction using a trend test for proportions. During the pre-vaccine period, Shigella was isolated from 130 (7.3%) of 1,778 stool specimens (S. flexneri 80 [61.5%] and S. sonnei 24 [18.5%] were the most common serotypes). Post rotavirus vaccine introduction, Shigella was isolated from 133 (8.6%) of 1,554 stool specimens (S. flexneri 84 [63.2%] and S. sonnei 35 [26.3%] were the most common serotypes). There was no significant difference in AMR between pre and post vaccine introduction among the antimicrobials tested: cotrimoxazole (125/129 [96.9%] vs 127/132 [96.2 %]; p= 0.76); nalidixic acid (6/129 [4.7%] vs 5/132 [3.8%]; p= 0.73); ceftriaxone (1/128 [0.8%] vs 2/130 [1.5%]; p= 0.58); ciprofloxacin (2/129 [1.6%] vs 0/132 [0.0%]; p= 0.15); resistant to ≥2 antimicrobials (8/130 [6.2%] vs 6/133 [4.5%]; p= 0.55). We observed an increase in Shigella isolation post-rotavirus vaccine introduction. Continued monitoring of Shigella AMR trends for effective clinical treatment of shigellosis is important in this setting.

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PARASITIC AND ANTIBIOTIC-RESISTANT BACTERIAL CONTAMINATION OF RAW SALAD VEGETABLES SOLD IN LOCAL MARKETS OF DHAKA, BANGLADESH

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Salad vegetables are widely eaten raw in Bangladesh because of their high nutritional content and health benefits. But contamination with parasites and bacteria poses a significant health risk. The purpose of this study was to document the presence of parasites and antibiotic-resistant bacterial contamination of raw salad vegetables to provide insight into the parasitological and bacteriological quality. 108 samples of raw salad vegetables: carrot, cucumber, tomato, coriander, mint, and lettuce were subjected to parasitological examination. After washing in saline water, sediments were centrifuged and analyzed using a microscope. 29.6% (32/108) of the vegetables were contaminated with parasites. Ascaris lumbricoides (20.4%), Entamoeba sp. (13.0%), Hymenolepis nana (9.3%), Cystoisospora sp. (5.6%), Ancylostoma duodenale (3.7%), Trichuris trichiura (3.7%), Taenia sp. (2.8%), and Hymenolepis diminuta (1.9%) were found. Leafy vegetables (e.g., coriander 66.7%, mint 44.4%, and lettuce 38.9%) were most contaminated compared to non-leafy vegetables (carrot 11.1%, tomato 11.1%, and cucumber 5.6%). Parasitic contamination was significantly related ($p < .05$) to the type of vegetable and the vendor's hygiene practices. Thirty-six samples were subjected to bacteriological analyses and antibiotic susceptibility tests. 61.1% (22/36) of samples were contaminated with three different types of pathogenic bacteria. Escherichia coli O157 (19.4%), Vibrio cholerae (61.1%), and Escherichia coli (33.3%) were detected, but no Salmonella was detected. The highest bacterial contamination was recorded in coriander (83.3%) and lettuce (83.3%). No antibiotic was found to which all (100%) isolates were sensitive. All (100%) isolates were Penicillin and Amoxicillin resistant. This study demonstrated the presence of pathogenic parasites and antibiotic-resistant bacteria in raw salad vegetables which makes the scenario very alarming. Unless adequately cleaned and disinfected, eating raw salad vegetables may spread food-borne diseases in Dhaka.

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HOSPITALISATION AND MORTALITY RATES AMONG CHILDREN WITH MODERATE TO SEVERE DIARRHOEA TREATED WITH AZITHROMYCIN OR PLACEBO: A RANDOMISED CONTROLLED TRIAL

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Children under the age of five in South Asia and Sub-Saharan Africa are at the highest risk of dying from diarrhoeal diseases. Standard of care for treating diarrhoea includes breastfeeding and oral rehydration. The Antibiotics for Children with Diarrhoea (ABCD) trial hypothesised that addition of antibiotics to the standard care for acute watery diarrhoea (AWD) may help lower hospitalisation and death in low- and middle-income countries. We analysed the site specific data from Pakistan for the ABCD trial. Children between the ages of 2 - 23 months with AWD, some or severe dehydration, and/or moderate wasting and/or severe stunting were eligible.Participants were randomised into either the oral azithromycin or placebo arms in addition to standard care as per WHO guidelines. The outcome measure was hospitalisation and all-cause mortality within 180 days of enrolment. At day 180 there was no hospitalisation attributed to diarrhoea though up to 25% of participants in both arms were malnourished. Causes of hospitalisation included anaemia (n=1), blood in stool / dysentery (n=1), fever (n=2), and urolithiasis (n=1). Causes of mortality included drowning (n=2), cough and cardiac arrest (n=1), breathlessness (n=1), measles and pneumonia (n=1), skin infection (n=1) and skin rash (n=1). Since all children in both groups also received standard of care this could be one of the reasons for observing reduced hospitalisation and mortality. This data supports the avoidance of antibiotics except in cases of dysentery or cholera and the reaffirmation of recommended guidelines.

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THE ROLE OF VILLAGE DOCTORS IN THE TREATMENT OF PEDIATRIC DIARRHEA AND POTENTIAL FOR ANTIMICROBIAL STEWARDSHIP IN RURAL BANGLADESH: A DESCRIPTIVE ANALYSIS

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Diarrheal diseases are a leading cause of death in children and a significant reservoir of antimicrobial resistance. In Bangladesh, many people seek healthcare from informally trained providers ("village doctors") who dispense unregulated antibiotics. This study aimed to understand the role of village doctors in treating pediatric diarrhea and the potential for antimicrobial stewardship in this population. We aimed to identify all village doctors in the Sitakunda subdistrict of Bangladesh. Village doctors (n = 125) were consented and verbally administered a questionnaire. The mean age was 41.3 (SD = 11.1). Participants were all male and had been practicing for an average of 15.8 years (SD = 10.1). The majority practiced in a permanent roadside building (62.4%, n = 78) and made household visits (86.0%, n = 104). Per week, participants reported seeing 106 patients (SD = 79.0); of these, 6 (SD = 7.8) were children (<5 years) with diarrhea. Almost all (99.2%, n = 120) stocked medications. The most commonly stocked antibiotics were metronidazole (95.2%, n = 119), azithromycin (95.2%, n = 119), ciprofloxacin (93.6%, n = 117), and nitazoxanide (77.6%, n = 97). The most commonly prescribed antibiotics for treating diarrhea were ciprofloxacin (90.4%, n = 113), metronidazole (73.6%, n = 92), and nitazoxanide (59.2%, n = 74). Almost all (81.8%, n = 99) participants had a smart phone with internet access, and over half (63.2%, n = 79) used their phone to assist with making clinical decisions. Village doctors provide care to a large number of patients in rural Bangladesh and care for a significant number of children with diarrhea. Village doctors commonly stock and prescribe numerous antibiotics, making this population an important target for antimicrobial stewardship interventions. Widespread smart phone use, coupled with current use of phones for clinical decision making, supports the introduction of mHealth tools to assist with antibiotic stewardship for pediatric diarrhea. Data collection is ongoing and full results will be presented at the conference.

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SAFETY, IMMUNOGENICITY, AND EFFICACY OF ETVAXÂ VACCINE AGAINST ENTEROTOXIGENIC E. COLI-ASSOCIATED DIARRHEA IN GAMBIAN CHILDREN AGED 6 TO 18 MONTHS

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This is a double-blind, placebo controlled (1:1) trial evaluating the safety, immunogenicity, and efficacy of three ETVAX® doses (Day 1, 15, and 90) to healthy Gambian children aged 6 to 18 months. ETVAX® is an oral, whole-cell, multivalent inactivated vaccine against enterotoxigenic E. coli (ETEC) associated diarrhea. The vaccine, adjuvanted with dmLT, includes four E. coli strains over-expressing colonization factors (CFs) CFA/I, CS3, CS5, and CS6 with a CTB/LTB hybrid toxoid (LCTBA). ETVAX® was safe and induced strong intestinal-mucosal antibody responses to CFs and LTB in Swedish adults, Bangladeshi adults and children, and Zambian children. A trial in Finnish travelers to Benin showed broad protection against moderate-to-severe ETEC diarrhea when allowing for co-pathogens. This trial was implemented in the North Bank and parts of the Central River and Lower River Regions of The Gambia. The enrolment started in February 2021 and recruited 4,936 children over 16 months. Passive surveillance for acute moderate-to-severe diarrhea (four or more loose/liquid stools in 24 hours) will end in October 2023. For safety, 350 children were actively visited at home within seven days of any dose. A vaccine-preventable outcome (VPO) is moderate or severe culture-confirmed ETEC diarrhea producing LT with or without ST toxin and/or strains expressing vaccine homologous colonization factors. Immunogenicity against LT and CFs is measured in 150 children. Active surveillance among the 350 children detected 88 adverse events, two of them severe and considered product related (1 vomiting, 1 fever). Among all other children (n = 4586), there were 420 adverse events; four events were severe and not product related. There were 47 serious adverse events, none of them considered product-related. By March 2023, 453 moderate-to-severe diarrhea cases had been detected; testing for ETEC phenotypes and co-pathogens is ongoing. Although data is blinded, ETVAX® appears safe with mainly mild and moderate adverse events. Efficacy results are expected by March 2024.

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A LONGITUDINAL COMMUNITY ASSESSMENT OF PLASMA CITRULLINE IN TWO COHORTS OF BANGLADESHI INFANTS

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Plasma citrulline (CIT) is an emerging biomarker for environmental enteric dysfunction (EED). In Peruvian children, CIT was inversely related to markers of systemic inflammation. We sought to describe CIT longitudinally, and to investigate the association between CIT and socioeconomic factors and diarrheal episodes in community-dwelling infants. Two hundred children between age 6-8 months in Mirpur, Bangladesh were enrolled in two cohorts, the first beginning in December 2020 and the second, August 2021. Each cohort was followed with biweekly visits for 8 months. Baseline and end of study serum was collected and tested for plasma citrulline. At baseline, the mean CIT levels for the two cohorts were significantly different (24.0 μmol/L, SD= 9.2 μmol/L versus 17.7 μmol/L, SD = 6.0 μmol/L) (t-test, $p < 0.001$). The end of follow up mean CIT levels were lower than baseline in both cohorts, 22.4 μmol/L (SD = 7.8 μmol/L) and 15.2 μmol/L (SD = 6.1 μmol/L). There was no significant difference ($\alpha = 0.05$) in demographic or socioeconomic factors between the two cohorts, including age, sex, household overcrowding, income, water treatment, water source, maternal education, baseline height-for-age adjusted z-score (HAZ) and weight-for-age adjusted z-score (WAZ). The number of diarrheal episodes per child was not associated with the change in CIT over time. The direction of individual CIT change was also not correlated with either (HAZ) or (WAZ) trend. We found that CIT decreased after 8 months of follow up among most of the children in this study, which suggests that most children had an increasing level of systemic inflammation as they aged. This change in CIT was not associated with number of diarrheal episodes. We propose that this increase in systemic inflammation could be related to subclinical insults to the gut due to non-diarrheal enteric infection. Future studies should investigate whether common enteric pathogens are associated with CIT, to further define the relationship between enteric pathogens and chronic inflammation in infants living in impoverished settings.

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ANTIMICROBIAL RESISTANCE TO ANTIBIOTICS AT A COMMUNITY-LEVEL HEALTH FACILITY IN MALI: A NANOPORE SEQUENCING AS A TOOL FOR AMR SURVEILLANCE

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Antimicrobial resistance remains a real threat to health throughout the world and resource limited countries such as Mali are not spared from this threat. The AMR detection is not a routine in most of health facilities. Antibiotic treatments are administered presumptively without laboratory tests. The lack of information of AMR could comprise treatment outcomes. To better gain insights on the extent of AMR at the community health center level, we have conducted a prospective study to phenotype bacteria involved in diarrhea in children in Bamako. Our results indicate that multi-drug resistant bacteria are circulating at the community level. More importantly, Enterobacteriaceae producing carbapemenase were detected. We are undertaking a long-read nanopore sequencing to better capture the microbial composition of stools from children with diarrhea. In addition, we will identify AMR genes involved in the resistance phenotype and fully characterize the pattern of transmission of these genes. Our results will inform healthcare workers and policy makers of rational antibiotic prescription.

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CHOLERA DEATHS DURING OUTBREAKS IN UVIRA, EASTERN DEMOCRATIC REPUBLICOF CONGO, SEPTEMBER 2021-JANUARY 2023

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Estimates of the true burden of cholera are uncertain due to poor surveillance systems that do not routinely identify or test suspected cholera cases, and the limited documentation of community cases and deaths. We describe cholera deaths across 2 seasonal outbreaks after cholera vaccination campaigns in Uvira, DR Congo in 2020. We recruited all suspected cholera cases presenting to 2 cholera treatment facilities in Uvira between September 2021 and January 2023. Suspected cases were eligible for enrollment if they were ≥ 1 year old and reported ≥ 3 watery, non-bloody diarrheal stools 24 hours before admission. Cholera was confirmed by enriched rapid diagnostic test (RDT) and culture or PCR. 1237 suspected cholera cases were admitted to health facilities in Uvira, including 777 (65.6%) confirmed by culture/PCR. We recorded 18 suspected cholera deaths, of which 15 (83%) occurred within health facilities and three in the community. The confirmed facility-based CFR was 1.2% when using culture or PCR (n=9/777) and 1.5% when using RDT (n=12/777); one of the health facility deaths was not tested for cholera. Cholera deaths were older (median: 62 years) than survivors (median: 18 years, p<0.001), with no difference by sex. While only 1 death occurred among children < 5 years, over half (55%) of all deaths were ≥ 60 years old, and 60% of health facility deaths happened after ≥ 1 day of hospitalization. Cases who died were twice as likely to have been admitted with severe dehydration compared to those who survived (93.3 vs 45.7%, p<0.001), and appeared to present for care later than those who survived, but this difference was not statistically significant. Two of the cases who died, both culture positive, reported having received 1 dose of the oral cholera vaccine in the 2020 vaccination campaign. We found that most of the deaths occurring in cholera treatment facilities in Uvira tested positive for cholera. Documenting both community and confirmed facility deaths is critical to identify drivers of cholera deaths, better target preventative measures-like vaccination-and treatment to those most at risk, improve patient care and estimates of cholera burden worldwide.

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A PATHWAY TO A MORE DURABLE CHOLERA RAPID DIAGNOSTIC TEST

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High throughput molecular and mass spectrometry technologies have provided insight on the impact of virulent bacteriophage and antibiotics on cholera diagnostic performance, including rapid diagnostic tests (RDTs). The odds of a cholera RDT testing positive decrease by more than 80% when virulent phage and antibiotics (azithromycin) are present. These factors contribute to variable performance and limit the use of RDTs. When the common Vibrio cholerae-specific virulent bacteriophage ICP1 is present, we hypothesize adding a monoclonal antibody (mAb) that targets ICP1 to the RDT will increase sensitivity without compromising specificity. To test this hypothesis, we developed an alpha RDT prototype that used an anti ICP1 capsid protein (ORF122) mAb for both the mobile and fixed antibody components in the lateral flow device. The alpha prototype failed because the fixed mAb did not capture the phage bound to the mobile colloidal gold labeled mAb. To address this problem, we proposed a beta prototype with distinct mobile and fixed mAbs. We performed bioinformatic analyses on ICP1 from the Democratic Republic of Congo and Kenya compared to Bangladesh. We found that the capsid decoration protein (ORF123) and two tail fiber proteins (ORF69 and ORF93) of ICP1 were sufficiently conserved; the percent conservation at the nucleotide and amino acid levels were 99.4-100% and 98.4-100% for ORF 123, 99.5-100% and 98.5-100% for ORF69, and 90.4-100% and 94-100% for ORF93, respectively. Production of mAbs to these new targets was subsequently initiated. These candidate mAbs will be analyzed using competitive ELISA assays. One of the two leading mAbs will be gold labeled and used in the mobile component and the second will be used as the fixed component in the mAb::ICP1::mAb 'sandwich' of the RDT. If successful, the beta prototype will be validated in a prospective clinical study in Bangladesh. We hope this research will address the negative impact the common virulent bacteriophage ICP1 has on cholera RDT performance. Future steps include a pivot to address the negative impact antibiotic exposure has on diagnostic performance.

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GENOMIC EPIDEMIOLOGY OF CAMPYLOBACTER SPP. ISOLATED FROM CHILDREN WITH MEDICALLY ATTENDED DIARRHEA IN IQUITOS, PERU

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Campylobacter is one of the leading causes of bacterial diarrheal disease worldwide. Within resource poor countries, Campylobacter burden is concentrated in young children, with most children exposed to this pathogen by the age of two. Campylobacteriosis is clinically characterized by symptoms including diarrhea, abdominal pain, and fever, all of which are usually self-limiting. However, antimicrobial treatment is recommended in severe clinical cases. This study aimed to describe the genomic characteristics of Campylobacter isolated from children 0 to 36 months of age seeking medical care for diarrheal illness in primary health posts in the city of Iquitos, Peru. A fecal swab from whole fecal samples or a rectal swab were placed in Cary Blair and transported within less 6 hours for processing. Samples were cultured in Columbia blood agar base supplemented with 5% lysed horse blood and incubated in microaerophilic conditions at 37oC for 48 hours. Colonies morphologically and biochemically compatible with Campylobacter spp. were replicated and confirmed by qPCR. Genomic libraries were prepared using the Illumina DNA Prep Tagmentation kit. Libraries were sequenced using a 2 x 250 bp paired end v2 reagent kit on a MiSeq instrument (Illumina). Genomes were assembled using the Spades assembler. Multi Locus Sequence Types were determined through the PubMLST allelic database. Clinical isolates from other high resource and low resource settings were downloaded from PubMLST for phylogenetic comparisons. Between November 2019 and February 2023, a total of 153 Campylobacter genomes were isolated and sequenced from 45 different children seeking care. Phylogenetic comparison between Loreto isolates and isolates of other regions is presented. Antimicrobial resistance genes and point mutations are presented. Ongoing analysis intends to determine genomic differences between Campylobacter isolates obtained from samples from children with different diarrhea severity scores. This is one of the first analysis describing genomic characteristics of Campylobacter isolates from pediatric cases of gastroenteritis in the Peruvian Amazon.

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SEROINCIDENCE OF ENTERIC FEVER IN RURAL AND URBAN POPULATIONS OF SIERRA LEONE

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Enteric fever remains a major global health problem. The recent availability of typhoid conjugate vaccine (TCV) is a promising control strategy to reduce disease burden. However, lack of an optimal diagnostic and limitations of blood-culture surveillance (e.g. cost, requirement of laboratory capacity, low sensitivity) have left many low- and middle-income countries (LMICs), including Sierra Leone, without any estimates of burden data. To address this gap, we have developed a serosurveillance tool based on detection of HlyE IgG and IgA, that overcomes the limitation of blood culture surveillance. In this analysis, we leveraged archived dried-blood spots collected in 2022 from a cross-sectional population-based serosurvey in Bo, Sierra Leone. We included 656 representative samples from individuals 5-15 years of age and stratified our analysis by rural/urban setting. We found that the enteric fever seroincidence rate was highest in children from rural areas (57 cases per 100 person-years) compared to urban areas (44 cases per 100 person-years). In conclusion, Sierra Leone has a high force of infection for enteric fever. These findings demonstrate the need for further surveillance and study capacity for enteric fever in Sierra Leone, for which seroincidence can be a great tool.

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A SPOTTED RASH HELPS SPOT A RARE PATHOGEN : CAPNOCYTOPHAGA CANIMORSUS ENDOCARDITIS WITH GLOMERULONEPHRITIS

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Capnocytophaga canimorsus is a gram-negative bacterium commonly found in the saliva of dogs. Despite the frequency of dog bites, infection with this organism is rare, and severe infections are usually associated with risk factors. Infective endocarditis is a rare presentation of C. canimorsus infection, and post-infectious glomerulonephritis has never since been reported. We present a case of a 67-year-old male with alcohol use, and intravenous methamphetamine use who presented with a lower extremity rash and bilateral swelling of four weeks. He had a history of multiple dog bites. Blood cultures revealed Capnocytophaga canimorsus. A trans-esophageal echocardiogram (TEE) revealed tricuspid valve vegetation, with severe regurgitation. The rash was considered secondary to leukocytoclastic vasculitis resulting from the endocarditis, although C. canimorsus bacteremia could have caused the rash. Worsening renal dysfunction prompted a renal biopsy which revealed acute post-infectious glomerulonephritis. Following six weeks of treatment with cefepime, he developed first-degree atrioventricular block and pulmonary emboli. A repeat TEE revealed enlarging vegetations and the tricuspid valve was replaced. 16s ribosomal RNA amplicon sequencing performed on the resected valve tissue revealed C. canimorsus. Treatment was planned with piperacillin-tazobactam. However, three weeks after surgery, he developed intractable gastric bleeding and died. Prevalence of dog bites in the Unites States as of 2014 is 0.2%. Hino et al. describe <2% of bacteremia cases being complicated with endocarditis, and 80% of such cases being associated with predisposing conditions such as asplenia, alcoholism, lung disease, immunocompromise, or cirrhosis. Our patient had no classic risk factors, but rather possessed a drug use and alcohol use history. This is the first reported case of C. canimorsus endocarditis associated with post-infectious glomerulonephritis and adds to the array of severe manifestations described for this organism.

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EVALUATION OF VIRULENCE GENE REPERTOIRE AS A MEANS TO ESTABLISH THE ROLE OF ESCHERICHIA COLI ISOLATED POSTMORTEM IN THE CAUSAL PATHWAY TO DEATH

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Interpretation of post-mortem microbiology is challenging, particularly when E. coli and other Enterobacterales are isolated. Here we evaluate if virulence gene profiles distinguishing extraintestinal E. coli (ExPEC) from non-ExPEC discriminated E. coli in the causal pathway to death from those translocating post-mortem. We enrolled pediatric and adult febrile deaths in a prospective autopsy study at two hospitals in Moshi, Tanzania. At autopsy, we collected specimens for culture from blood, lung, and, liver, and, when possible, cerebrospinal, pericardial, pleural, and peritoneal fluid. E. coli isolates underwent whole genome sequencing and classification as ExPEC or non-ExPEC based on a validated set of virulence genes. Adjudication of the role of E. coli in the causal pathway was done by review of clinical history, microbiologic results, and pathologic findings and was blinded to virulence gene data. Data were analyzed using frequencies, proportions, and bivariate logistic regression. From October 2016 through May 2019, we enrolled 218 decedents yielding 75 E. coli isolates from 55 (25.2%) decedents. Of decedents with E. coli isolated, median (IQR) age was 40 (22-63) years, 14 (25%) were female, and E. coli was adjudicated as in the causal pathway to death in 15 (27.3%). Among isolates, the three most common sequence types (ST) were ST131 (n=14, 18.7%), ST38 (n=9, 12.0%), and ST648 (n=9, 12.0%). For decedents with E. coli adjudicated as in the causal pathway to death, 13 (86.7%) had at least one isolate that was categorized as ExPEC compared with 24 (60.0%) of 40 decedents for whom E. coli was not adjudicated as in the causal pathway to death. The odds of isolating ExPEC when E. coli was adjudicated as on the causal pathway to death was 4.33 (95% CI 0.86-21.84, P=0.076). Our results suggest that evaluating virulence gene profiles may help clarify the role of E. coli in the causal pathway to death. However, ExPECs were frequently isolated from decedents not adjudicated to have E. coli on the causal pathway, suggesting that ExPECs may also have a higher propensity compared with commensal E. coli to translocate to normally sterile sites post-mortem.

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FACTORS ASSOCIATED WITH IN-HOSPITAL MORTALITY IN ADULT PATIENTS WITH SEPSIS AT TWO RURAL BORDER PROVINCES OF THAILAND

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Sepsis is a leading cause of morbidity and mortality among hospitalized patients in Thailand. We conducted a retrospective medical record review at 12 hospitals in northern provinces in Thailand during October to December

2017 to evaluate demographic, clinical management characteristics and outcomes among adult patients with sepsis, severe sepsis, or septic shock as defined in the 2012 consensus guidelines (Sepsis-2). Bivariate and multivariate regression analyses measured factors associated with in-hospital mortality within 28 days of admission. Among 719 patients who met a Sepsis-2 case definition, 53% were > 60 years old, and 49% were male. Of the 153 (21.3%) patients who met the criteria for sepsis, 1 (0.7%) died within 28 days of admission; of 442 (61.5%) for severe sepsis, 45 (10.7%) died; of 124 (17.2%) for septic shock, 51 (41.8%) died. Of the 552 (77%) sepsis patients with available hemoculture results, 270 patients (49%) had positive bacterial cultures; the three most detected bacteria were Escherichia coli (n=86, 32%), Klebsiella species (n=41, 15%), and Pseudomonas species (n=28, 10%). A greater proportion of septic shock patients were referred from district hospitals to provincial hospitals with critical care capability (p<0.001). Multivariate regression analysis found risk factors independently associated with in-hospital mortality: admission through an emergency room (adjusted relative risk [aRR] 2.98; 95% confidence interval [95%CI] 1.00, 8.93); respiratory infection (aRR 1.76; 95%CI 1.22, 2.53); malignancy (aRR 2.29; 95%CI 1.36, 3.85); skin, soft tissue or bone infection (aRR 5.08; 95%CI 2.58, 10.02); and, compared to sepsis, severe sepsis (aRR 8.68; 95%CI 1.18, 63.88) and septic shock (aRR 28.51; 95%CI 3.91, 207.92). In-hospital mortality for septic shock was higher at general hospitals than at district hospitals (aRR 2.37; 95%CI 1.32, 4.26). Our findings could inform development of, locally driven, early sepsis detection and management algorithms to reduce sepsis mortality in both district and general hospitals.

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DETECTING AND TREATING SEPTIC SHOCK IN DIARRHEAL PATIENT WITH POINT OF CARE (POC) LACTATE TESTING: A LIFE-SAVING STRATEGY BEYOND ICU

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Increased lactate level corresponds with deteriorated metabolic status in critical illnesses such as severe sepsis and septic shock. Progression to septic shock from severe sepsis was 69% in adults with diarrhea, and mortality was 30-50%. Identifying a bedside test to guide clinicians to make a timely decision is crucial in managing severe sepsis and septic shock. In this prospective observational study, we enrolled diarrheal adults ≥18 years from November 2021- March 2023 in Dhaka hospital, icddr,b. POC lactate test is done at hours 1st, 2nd, and 6th by StatStrip Lactate meters from Nova Biomedical, US. Patients fulfilling surviving sepsis-3 septic shock criteria comprise a case, and hypovolemic shock includes as control. For comparison of POC Lactate levels, we used paired t-test. The odds ratio (OR) and their 95% confidence intervals (CIs) were used to demonstrate the strength of the association. The study was registered in Clinicaltrials.gov (NCT05108467) and received institutional ethical approval (PR-21097). Of 360 patients, 100 had septic shock, and 100 had a hypovolemic shock. The death rate was 18% among septic shock group. The Patients with septic shock residing outside Dhaka city than the hypovolemic shock patients (55% vs. 28%; p <0.001). Comparison of median POC Lactate in hours 1st, 2nd, and 6th between the two groups are statistically significant (p=0.004; p<0.001; p<0.001), respectively. POC Lactate test can detect septic shock in a diarrheal patient with variable levels of dehydration. This test can help clinicians quickly diagnose and treat time-sensitive conditions like septic shock by providing quick, reliable, and accurate results before arriving in ICU.

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GRAM (-) BACTEREMIA IS ASSOCIATED WITH AN INCREASED BURDEN OF CHILDHOOD SEVERE MALARIAL ANEMIA IN A HOLOENDEMIC PLASMODIUM FALCIPARUM TRANSMISSION REGION OF WESTERN KENYA

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In Plasmodium falciparum holoendemic transmission regions such as Siaya, Kenya, clinical malaria can be accompanied by concurrent bacteremia. The primary manifestation of severe malaria in children <5 years in such regions is severe malarial anemia [SMA, hemoglobin (Hb)≤6.0g/dL]. In a cohort of children in Siaya (n=585), we showed that malaria and bacteremia co-infections can result in higher rates of anemia than witnessed in mono-infections. To further characterize the influence of malaria and bacteremia co-infection on clinical outcomes, we performed combined analyses in three cohorts of children (aged <5 years) presenting at Siaya County Referral Hospital with acute malaria: cohort 1 (n=783; 3/2004 to 12/2005), cohort 2 (n=876; 2/2009 to 12/2012), and cohort 3 (n=752; 3/2017 to 5/2022) for a total of 2,411 children. The prevalence of malaria in the combined cohorts was 68.4%, with 23.8% of the cases being SMA. The prevalence of bacteremia was 5.6%: 4.1% Gram(-) and 1.5% Gram(+). The most common Gram(-) isolates were non-typhoidal Salmonella (NTS), while the most prevalent Gram(+) isolates were Staphylococcus aureus. In the combined cohorts, 3.8% of the children had both malaria and bacteremia: 2.8% Gram(-) and 1.0% Gram(+). The overall rate of bacteremia was enriched in children with SMA (7.4%, P=0.034), with most of the SMA cases occurring in children with Gram(-) bacteremia (6.0%, P=0.009). Although logistic regression modeling, controlling for covariates (age, sex, HIV-1, and sickle cell trait status) failed to predict the association of overall bacteremia and SMA [Odd Ratio (OR)=1.332, 95% confidence interval (CI) 0.897-1.976; P=0.155], children with Gram(-) bacteremia presented with 1.59 times higher odds of developing SMA (OR=1.593, 95% CI 1.023-2.481; P=0.039). Collectively, these results demonstrate that Gram(-) bacteremia is an important contributing factor in the development of SMA. Improved management of community-acquired Gram(-) could be an effective strategy for reducing the burden of SMA.

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CHARACTERIZATION OF ACINETOBACTER SPP. ISOLATED FROM BLOOD AND URINE OF PATIENTS IN RURAL GHANA

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Acinetobacter spp. is an important cause of nosocomial infections, mainly affecting patients in the intensive care unit and in the immunocompromised. Furthermore, its spread in hospital wards and long-term care facilities is of particular concern as infections can be life-threatening, such as bacteremia in immunocompromised patients. In recent years, Acinetobacter spp., associated with multidrug resistance (MDR) has been on the rise worldwide. Despite being among the most common causes of hospital outbreaks often resulting in difficult-to-treat infections, studies on Acinetobacter spp. in Ghana are rare. In this study, we investigated clinical isolates of Acinetobacter spp. and their antibiotic profiles from Ghanaian patients.

Blood (456) or urine (258) samples were collected from patients visiting the St. Francis Xavier Hospital in Assin Fosu, Ghana. The samples were collected from January 2020 to February 2022 Identification and antibiotic profiles of Acinetobacter spp., isolated from the samples were performed using the VITEK 2 compact system. Isolates resistant to at least three classes of antimicrobial agents were classified as MDR. Twenty-nine (29) Acinetobacter spp. were isolated during the 2-year period, among which, 22 were isolated in the duration of 7 months (August 2020 to April 2021). The majority of the isolates were isolated from urine (55.17%, n/N = 16/29) and the remaining (44.83%, n/N = 13/29) were from blood cultures samples. 58.6% (n/N = 17/29) of the isolates were resistant to tetracycline, 51.7% (n/N = 15/29) to cotrimoxazole and 27.6% (8/29) to ceftazidime. Resistance to carbapenems was 20.7% (n/N = 6/29). Of most concern was the presence of MDR, which was detected in 24.13% (n/N = 7/29) of the isolates. We report a high frequency of Acinetobacter spp likely indicating an outbreak which will be confirmed through a further investigation into the molecular epidemiology. Antibiotic resistance observed for the locally available antibiotic is a concerning finding that necessitates the implementation of effective prevention measures to control the spread of the bacteria in the hospital environment.

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LEPTOSPIROSIS AMONG HOSPITALIZED PATIENTS WITH ACUTE FEBRILE ILLNESS IN BANGLADESH

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The burden of leptospirosis is underestimated in developing countries such as Bangladesh. In the current study, we aimed to evaluate the presence of leptospirosis through sentinel surveillance among hospitalized patients with acute febrile illness (AFI) in Bangladesh. We conducted the study at five tertiary care hospitals from September 2021 to February 2023 to identify the circulating pathogens causing AFI. Eligible patients were aged ≥2 months with measured fever or history of fever (≥ 100.4°F) within the past 14 days, without focal-infection symptoms and not already in treatment for a fever-causing condition. We randomly enrolled 1,544 patients, consisting of 778 adolescents and adults above 12 years and 766 children ranging from 2 to 12 years. Blood samples were collected within 24 hours of admission. Leptospira species were detected in 67 (4%) patients of which 59 (88%) were adults. Among the positive patients 51 (76%) were male. Of the Leptospira positive cases 59 (88%) were detected through Leptocheck rapid diagnostic test (RDT) kit alone (Zephyr Biomedicals), and eight were detected exclusively by RT-PCR. For the RT-PCR confirmed cases, the onset of fever ranged from 1-4 days (median: 2 days), while for RDT, the onset of fever ranged from 2-14 days (median: 7 days). None of the cases were positive for both PCR and RDT. Out of the five study sites the highest number of positive cases (21) were detected in Khulna Division (southwestern region), and the lowest number (3) were from Rangpur Division (Northwestern region). Ceftriaxone was the most frequently (58%) used antibiotic whereas the recommended drug doxycycline was used in only 10% of the patients. The finding of Leptospira species among AFI patients suggests that, physicians should more often consider Leptospira infection as a differential diagnosis of AFI. In addition, appropriate diagnostic tools for a low resource setting should also be made available to aid in the proper management of leptospirosis.

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NANOPORE SEQUENCING USING THE FULL LENGTH 16S RRNA GENE IS A PROMISING VETERINARY DIAGNOSTIC TOOL FOR THE DETECTION OF BLOOD-BORNE BACTERIAL PATHOGENS

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Animals of veterinary importance are afflicted by diverse blood- and vector-borne bacteria (VBB), of which many cause severe disease and can be fatal. Diagnosis of VBB infections can be challenging due to the low concentration of bacteria in the blood, the frequent occurrence of coinfections and the wide range of known, emerging, and potentially novel VBB species encounterable. Therefore, there is a need for diagnostics that address these challenges by being both sensitive and capable of detecting all VBB simultaneously. We detail the first employment of a nanopore-based sequencing methodology conducted on Oxford Nanopore Technologies' (ONT) MinIONTM device to accurately elucidate the 'haemobacteriome' from canine blood through sequencing of the full-length 16S rRNA gene. We detected a diverse range of important canine VBB, including Ehrlichia canis, Anaplasma platys, Mycoplasma haemocanis, Bartonella clarridgeiae, Candidatus Mycoplasma haematoparvum, a novel species of haemotropic mycoplasma and Wolbachia endosymbionts of filarial worms, indicative of filariasis. Our nanopore-based protocol was equivalent in sensitivity to both qPCR and Illumina sequencing when benchmarked against these methods, achieving high agreement as defined by the Kappa statistics (k > 0.81) for three key VBB. Utilising ONT's ability to sequence long read lengths provides an excellent alternative diagnostic method through which the 'haemobacteriome' can be accurately characterised to species-level in a way previously unachievable using short-reads. We envision our method to be translatable to multiple contexts such as the detection of VBB in other vertebrate hosts, including humans, whilst the small size of the MinIONTM is highly amenable to field use.

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BACTERIOLOGICAL RESISTANCE PROFILES TO ANTIBIOTICS AS REPORTED AT THE MEDICAL SERVICE, CENTRE HOSPITALIER UNIVERSITAIRE DE KATI, KATI, MALI

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The emergence and spread of antibiotic resistance remain major public health threat. Globally, the main cause of this emergence of resistance is an unreasonable consumption of antibiotics. Few data available at BSS Teaching Hospital of Kati. To study bacterial infections and the resistance profile of antibiotics at Kati Teaching Hospital. Cross-sectional analytical study using prospective data on a period of 20 months from January 2019 to August 2020. The study involved 102 patients out of 840 hospitalizations. The mean age was 55.5 dominated by patients aged 60 years (47.1%). Most of participants are male (72.5%) and the sex ratio is M/F of 2.6. Urine samples (78.4%), pus (16%), blood samples (12.7%), stool (2%) were tested. The main germs isolated were Escherichia coli (52.9%); Klebsiella pneumonia (14.5%); Staphylococcus aureus (9.9%); Acinetobacter baumannii and Enteroccocus faecium (4.9%). The level of resistance of Escherichia coli and Klebsiella pneumonia was very high to ampicillin, amoxi-clavulanic acid; relatively high in C3G, and fluoroquinolones; but it retains a relative sensitivity to aminoglycosides. However, the Imipenem, Amikacine, Ertapenème remain the most active. Staphylococci were resistant to penicillin, ciprofloxacin, and oxacillin. Thus Acinetobacter baumannii had a high level of resistance to C3G, Ticarcillin,

and Piperacillin-tazobactam. Enteroccocus faecium had strong resistance to Cotrimoxazole and Ciprofloxacin. 51% multi-resistant bacteria. HIV infection; antibiotic therapy; a long hospital stay had a relatively significant risk of acquiring BMRs (p=0.000; p=0.000; p=0.004). In conclusions, these results show a variable proportion of resistance and should be guided by practitioners during probabilistic antibiotic therapy in this context

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ANTIMICROBIAL SUSCEPTIBILITY PATTERNS OF GRAM NEGATIVE BACTERIA GRAM POSITIVE BACTERIA AND FUNGI SPECIES ISOLATED FROM BLOOD CULTURE BOTTLES IN YAOUNDE CAMEROON

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Bloodstream infections (BSIs) are the leading cause of mortality and morbidity worldwide. The aim of this study was to determine the antimicrobial susceptibility patterns of bacteria and fungi species isolated from blood culture bottles.This was a retrospective study. It carried out in Yaounde, at the Centre Pasteur of Cameroon from January 2010 to December 2019. Samples from patients with a clinical picture of a BSI were contained in the Bact/Alert FA, FN, and PF Plus bottles and incubated in the Bact/Alert 3D automaton. Antimicrobial susceptibility testing was performed immediately for positive cultures using the diffusion method and the Vitek 2-Compact device.A total of 5687 samples were analyzed during the study period for a prevalence of contaminated samples of 95.4%. Among the germs isolated from blood culture bottles, the most bacteria represented were: Staphylococcus sp. (13.3%), Klebsiella pneumoniae (11.9%), Micrococcus sp. (6.3%), Staphylococcus epidermidis (6.2%), Staphylococcus aureus (5.3%), Staphylococcus haemolyticus (4.7%), Escherichia coli (4.6%), Enterobacter cloacae (4.2%), Acinetobacter baumannii (4.0%) and Staphylococcus hominis (3.6%). For fungi species, Candida sp. and Candida parapsilosis were most represented (0.9% and 0.5% respectively). Antimicrobial susceptibility patterns showed that, the most represented germs were resistant to the antibiotics of penicillin family (>80%) and the cephalosporin family (>70%). However, most antifungal agents tested during the study period showed high sensitivity results. The high prevalence of a bloodstream infections and the high rates of antibiotic resistance show the need to expand the surveillance of multidrug resistance in all regions of the country.

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NEONATAL PAENIBACILLIOSIS: A NOVEL INFECTION LEADING TO INFECTIOUS HYDROCEPHALUS IN INFANTS

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Worldwide, the majority of pediatric hydrocephalus is acquired after an early life infection. In most cases we do not know the causative agents. In Uganda, in 2020, we found that a novel strain of Paenibacillus thiaminolyticus was the most common organism associated with postinfectious hydrocephalus. We performed two prospective case-control studies in 100 maternal-newborn pairs enrolled at birth and 400 infants undergoing surgery for hydrocephalus at less than 90 days of age; as well as a cohort study of 800 neonates with sepsis. In these 1400 patients, we employed 16S gene sequencing to identify bacterial species, accompanied by targeted qPCR for P thiaminolyticus. P thiaminolyticus was the dominant organism and was identified in 44% of postinfectious hydrocephalic patients. We found no evidence of P thiaminolyticus in specimens from vaginal, placental, or maternal/cord blood samples obtained at birth. From 800 neonates with sepsis, we identified P thiaminolyticus in the blood and/or cerebrospinal fluid (CSF) of 6% of patients. Among 37 neonates with P thiaminolyticus sepsis, 14% died and 14% of survivors developed postinfectious hydrocephalus with persistence of P thiaminolyticus in the CSF. We characterized a new disease syndrome - Neonatal Paenibacilliosis - underlying infant hydrocephalus in the East African country of Uganda.

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ASSESSMENT OF THE ANTIGEN DYNAMICS DURING THE CALCIFICATION PROCESS IN NATURALLY INFECTED PIGS

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Cysticercosis is a neglected disease caused by the infection of Taenia solium larvae and takes special attention when invading the central nervous systems (CNS) causing Neurocysticercosis (NCC), the principal cause of epilepsy around the world. Natural degeneration process concludes in calcified lesions, which are associated with inflammation and relapsing seizures. Although it is known that calcified lesions are usually associated with negative antigen detection by enzyme-linked immunosorbent assay (Ag-ELISA), the dynamics of circulant antigens during the calcification process are poorly known. We assessed the antigen dynamics of three experimental groups of pigs infected with NCC that were sacrificed after 4 (n=5), 8 (n=5) and 12 (n=5) months after antiparasitic treatment. Calcifications were evident on CT since month 4. We compared the capacity of two Ag-ELISA based on monoclonal antibodies (MAbs) against T solium (TsW8/TsW5) and the reference test B158/B60 Ag-ELISA. Additionally, we evaluated antibody response using EITB assay, and histopathological stainings to describe the calcification process. Calcified lesions were found in 4/5 pigs from 4 and 8 months (60.9% and 79.3% of calcifications in brain cysts, respectively); and all 5 pigs of 12 months group (48.5% of calcifications in brain). Calcifications from the 8 months group presented calcium deposits within the cysts and higher of inflammation on histopathology. Circulating antigen levels followed a similar trend that was described for both assays, presenting a notable decay after 5 or 6 months of treatment. Unlike antigen drop, the antibody response decreased slowly and continued being maintained positive even after an entire year of follow-up. Calcification of brain NCC cysts is a dynamic process in which antigen is still present for a long time after treatment onset. Circulating parasitic antigen is a consistent biomarker which can be of help to monitor this process.

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CONCORDANCE BETWEEN TWO ANTIGEN-DETECTION ENZYME-LINKED IMMUNOSORBENT ASSAYS IN DETECTING URINARY ANTIGENS AND MONITORING ANTIGEN DECAY IN PATIENTS WITH NEUROCYSTICERCOSIS

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Neurocysticercosis (NCC) is caused by the invasion of the Taenia solium metacestode into the central nervous system. NCC is one of the most important zoonotic diseases and contributes to neurological morbidity worldwide. Imaging diagnosis (CT or MRI) is supported by with serology techniques that detect antibodies or antigens (Ag) into the host circulation. Monoclonal antibody (mAb)-based enzyme-linked immunosorbent assay (ELISA) represents a useful immunological tool to confirm an active infection, correlates well with the parasitic load, and can be performed in urine, a non-invasive sample. We evaluated the concordance between the most widely used B158/B60 Ag-ELISA and our in-house TsW8/TsW5 Ag-ELISA based on T soliummAbs for the detection of parasite antigens in

the urine of patients with NCC. A total of 172 urine samples were collected and classified as in subarachnoid (n=51), parenchymal (n=18) and calcified (n=103) NCC. Concordance analysis was performed by determining the agreement and the Lin's concordance coefficient (LCC) in all the samples, as well as stratified by NCC type. Agreement between assays in all samples and stratified by NCC cases was over 90%. Equally, an overall concordance of 0.89 was obtained, and subarachnoid NCC patients presented the highest correlation (LCC=0.93), followed by calcified and parenchymal NCC (LCC= 0.77 and 0.66, respectively). Despite this high correlation, variations around a cutoff point resulted in TsW8/TsW5 Ag-ELISA categorizing 105/176 NCC cases as positive, compared to 78/176 in, the reference test B158/B60 Ag-ELISA. So far, our results indicate that urine testing with the novel TsW8/TsW5 Ag-ELISA provides comparable results to B158/B60 Ag-ELISA, providing an alternative assay for the diagnosis of NCC in a non-invasive sample, which can be applied in community settings where neuroimaging is limited.

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PHENOTYPIC DETERMINATION OF REGULATORY T AND B REGULATORY CELLS IN NEUROCYSTICERCOSIS PATIENTS

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Taenia solium causes neurocysticercosis (NCC), a neglected disease that is the leading cause of acquired epilepsy worldwide. Although NCC is a heterogeneous disease, the most determinant factor for clinical manifestations is the location of parasites into the brain parenchyma or in subarachnoid spaces and the host immune responses contribute with inflammatory component as parasite apply several strategies to diminish the host inflammatory response and preserve their permanence. In this context, regulatory T cells (Tregs) play a crucial role for the parasite survival, permanence, and longevity. Although regulatory B cells (Bregs) have been associated with their participation in neurological disorders, their role in NCC infection has not been addressed before. This study aims to characterize the phenotype of Tregs and Bregs in patients with parenchymal and subarachnoid NCC. For this purpose, we evaluated peripheral blood mononuclear cells (PBMC) from untreated NCC patients with parenchymal (n=4) or subarachnoid (n=15) infection and compared it with control patients (n=6) matched by age and gender. PBMC were phenotyped by flow cytometry in the FACS Canto II using antibody panels to determine T (CD45RO+CD4+CD25+FoxP3+) and B (CD19+CD5+) regulatory cells, as well as cytokines such as IL-10 and were analyzed using FlowJo (v10.8). Statistical analyses were made using GraphPrism V6. So far, our results described a marked difference between NCC cases and controls showing high levels of regulatory cells and upregulated production of IL-10. However, the stratified analysis by NCC type has not evidenced notably differences yet.

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CALCIFIED PORCINE NEUROCYSTICERCOSIS: IMMUNOHISTOCHEMISTRY BASED ON MONOCLONAL ANTIBODIES

(MABS) FOR RESIDUAL ANTIGENS DETECTION

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Cysticercosis is a parasitic disease caused by Taenia solium larvae and is a major problem of public health when established in the central nervous system (CNS) producing neurocysticercosis (NCC). NCC is the principal cause of acquired epilepsy worldwide. Numerous reports have described calcified lesions as a common cause of focal epilepsy, and pericalcification edema is consistently found by the time of a seizure, suggesting intermittent release of residual parasite antigens. To assess whether parasite antigens can be demonstrated in calcified NCC lesions, we developed an immunohistochemistry (IHC) assay based in our in-house T solium mAbs, directed against total cysts (TsW2, TsW5, TsW8 and TsW12), vesicular fluid (TsV3 and TsV4) and secretory/excretory products (TsE1) in degenerate cysts (granulomas n=7) and calcifications (n=22) from 17 pigs slaughtered at 2,4, 8 and 12 months after antiparasitic treatment. IHC was standardized, processed and images were digitized. Quantification of immunoreactive areas and intensity was performed using Image J software. TsW8 and TsV3 reacted, in different intensities, in all the samples evaluated from 2, 4, 8 and 12 months; followed by TsW12 (96%) and others in a lower percentage (79%-76%). Reaction was absent in control samples. On visual examination intensity and immunoreactive areas decreased gradually along time, being less reactive in 12 months calcifications (p-trend<0.05). We also identified two immunoreactivity patterns, immunoreaction within the cyst (TsW2, 5,8,12 and TsV4) and in the pericystic tissue only (TsV3 and TsE1). This finding could hint to antigen diffusion into the tissue surrounding the lesions. Therefore, we developed a novel IHC based in the best performing mAb (TsW8) that specifically identify cysticercosis lesions and confirmed the presence of residual antigen in calcified lesions, which could contribute to an inflammatory response and consequently focal epileptic seizures in calcified NCC.

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RESIDUAL CALCIFICATION IN NEUROCYSTICERCOSIS: NOT ONLY IN PARENCHYMAL CYSTS

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Considered as the most severe presentation of neurocysticercosis (NCC), subarachnoid NCC can cause inflammation and mass effects in adjacent tissues, due to the unorganized and massive growth of the parasitic membrane. Whereas abundant literature exists about the presentation and clinical impact of intraparenchymal NCC calcifications, there is basically no mention to whether subarachnoid cysts will result in residual calcification. We present 4 four adult patients from an endemic country, with a history of subarachnoid NCC, confirmed by neuroimaging and antigen enzyme linked immunosorbent assay (Ag-ELISA), who received antiparasitic treatment and developed residual calcifications in the locations of prior subarachnoid NCC lesions. All patients were very strongly positive for circulating antigen at baseline and became negative during follow up. CT was performed at least 4 years after resolution of subarachnoid NCC, and calcifications in the area adjacent to the primary lesion were observed in two patients. In two cases, cystic lesions in the Sylvian fissure resulted in a punctate calcification as those seen in parenchymal NCC lesions. In the other two, larger, irregular areas of calcification were seen. Subarachnoid NCC lesions may occasionally result in residual calcification. Further studies must determine the frequency, possible causes and consequences of the presence of calcification in subarachnoid spaces and/or adjacent tissues, as a possible cause of neurological symptoms after cysts resolution.

6991

MRI SPECTROSCOPY OF PATIENTS WITH SUBARACHNOID AND PARENCHYMAL NEUROCYSTICERCOSISRACEMOSA AND PARENCHYMAL NEUROCYSTICERCOSIS OF THE NATIONAL INSTITUTE OF NEUROLOGICALSCIENCES, LIMA, 2021-2022

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Neurocysticercosis is the most common parasitic disease of the central nervous system. Its location on the brain can be parenchymal or extraparenchymal, the latter being more aggressive and associated with a poor prognosis. The clinical presentation of NCC depends on many variables including the location, number, and size of lesions, and the immunologic response of the host. Diagnosis criteria prioritize the use of neuroimaging techniques such as MRI or CT depending on the stage of life of the parasite, as well as location. MRI spectroscopy determines the tissue concentrations of specific metabolites and may be used to diagnose that has been used in recent years in various neurological disorders such as abscesses, tumors, and cystic lesions. We assessed MRI spectroscopy findings and performed this technique in 4 four subarachnoid cysts and two parenchymal cysts. MRI spectroscopy showed peaks of lactate (1.31 ppm), lipids (0.92-1.41 ppm), isoleucine- leucine-valine (0.87 ppm), N-acetylaspartate (2 ppm), creatinine (3 ppm) and choline (3.2 ppm) in all NCC cases. When separated, we obtained a bigger Subarachnoid lesions that had higher peaks for in all metabolites in comparison to parenchymal cysts, for subarachnoid NCC, except for Glutamine-Glutamate beta region which was higher in parenchymal NCC. These preliminary results demonstrate the ability of MRI spectroscopy to identify NCC lesions and suggest a differential pattern between subarachnoid and parenchymal lesions.

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TRANSCRANIAL DOPPLER ULTRASONOGRAPHY TO DETECT VASCULITIS IN NEUROCYSTICERCOSIS

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Arteritis is a complication of neurocysticercosis (NCC), which is not always known and could trigger strokes. Transcranial Doppler Ultrasound (TCD) is a non-invasive method for detecting, staging, and monitoring cerebrovascular disease. This study aimed to detect arteritis using TCD in patients with subarachnoid and parenchymal NCC. Fifty-three patients with NCC evaluated in a reference hospital of neurological diseases were included (29 with subarachnoid and 24 with parenchymal NCC). Participants underwent a clinical interview and serology for cysticercosis, and had a TCD performed within two weeks of the enrollment. Mean flow velocity (MFV), peak systolic velocity, end diastolic velocity and pulsatility index were recorded. The participants included 23 (43.4%) females and had a median age of 37 years (IQR: 29-48). Vasculitis was detected in 12 patients (22.64%), of whom the most commonly compromised vessel was the median cerebral artery, in 11 (91.67%) patients. There were more females in the group with vasculitis (10/12, 83.33% versus 13/41, 31.71%; p=0.002), and vasculitis was more frequent in the group with subarachnoid NCC (9/29, 31.03% versus 3/24, 12.5%; p=0.187), although this difference did not reach statistical significance. Vasculitis is a frequent event in patients with NCC and can be detected by TCD.

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CONCORDANCE BETWEEN TWO MONOCLONAL ANTIBODY-BASED (MAB) ENZYME-LINKEDIMMUNOSORBENT ASSAYS (ELISAS) FOR MEASURING CYSTICERCUS ANTIGEN LEVELS INSERA FROM PIGS EXPERIMENTALLY INFECTED WITH TAENIA SOLIUM AND T. HYDATIGENA

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Antigen detection in cysticercosis confirms viable infection in the intermediate host(either pig or human). The reference B158/B60 Ag-ELISA for antigen detection hasacceptable levels of sensitivity and specificity in NCC cases with two or morecysticerci (85% and 87% respectively), although sensitivity is lower in NCC caseswith single infections (60%), whereas in rural pigs the specificity is very low (~50%)due to its frequent cross-reaction with Taenia hydatigena. Our group has produced 21anti-Taenia solium monoclonal antibodies (mAbs) reacting against antigens of thewhole cyst, vesicular fluid, and secretory/excretory products, identifyingTsW8/TsW5 as the most promising pair of mAbs for a sandwich Ag-ELISA format.This study reported the use of our in-house TsW8/TsW5 Ag-ELISA for measuring antigen levels (OD values) in two panels of sera from pigs experimentally infectedwith T. solium (n = 26) and T. hydatigena (n = 12) and assessed the concordanceof this assay with the reference B158/B60 Ag-ELISA using Bland-Altman (BA) plotsand Lin's concordance coefficients (LCC). In pigs infected with T. solium, almost allpaired log-OD values between assays were within the limits of agreement (LoA) inthe BA plot at days 0, 28, and 90 post-infection (92.3%, 100%, and 100%), andincreased concordance between assays was also found (LCC: 0.69, 0.92, and0.96, respectively, all P<0.001). In pigs infected with T. hydatigena, almost allpaired log-ODs were within the LoA, whereas paired concordance between assayswas low or moderate at days 0, and 28 PI, (LCC: 0.24 and 0.88). but was higher atday 90 PI (LCC: 0.98, P<0.001). Our TsW8/TsW5 Ag-ELISA recognize antigens in pigs with T. solium cysticercosis but its diagnostic use is hampered by cross-reactions with T. hydatigena, as in other mAb-based antigen detection ELISA assays.

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THE EARLY STAGE OF TAENIA SOLIUM CYSTICERCUS SECRETE TRANSFORMING GROWTH FACTOR-BETA MIMIC PROTEINS

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The cysticercus is the stage of Taenia solium that causes neurocysticercosis, a central nervous system disease. When the parasite reaches the brain, it settles in the tissue and develops to the postoncospheral form (the early stage of cysticercus); this form needs to

grow and survive to complete its development to cysticercus; however, the mechanism that this parasite uses to evade the host immune response at this stage is not yet known. Taenia solium has been reported to express Transforming Growth Factor-beta (TGF-β) receptors, which exert an essential role in the parasite's growth and survival, suggesting that this parasite could secrete a TGF-β mimic protein. This study aimed to evaluate if the different developmental times of T. solium postoncospheral form secrete a TGF-β mimic protein. For this, T. solium activated oncospheres were grown on HCT-8 monolayers for 15, 30, and 60 days in vitro. The postoncospheral forms obtained at different times of culture were collected and co-culture for 24 h with the MFB-F11 cells (transfected mouse fibroblast cells) using a Transwell permeable supports (the MFB-F11 can detect biologically activated TGF-β in a cell co-culture system). Our results showed that postoncospheral form can activate the TGF-β signaling pathway in MFB-11 cells, suggesting that the parasite has a protein that mimics TGF-β. Further studies are needed to identify this protein and evaluate its role in modulating the host's immune response.

6995

EVALUATION OF AXONAL TRANSPORT DAMAGE IN AN ANIMAL MODEL OF NEUROCYSTICERCOSIS

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Neurocysticercosis (NCC) is a parasitic disease of the central nervous system caused by Taenia solium larvae, which causes acquired epilepsy and seizures in people from endemic countries. In a previous study with the rat infection model, axonal damage is evidenced in the tissue surrounding the parasite characterized by the formation of spheroids, which are areas of axonal swelling with accumulation of proteins of the axonal cytoskeleton as neurofilament (NFP) and that could be associated to a probable alteration in axonal transport. For this reason, in this study we evaluated by immunohistochemistry the reactivity of the motor protein kinesin and NFP in brain tissue from 3 experimental groups (treated, untreated and control rats with NCC). Rats 12 days old were inoculated intracranially with activated T. solium oncospheres and at 6 months post-infection one group received antiparasitic treatment (oxfendazole and praziquantel) orally for 5 days and the untreated group received a vehicle and were sacrificed at different post-treatment times (48 hr, 5 days, 2 months, 8-10 months and 12 months). When evaluating NFP reactivity in the treated and untreated groups, the number of spheroids reactive to NFP was higher in gray matter than in white matter and was maintained over time; in healthy rats no reactivity to NFP in the form of spheroids was found. When evaluating kinesin reactivity around the cyst in the treated and untreated groups, reactive areas in the form of clusters called kinesin-reactive varicosities were found, with a smaller reactive area size than that observed in NFP. The number of kinesin-reactive varicosities around the cyst was similar in the groups of treated and untreated rats and was maintained over time, being higher in gray matter than in white matter; in healthy rats no kinesin-reactive varicosities were found. These results show the existence of axonal transport damage in rats with NCC, where a pathological accumulation of kinesin protein and NFP is observed over time, which would contribute to neurodegeneration and symptomatology in NCC.

6996

EVALUATION OF OLIGODENDROCYTE DENSITY AND APOPTOSIS DAMAGE AT DIFFERENT POST-INFECTION TIMES IN A RAT MODEL WITH NEUROCYSTICERCOSIS

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Neurocysticercosis (NCC) is a disease caused by the infection of the larval stage of Taenia solium in the central nervous system (CNS) and is the main cause of late epilepsy in endemic regions such as Latin America, Asia and Africa. It is well known that NCC causes axonal damage, however, it is undetermined whether the death of oligodendrocytes (OL) increases axonal damage. In addition, it is unknown if the presence of the parasite in the CNS is affecting the density of oligodendrocytes throughout the post-infection process. Using rats as an animal model of NCC, they were intracranially infected with activated T. solium oncospheres in the brain tissue. The animals were sacrificed at ten post-infection times and classified into five groups: group A (one and one and a half months), group B (two and two and a half months), group C (three months), group D (four, six and eight months) and group E (ten and twelve months). Olig2 marker was used to evaluate the oligodendrocyte lineage using immunohistochemistry. The presence of oligodendrocytes was observed heterogeneously distributed throughout the brain, with the white matter being the area of the brain with the highest number of OL, especially in the corpus callosum. It was also observed that infected brains showed a statistically significant decrease in OL over time compared to the control group. Subsequently, oligodendrocytes that undergo apoptosis were evaluated using Olig2 and caspase-3 markers. A higher number of apoptotic OL were found in infected brains compared to healthy brains. From the obtained results, it can be concluded that OL decrease and may be associated with apoptosis.

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GASDERMIN D IMMUNOREACTIVITY IN RAT BRAIN TISSUES WITH NEUROCYSTICERCOSIS

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Neurocysticercosis (NCC) is a parasitic disease affecting the brain caused by the larval form of the parasite Taenia solium; seizures are the predominant clinical feature when the cyst is located at the level of the brain parenchyma, but asymptomatic cases also occur. During the development of the parasite in the central nervous system (CNS) tissue, a mild to moderate inflammatory response is observed, which becomes chronic over time and after three months post-infection, fibrotic tissue formation around the cyst is evident. Treatment of NCC with anthelmintic drugs has been shown to exacerbate the clinical symptoms, which are associated with parasite damage and increased inflammatory response in the tissue around the parasite. Many CNS diseases are closely related to pyroptosis cell death which is a type of programmed cell death mediated

by gasdermin. The gasdermin complex is formed by gasdermins A, B, C, D and E, which possess an N-terminal domain that forms pores in the cytoplasmic membrane thus executing cell death. This type of cell death is characterized by swelling, lysis and release of cytoplasmic contents. However, excessive pyroptosis is detrimental to normal tissues and cells. For this reason, in this study the expression of gasdermin D (GSDMD) around the cyst was determined, by immunohistochemistry, in rat brain tissues with NCC treated with antiparasitic drugs and in NCC untreated rat brain tissues. Demonstrating that GSDMD had higher immunoreactivity in fibrotic tissue compared to non-fibrotic tissue in both treated and untreated rat brain tissues, being higher in untreated rat brain tissues. In conclusion, these results reveal that while the parasite is viable, GSDMD expression is elevated and begins to decrease with treatment.

6998

NITRO-OXIDATIVE STRESS AND NEURONAL DAMAGE IN A RAT MODEL FOR NEUROCYSTICERCOSIS PRESENTING EPILEPSY

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Neurocysticercosis (NCC) is an infection of the Central Nervous System (CNS) by the larval stage of the flatworm parasite Taenia solium; epilepsy is the most common clinical manifestation of this infection and is associated with inflammatory processes such as angiogenesis, gliosis, and neuronal damage; however, whether nitro-oxidative stress plays a role in the epileptogenic process in NCC has not yet been evaluated. In this study, an indicator of nitro-oxidative stress (iNOS) and its relationship with the presence of recurrent seizures (Epilepsy) in rats were evaluated by immunohistochemistry, as well as whether the presence of nitro-oxidative stress is associated with the presence of spheroids or axonal swelling, and gliosis (CD68) or astrogliosis (GFAP) in the NCC animal model comparing NCC rats with epilepsy, NCC rats without epilepsy and healthy rats. iNOS expression was found to be higher in NCC rats presenting with epilepsy ($p<0.05$); the presence of macrophages and astrocytes around the cyst is also increased in rats with NCC presenting with epilepsy ($p<0.05$) and is associated with iNOS immunoreactivity (rho=0.75); Finally, the presence of spheroids reactive to NFP and SOD1 was higher in rats with NCC that developed Epilepsy with $p<0.05$ and $p=0.06$ respectively; In addition, there is an association between the number of spheroids and iNOS immunoreactivity (Spearman rho=0.81 for NFP spheroids and Spearman rho=0.75 for SOD1 spheroids). These results indicate that there is nitro-oxidative stress in the brain tissue of rats with NCC that present epilepsy and is associated with the severity of gliosis and astrogliosis as well as the presence of neuronal damage in the form of axonal swelling, so it is necessary to deepen the study of this event in order to find therapeutic targets in epilepsy due to NCC.

6999

AN UPDATE ON THE CLINICAL-EPIDEMIOLOGY OF NEGLECTED SEXUALLY TRANSMITTED INFECTIONS IN IMPOVERISHED SOUTHERN USA ADOLESCENT POPULATIONS

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While sexually transmitted infections are not traditionally considered a neglected tropical disease, the health disparities aspects of these infections makes a strong case for their neglected nature among vulnerable populations—as highlighted in an AJTMH neglected parasitic infections editorial. South Carolina is home to some of the highest national poverty rates and sexually transmitted infection rates. Here, 60% of at-risk adolescents are positive for at least one infection: half being pregnant girls. Further, 18% are triply infected with concomitant gonorrhea, trichomoniasis and chlamydia. The clinical and immunologic impact of co-infection is unknown, especially among adolescents, yet hypothesized to contribute to growing drug resistance and treatment failure. The South Carolina STICK study was started in October 2022 to evaluate the long-term clinical, epidemiological, and immunological impact of gonorrhea, trichomoniasis and chlamydia concomitant infection in adolescents and young adults. This presentation will describe the risk factors for treatment failure, prospective vaginal microbiome changes by disease group, and host immunologic response to concomitant infection from the first enrolled cohort. This study sheds light on an emerging neglected group of diseases, whose clinical-epidemiologic profile is changing in real-time.

7000

CLINICAL, EPIDEMIOLOGICAL, HISTOPATHOLOGICAL, AND SOCIO-ECONOMIC PANORAMA OF LEPROSY PATIENTS IN A TERTIARY CENTER ACROSS THE NEPAL-INDIA BORDER IN THE POST-ELIMINATION ERA: A CROSS-SECTIONAL STUDY

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IntroductionLeprosy is an infectious granulomatous disease that is a re-emerging threat in Nepal and India due to neglected anti-leprosy programs and community stigma leading to deformity. ObjectivesThis study aimed to evaluate the clinical, epidemiological, socioeconomic, and histological profiles of leprosy patients across the Nepal-India border. Materials and MethodsA descriptive, prospective study was conducted for three years in the dermatology department of a tertiary care center in Nepal using non-probability purposive census sampling with a minimum sample size of 30 patients per year. Ethical approval was obtained, and descriptive and inferential statistics were used for data analysis. ResultsThe study included 110 patients with a mean age of 33.54 years (SD +- 16.5), with 3/4 of patients being Nepalese. The mean distance between the patient's home and hospital was 30.7 km (Std Error +-4.049). 97% of patients were of low to middle-class, and 45% were farmers. The mean duration of the disease was 17.6 months (1 month to 80 years). The average bacteriological index was 1.6. Borderline tuberculoid (27.3%) was the most common type of leprosy, followed by tuberculoid leprosy (25.5%). Bacteriological positivity was observed in 85% of patients. Family history, neuritis, and deformity were observed in 85.5%, 64%%, and 23.6% of patients, respectively. There was a significant association between the distance of the patient from the hospital and the bacteriological index ($p=0.004$). ConclusionsLeprosy remains a public health problem across borders despite the level of elimination at the national level. Clustering of cases emphasizes the need for both countries to spread awareness about the disease for early diagnosis and unhindered provision of therapy to prevent deformities.

7001

SPOT SEPSIS: PREDICTION OF DISEASE SEVERITY IN YOUNG CHILDREN WITH ACUTE FEBRILE ILLNESSES IN RESOURCE LIMITED SETTINGS

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Infections remain the leading cause of preventable childhood mortality in low- and middle-income countries. Reliable guidelines to help community healthcare providers identify children whom may benefit from referral to higher-level care are lacking. This talk will present findings from a multi-country prospective observational cohort study (NCT04285021) which recruited children under the age of five presenting with acute febrile illnesses to seven hospitals in Bangladesh, Cambodia, Lao PDR, Indonesia, and Vietnam. The primary objective was to develop and externally validate a clinical prediction model containing simple clinical parameters and host biomarkers amenable to measurement using point-of-care tests, to support risk stratification of children presenting in resource-limited primary care settings and decentralised models of care. The primary outcome was severe febrile illness, defined as death, vital organ support, or admission to any health facility for > 2 days in the 28 days following enrolment. Between March 2020 and October 2022, 3,450 children were recruited, of whom 6.1% met the primary outcome. Penalised logistic regression was used to develop the model using data from Bangladesh, Lao PDR, Indonesia, and Vietnam, which will be externally validated in the dataset from Cambodia. Discrimination, calibration, and classification at clinically plausible referral thresholds will be reported. Generalisability of the model will be evaluated using decision curve analyses to account for heterogeneous contexts commonplace in community care settings in many LMICs. Targeted aetiological investigations will allow exploration of the performance of the model in confirmed bacterial and viral infections. The results of the study will inform planning of an interventional trial to evaluate the clinical impact of the model on improving health outcomes for children presenting with acute febrile illnesses in resource-limited community settings.

7002

NANOPORE SEQUENCING OR MICROARRAY DETECTION OF PATHOGENS IN BLOOD: SIDE-BY-SIDE COMPARISON

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The large number of infectious agents in blood and their continued emergence are constant challenges for diagnostic and blood donor screening devices. To increase multiplicity while maintaining sensitivity and specificity, new technologies must be designed and tested. Effective platforms must also achieve rapid processing and provide results that are easy to interpret. For example, dozens of patients arrive at a clinic in Uganda with a fever of unknown origin each week. To diagnose under such conditions, a single, affordable, multiplex molecular test could replace a multitude of costly assays. We have developed and published a resequencing microarray and are now completing work on an expanded blood borne pathogen microarray (BBPv2) that could satisfy that need. To determine whether the portable DNA sequencing technology can replace the microarray for pathogen identification, we are conducting a comparative analysis of the Oxford Nanopore MinION sequencing device and the BBPv2. Our study involves testing both devices to determine the infectious agents in various samples, such as blood and plasma samples, spiked with lab cultured pathogens, infectious agent reference panels and blood donor specimens. The accuracy, speed and complexity of each device will be compared and evaluated to determine the method most suited for use in endemic areas. My comments/My contributions] are an informal communication and represent my own best judgement. These comments do not bind or obligate FDA

7003

EVALUATION OF THE IMPACT ON CHILDHOOD MORTALITY OF AZITHROMYCIN PLUS INTERMITTENT PREVENTIVE TREATMENT ADMINISTERED THROUGH THE EXPANDED PROGRAM OF IMMUNIZATION IN SIERRA LEONE

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Sub-Saharan Africa (SSA) continues to concentrate the highest child mortality rate with half of the 5.3 million deaths of children under 5 years of age (U5) in 2018 worldwide. Infectious diseases, such as respiratory and gastrointestinal infections are common mortality causes preventable by treatments and prevention. Sierra Leone is one of the countries with the highest malaria and U5 mortality rates worldwide with malaria prevalence among U5 ranging from 20.9 to 40.4% and an infant mortality rate of 75 infants per 1,000 live births. It is also the only country that nationally implemented the Intermittent Preventive Treatment of malaria in infants with sulfadoxine-pyrimethamine (IPTi-SP) as recommended by the World Health Organization (WHO), which is now renamed Perennial Malaria Chemoprevention (PMC). The ICARIA (Improving Care through Azithromycin Research for Infants in Africa) clinical trial is carried out in Sierra Leone to provide the evidence needed to inform policy and accelerate the implementation of this intervention. The trial is designed as an individually randomized doubled blind two-arm placebo-controlled superiority trial, where AZi will be administered three times alongside routine preventive health interventions of the EPI, such as immunizations and IPTi-SP, as recommended by the WHO for malaria prevention in this age group. Additionally, IPTi-SP administration will be increased to six doses and expanded to the second year of life up to 15 months of age. Implemented in March 2021, the trial aims to recruit 20,560 children visiting health facilities for the first EPI pentavalent vaccine and follow up until they reach 18 months of age. The potential development of antibiotic resistance, SP resistance, interactions with routine immunizations, safety, and the impact on the health system of AZi and IPTi-SP administration will be all assessed in this trial.

7004

A RANDOMIZED CLINICAL TRIAL INVESTIGATING THE EFFECT OF BCG REVACCINATION ON THE RESPONSE TO UNRELATED VACCINES IN UGANDAN ADOLESCENTS: THE POPVAC C TRIAL

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There is evidence that BCG immunisation may protect against unrelated infectious illnesses. we hypothesized that administering BCG before unrelated vaccines modifies responses to subsequent vaccines.
We designed a randomised controlled trial of BCG versus no BCG immunisation to determine the effect of BCG on subsequent unrelated vaccines, among adolescents (aged 13–17 years) from a Ugandan, urban birth cohort. Our schedule comprised three main immunisation days (week 0, week 4 and week 28): BCG (or no BCG) revaccination at week 0; yellow fever (YF17D), oral typhoid (Ty21a) and human papillomavirus (HPV) prime at week 4; and HPV boost and tetanus/ diphtheria (Td) boost at week 28. The primary outcomes were anti-YF-17D neutralising antibody titres, Salmonella typhi lipopolysaccharide-specific IgG concentration, IgG specific for L1-proteins of HPV-16/HPV-18, all assessed at 4 weeks after immunization and tetanus and diphtheria toxoid-specific IgG concentration assessed at week 28. We enrolled 300 participants of which 151 were in the BCG revaccination arm and 149 in the no BCG revaccination arm. 178 (58%) of the participants were male. 142 (94%) of the participants in the BCG arm and 136 (91%) in the no BCG arm completed the trial. Comparing trial arms, no difference in response was observed for any vaccine: Geometric Mean Ratios (GMR) (95% CI) were, for yellow fever 0.97 (0.77-1.22), Ty21a 0.981 (0.82-1.18) at week 8 and 1.17 (0.91-1.50) and 0.982 (0.85-1.13) respectively, at week 52. The GMR for TT and DT IgG responses at week 52 was 1.04 (0.81-1.33) and 0.95 (0.84-1.08) at week 52 respectively. The outcomes for HPV are still being processed. BCG revaccination had no impact on antibody responses generated to yellow fever, oral typhoid, tetanus, and diphtheria vaccine antigens among urban Ugandan adolescents who received BCG at birth.

7005

DIFFERENTIATION OF ACUTE EXACERBATIONS OF CHRONIC HEPATITIS B AND ACUTE HEPATITIS B IN ANTIHBC IGM POSITIVE PATIENTS AT HOSPITAL FOR TROPICAL DISEASESIN VIETNAM

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Acute exacerbations of chronic hepatitis B (CHBAE) are common in endemic areas and difficult to distinguish from acute hepatitis B (AHB) in antiHBc IgM positive patients with prior HBV history infection. We performed a retrospective and prospective observational study for adult patients who presented with clinical features of acute hepatitis along with IgM antibody to hepatitis B core antigen (antiHBc IgM) positive at Hospital for Tropical Diseases (HTD), Hochiminh City, Vietnam from January 2018 to September 2022. Diagnostic confirmation was based on HBsAg loss after 6 months. Multivariates logistic regression was done to identify the factors that differentiated AHB from CHBAE in antiHBc IgM positive patients. A total of 610 patients were enrolled and divided into two groups: AHB (n = 491) and CHB-AE (n = 119). AntiHBc IgM cutoff of 8 S/CO provided the best sensitivity and specificity for predicting patients with CHB-AE (91.2% and 90.8% respectively). The multivariate analysis demonstrated that the level of platelet, AFP and the S/CO ratio of antiHBc IgM were significant factors. AFP and the S/CO ratio of IgM antiHBc were significantly higher in CHBAE group (OR 0.995, (95% CI 0.991 - 0.999) and OR 1.356, (95% CI 1.124 - 1.635), respectively), while the platelet level was significantly higher in the AHB group (OR 1.031, (95% CI 1.008 - 1.056). In conclusion, antiHBc IgM should be included concurrently with liver fibrosis biomarkers, particularly the levels of platelet and AFP to discriminate CHBAE and AHB.

7006

ALPHA-GAL ALLERGY SEROPREVALENCE IN RURAL AND MINORITY POPULATIONS, EVIDENCE ALPHA-GAL SYNDROME IS A NEGLECTED DISEASE IN THE SOUTHERN USA

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Alpha-gal syndrome (AGS) is an IgE mediated allergic response to galactose-α-1, 3-galactose (alpha-gal) following tick bite(s) and is exacerbated by consumption of mammalian meat products. While considered an emerging condition in the United States, AGS is a global phenomenon. Typical patients experience delayed diagnosis due to the non-specific reaction and/or being unaware of tick bite exposure. Acute reactions are preventable and treatable but potentially life-threatening without intervention. Nationally, AGS is predominantly reported in Caucasians with a recently reported median onset age of 53 years (IQR 42-60). In this study we present a seroprevalence and associated tick exposure survey of ~800 rural and minority residents in South Carolina. Three percent of respondents self-reported allergic reactions after eating red meat. Participants originate from 18 different ZIP codes with a median household income of <50,000 (USD). Alpha-gal IgE levels were measured cross-sectionally among this health cohort to estimate disease burden among a diverse sample. This study highlights a previously undescribed population potentially suffering from this treatable, yet undiagnosed condition in at-risk populations.

7007

STOOL CALPROTECTIN AND ASSOCIATED GUT-PATHOGENS IN A COHORT OF PATIENTS WITH GIT DISORDERS WITH AND WITHOUT IMMUNE-MEDIATED INFLAMMATORY INTESTINAL DISEASES IN SAUDI ARABIA

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Stool calprotectin is a neutrophil-specific zinc- and calcium-binding protein. It releases in the intestinal lumen in acute intestinal inflammation and is used as a biomarker for gut inflammation. This study's goal is to determine the distribution pattern of calprotectin in a cohort of patients with GIT disorders, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS) and other non-IBD/IBS GIT disorders. Also, to assess the association between the presence of stool calprotectin and patients' data, including stool test results for gut pathogens. Stool specimens and related data were collected from 408 patients attending the King Fahad Hospital of the University (KFHU), Eastern Province, Saudi Arabia whose stool examination was done in the microbiology lab as part of the management of the patient's clinical condition. Each stool specimen was examined microscopically for the pathogen, cultured on Jones for Blastocystis, and stool calprotectin was measured using ELISA assay. All related patients' sociodemographic and clinical data were recorded and analysed as associated factors/ variables.Except for structure colonic diseases (Anal fissure, fistula, abscess, colon polyp) and food allergies, calprotectin was detected in all GIT disorders mainly inflammatory bowel diseases. Results of calprotectin showed a pattern with age distribution, it was detected in all age groups with a decrease in positivity with increasing age. Males had more positive cases with calprotectin in their stool than females. Stool leukocytes, occult blood in stool, the presence of the gut parasite in stool and the presence of H. pylori antigen in stool were more common in calprotectin-positive patients. The presence of Clostridium difficile and negative stool culture was more common in calprotectin-negative patients. Stool calprotectin is present in with IBD and without IBD (including patients with IBS) in addition

to a relatively healthy gut. Further studies to assess the distribution of calprotectin in health and disease are needed, in order to provide a better understanding of the role of calprotectin as a biomarker in GIT disorders.

7008

CLINICAL CHARACTERIZATION AND ANALYSIS OF INFLAMMATION AND COAGULATION OF LASSA FEVER PATIENTS TREATED AT THE IRRUA SPECIALIST TEACHING HOSPITAL IN EDO STATE, NIGERIA IN 2022 AND 2023

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Lassa fever (LF) is a viral hemorrhagic fever occurring in West Africa with a high case fatality rate (CFR) in hospitalized patients. To date there is no approved treatment or vaccine and the diseases' pathophysiology is poorly understood. Hemodynamically relevant hemorrhagic presentations are rare; severe cases are complicated by renal failure and neurological manifestations. Here, we longitudinally characterized an observational cohort of currently 339 acute RT-PCR confirmed LF patients (March 23rd, 2023; recruitment ongoing) during two LF outbreaks in Edo State, Nigeria in 2022 and 2023. By combining detailed clinical examinations and testing for molecular markers of inflammation and coagulopathy, as well as transcriptomics we aim to identify correlates of severe disease. Our study visits consisted of physical examinations, brief neurological status, vital parameter measurement and point-of-care testing for PT and aPTT. In selected cases rotational thromboelastometry and ultrasound scanning is done. Besides standard laboratory analysis (hematology, clinical chemistry, electrolytes, blood gas analysis) we measure consecutive viral load and biomarkers of inflammation and coagulopathy such as plasminogen activator inhibitor-1 (PAI-1) and soluble thrombomodulin which have previously been shown to be associated with severe LF. In our currently analyzed subset of patients (n=278; mean age 32 years ± 13.2; 41 % female, CFR 11,2 %) we classified 67 (24%) as severe. Severe cases were hallmarked by elevated acute phase markers such as CRP and ferritin, acute kidney injury (AKI), septic shock and respiratory failure with massive pleural effusion. Bleeding was rare though some fatal cases had highly abnormal coagulation parameters and fulfilled DIC criteria. In summary we characterized relevant organ complications of LF and identified a hyperinflammatory state to be associated with severe disease which both have important implications for the development of appropriate medical countermeasures. Recruitment is currently ongoing until July 2023 and the study's final results will be presented at the meeting in November 2023.

7009

CHAGAS DISEASE CLINICS IN ENDEMIC LOCALITIES FROM ARGENTINA: RESULTS FROM 2015 TO 2022

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Chagas Disease (ChD), caused by Trypanosoma cruzi, is historically a vector-borne disease mostly present in Latin America with other minor forms of transmission. In Argentina, vector presence (Triatoma infestans) has been reported in 19 of the 24 provinces. Recently, 10 provinces were certified free of vector-borne transmission of ChD (Corrientes, Entre Ríos, Jujuy, La Pampa, Misiones, Neuquén, Río Negro, San Luis, Santa Fe, and Tucumán). In Chaco and Santiago del Estero, traditionally endemic, Mundo Sano (MS) implemented entomological surveillance and control (S&C) actions since 2008 in Pampa del Indio and 2002 in Añatuya, respectively. Given a decrease in vector populations due to sustained S&C and environmental/land changes, MS has been recently and actively promoting diagnosis and treatment (D&T) of ChD together with the local municipalities. For this purpose, specialized ChD clinic days were set up in municipal or provincial health posts of all three localities since June 2015 in collaboration with local professionals coordinated by MS. Up to December 2022, 3,433 individuals received medical attention specifically for ChD, of which 873 (25.4%) tested positive for T. cruzi. Prevalence varied depending on the locality: 39.3% for Pampa del Indio, 43.1% for Colonia Dora (Santiago) and 19.4% for Añatuya. Treatment was offered to positive individuals with indication for treatment based on national guidelines and medical consensus. From 873 positive individuals, 666 (76.3%) fit the treatment criteria and more than half of these (59.2%) started treatment with Benznidazole (Laboratorios Elea Phoenix S.A.). Some reasons for lack of treatment in eligible individuals included: fear, lack of trust, interest, or urgency, or unwillingness to adhere to the necessary dieting restrictions during treatment. This initial approach through specific clinics has shown the need for D&T in older population to avoid progression of the disease to more severe forms and generates evidence for integration of this model of attention into the regular public health system.

7010

ISOLATED HYPERPARASITEMIA IN IMPORTED SEVERE PLASMODIUM FALCIPARUM MALARIA: NO PREDICTOR FOR COMPLICATIONS

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Severe malaria remains a health threat for travelers to endemic areas. In addition to the criteria for severe malaria, WHO has included an entity termed uncomplicated hyperparasitemia (HP) (range: 4-10%) in its latest treatment recommendations. Such parasite density, however, usually defines severe disease in patients outside endemic areas where HP is not specified with recommendations ranging from ≥2 to ≥5%. We retrospectively analyzed all adult in-patients with HP defined as ≥4% and/or severe Plasmodium falciparum malaria according to WHO criteria, treated from 2013 to 2023 at Charité university hospital. The primary objective was to identify and stratify the risk for a critical disease trajectory based on the WHO criteria for severe malaria; in addition, HP was evaluated as an independent factor. The sum of positive criteria was calculated and analyzed for the primary endpoint "need for intensive care". Overall, 75 patients were included in this study. Median age was 48 (IQR 36-56) with 50 male patients (67%). Patients were tourists (n=36, 48%), VFRs (n=35, 47%) and visitors from endemic regions (n=4, 5%). 51 patients (68%) received artesunate, 17 (23%) an ACT and 7 (9%) quinine as primary treatment. The likelihood of requiring intensive care increased steadily with the number of criteria for severe malaria met by an individual, from 15% in patients with only one criterion to 58% for 2 criteria and 100% for ≥ 3 criteria. The exception were patients with severe clinical presentation (cerebral malaria, shock), who all required intensive care, whereas all other patients with only one criterion did not. This was especially true for the 39 patients (52%) with isolated HP, who formed the majority in the group of patients with only one criterion (39/44, 89%), all of whom did not require intensive care. Among these patients, median parasitemia was 7% (IQR 5-11%); 15 patients (38%) presented with a parasitemia of ≥10%. Patients with HP - even above 10% - in the absence of clinical or laboratory criteria for complicated malaria did not require ICU treatment in our patient population whereas severe clinical presentation regularly predicted need for ICU treatment.

7011

THE BURDEN AND IMPACT OF TORCH INFECTIONS AMONG PERINATAL WOMEN AND THEIR NEONATES IN EL SALVADOR

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TORCH pathogens are a group of congenitally transmitted infectious agents that can cause severe health outcomes in mothers and their fetus or neonate. TORCH pathogen burdens are higher in low-and-middle-income countries; however, they receive little public health attention. Therefore, the goal of this study was to investigate the prevalence of and maternal-fetal impact of four key TORCH pathogens (Toxoplasma gondii (toxoplasmosis), Trypanosoma cruzi (Chagas disease), Zika virus, and dengue virus) among women presenting for labor and delivery to a large referent hospital in western El Salvador. This study was approved by the Salvadoran National Health Research Ethics Committee, and 201 women ≥15 years of age were enrolled at parturition. From this cohort, 36% of women had diagnostic evidence of ≥ 1 TORCH pathogen, and 5% had evidence of ≥ 2 TORCH pathogens at the time of childbirth or within the last trimester of their pregnancy. Pathogen specific infection incidence were: 25% Zika or dengue virus, 9% T. gondii and 6% T. cruzi positive. Zika or dengue virus positive mothers were significantly more likely to have had Ministry of Health household fumigation or mosquito abatement within the past year. Maternal T. gondii infection was significantly associated with keeping animals in the home, and lower maternal education. Lastly, maternal T. cruzi positivity was significantly associated with older maternal age, lower maternal education level, and neonatal admission to the NICU. Clinicians and public health officials working in Central America should prioritize TORCH pathogen surveillance among pregnant women and women of childbearing age, as intervention efforts in this population have benefit to both mother and fetus. This presentation will review our findings and TORCH pathogen basics for practitioners needing a refresher on congenitally-transmitted neglected tropical diseases.

7012

HEALTH-RELATED QUALITY OF LIFE (HRQOL) AND FATIGUE IN THE DENGUE CONVALESCENCE PHASE DURING AN OUTBREAK (2019-2020) IN BUCARAMANGA, COLOMBIA.

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Dengue disease has been public health problem to prioritize due to its severity, the difficulty of control, and other factors that impact the mortality and disability of the illness. There are some biological markers related to the severity in the acute phase, but it has not been evaluated in predicting complications in the convalescence phase. The aim was to determine the association between clinical severity, C-reactive protein (CRP), and NS1 with the affectation of HRQoL and fatigue in the convalescence phase in dengue patients during an outbreak (2019-2020) in Bucaramanga, Colombia.We included 253 dengue cases in the acute phase which 78% (n=198) were children and adolescents. All cases had a clinical evaluation and provided a blood sample to determine levels of CRP and NS1. A subgroup of 127 patients completed a set of questionaries HRQoL (Kidscreen-52 in children and SF-36 in adults) and fatigue (ME-CFS and Chalder CFQ-11 questionaries) at months 1 and 6 post-dengue infection. Linear and logistic regression analysis were used by adjusting for age, sex, secondary infection, and comorbidities.In minors, the Moods & Emotions dimension score showed low levels of HRQoL and was related to an increase in CRP levels with 1.53 points (p<0.001). Likewise, the School environment showed a gradient according to CRP levels (0.38 points, p=0.022). High scores in the School environment were associated with low NS1 (0.21 points less, p= 0.013). Instead, CRP and NS1 were not associated with changes in HRQoL in adults. 27%(n=22/80) minors had scores compatible with fatigue at 6 months of evaluation explained by an increase in NS1 and age with OR: 1.06, CI95%:1.01-1.12, and OR: 1.33 CI95%: 1.09-1.62 respectively. Fatigue was not associated with Ns1 in adults. Overall sample, there was no relationship between CRP and post-dengue fatigue. Moreover, Clinical severity was not associated with HRQoL or fatigue.This study provided a preliminary result of the burden of the dengue convalescence phase in terms of quality of life and fatigue in children and adolescents in an epidemic context.

7013

FAS-2 ELISA FOR FOLLOW-UP OF SCHOOL-AGE CHILDREN WITH CHRONIC FASCIOLA HEPATICA INFECTION TREATED IN RURAL CUSCO, PERU

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Fascioliasis diagnosis relays on serology during liver tissue migration and serology/stool microscopy during biliary tree invasion. The role of serology in treatment follow-up has not been well studied. We evaluate the FAS-2 ELISA for F. hepatica antibodies after treatment in a cohort of 3,000 children from rural areas of Peru. Children 3-16 years in communities at 3200 meters of elevation in Cusco were tested for fascioliasis using Kato Katz (KK) and rapid sedimentation in 3 stool samples and Fas2 ELISA in serum. Children with any positive Fasciola test were treated with triclabendazole. Treatment response was assessed after 1-3 months with stool microscopy and serology. We analyzed the qualitative and optical density Fas2 ELISA results after treatment in children with chronic fascioliasis define as passing eggs in stool. Overall, 216 had positive FAS-2 ELISA and 160 had chronic fascioliasis. In the latter, 71.3% had positive FAS-2 ELISA, the Fas2 ELISA OD geometric mean (FAS2OD-GM) was 0.289, and the geometric mean of the KK (GM KK) was 41.6 eggs/gram of stool (epgs) at baseline. Follow up after the first treatment was in a median of 3 months (IQR 2-3), 40.6% of children were passing eggs, 54.4% cured, and 5% were lost to follow up. In those passing eggs, 80% had a positive Fas2 ELISA, the FAS2OD-GM was 0.329, and the GM KK was 50.5 epgs. In those cured, 30% had a positive Fas2 ELISA, the FAS2OD-GM was 0.104 (Wilcoxon rank test p < 0.001), and the median decrease in OD was 38.3% (IQR: 18.5 - 110.3). Follow up after the second treatment was in a median of 1 month (IQR: 1-2), 50.8% were passing Fasciola eggs, 36.9% cured, and 12.3% were lost to follow up. In those passing eggs, 76.6% had a positive Fas2 ELISA, the FAS2OD-GM was 0.312, and GM KK was 39 epgs. In those who cured, 30% had positive Fas2 ELISA, the FAS2OD-GM was 0.142 (Wilcoxon rank test p = 0.003), and the median decrease in OD was 50.2% (IQR 30.2 - 63.8). The FAS-2 ELISA sensitivity was low is subjects with chronic fascioliasis, a third of those cured still have positive Fas2 ELISA, but OD values decreased significantly.

7014

PHYSICIAN KNOWLEDGE OF CHAGAS DISEASE IN NEW ORLEANS

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Chagas disease has an annual burden of about $0.9 billion in the United States on par with estimates of Lyme disease and methicillin-resistant Staphylococcus aureus. Yet, <1% of cases are diagnosed and <0.3% are

treated in the United States. Contributing factors to these low estimates are multiple but include low physician awareness and knowledge. This study measured physician knowledge before and after training in New Orleans, Louisiana (2022-2023). Hybrid training was given at grand rounds, resident didactics, and conferences. Demographics data was collected. Questions were on disease epidemiology, diagnosis, and treatment. McNemar's test assessed the effect of the training on knowledge. A total of 248 physicians consented from two hospitals and four medical centers. Thirty six percent were from internal medicine, 29% pediatrics, 15% obstetrics and gynecology, 11% family medicine and 9% cardiology. Forty-three percent were residents, 24% attendings, 19% medical students, 10% fellows, 2% nurses and 2% others. Most (95%) had heard of Chagas disease; 62% had not taken a course or lecture on Chagas disease. At baseline, 80% answered correctly on causative agent, endemic regions, disease course but only 56% answered correctly on various transmission routes. A quarter knew diagnostic methods, 42% knew diagnostics for infants, and 38% knew treatment. Following training, knowledge increased and >90% answered questions correctly on the causative agent, endemic regions, disease course and transmission routes ($p<0.05$), 78% on diagnostic methods ($p<0.05$), 85% on diagnostics for infants, and 90% on treatment. In this sample, there was greater knowledge on disease basics compared to other reports, but inadequate knowledge of diagnostics and treatment prior to training physicians. In the short term, the training improved knowledge gaps in all areas tested, like a previous study. Sustained training of physicians on Chagas disease is needed to increase awareness and improve patient access to diagnostic and treatment.

7015

UNVEILING CONGENITAL SYPHILIS THROUGH MINIMALLY INVASIVE TISSUE SAMPLING: A CASE REPORT FROM CHILD HEALTH AND MORTALITY PREVENTION SURVEILLANCE, BANGLADESH SITE

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Despite the availability of preventive strategies such as antenatal screening for syphilis in the first trimester of gestation, congenital syphilis remains a serious public health problem worldwide, particularly in developing countries. Worldwide 12 million people are infected with syphilis annually. The Child Health and Mortality Prevention Surveillance (CHAMPS) network aims to determine the causes of stillbirth and under-5 years of child death in Sub-Saharan Africa and South Asia (including Bangladesh). The expert panel of CHAMPS Bangladesh site identified a case of congenital syphilis as the underlying cause of stillbirth. Here the samples were tissues from the brain, lungs, and liver through minimally invasive tissue sampling (MITS) and blood. The mother was hospitalized at 29 weeks of gestational age with complaints of less fetal movement, lower abdominal pain and per vaginal bleeding. The mother delivered a dead female baby by normal vaginal delivery after 2 days of admission. She had four ante-natal check-ups (ANC) from government facilities and the first ANC was taken at 4 months of pregnancy. There is no document available of any test for syphilis. The baby exhibited autolysis, consistent with macerated stillbirth and some facial deformities including saddle nose and wide nasal bridge. Treponema pallidum was detected by Real-time reverse-transcription PCR in postmortem blood samples by using a custom-designed multi-pathogen syndromic TaqMan Array Card. Histopathology of the liver, lungs, and CNS tissues revealed autolysis and abundant Treponema pallidum antigens staining by using a Spirochaetaceae immunohistochemical assay. The umbilical cord also showed autolysis with rare Treponema pallidum immunohistostaining. Placenta showed acute inter-villositis and features of fetal vascular malperfusion with no Treponema pallidum immunostaining. Early diagnosis of syphilis within the first trimester and treating the parents indicate the importance of quality antenatal care. The CHAMPS diagnostic platform plays a vital role in diagnosing congenital syphilis and other neglected but common diseases.

7016

RAISING STANDARDS IN DIAGNOSTIC PARASITOLOGY - PERSPECTIVES FROM AN INTERNATIONAL EXTERNAL QUALITY ASSESSMENT SCHEME

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Diagnostic Parasitology is approaching an identity crisis. Traditionally dependent on classical light microscopy, it now faces a scarcity of expert staff with the necessary morphological skills. At the same time, molecular techniques have entered the field and machine learning is being applied to the microscopical diagnosis of malaria. Whatever technique is deployed, individual laboratories must provide a quality-assured service. Data from the UK National External Quality Assessment Schemes for Parasitology highlight common errors such as failure accurately to report malarial parasitaemias, confusion of pollen grains with Taenia ova and confusion of plant fibres with nematode larvae. The possible role of machine learning and electronic EQA schemes in raising and maintaining standards is considered in this presentation.

7017

PURIFICATION OF EXTRACELLULAR VESICLES PRODUCED BY FILARIAL PARASITES FOR PROTEOMIC DETECTION OF BIOMARKER CANDIDATES IN HUMAN PLASMA

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Lymphatic filariasis (LF) is a neglected tropical disease caused by the nematodes Wuchereria bancrofti, Brugia malayi and Brugia timori. Tests to detect circulating filarial antigen as biomarkers for adult W. bancrofti are available, but there is no antigen test for brugian filariasis or a biomarker for microfilariae (Mf). Additionally, infection with Loa loa can render false positive results as well as causing severe adverse effects, both of which complicate LF elimination programs. Extracellular vesicles released by filarial parasites may carry antigen cargo suitable as a biomarker, but reliable protocols for isolation and proteomic analysis need to be evaluated. The main objective of these studies was to identify novel biomarkers in vesicles isolated from host plasma. Using the ME kit, vesicles were isolated from one gerbil and one cat, both infected with B. malayi, and sera from humans infected with loiasis. Patients with loiasis were selected due to their high Mf densities (between 29,120 and 81,120 Mf/ml) which are not typical of other filarial species. A more in depth bioinformatics analysis was completed to remove the host proteins that were identified with LC-MS to find proteins unique to B. malayi or L. loa. Gerbil and cat plasma contained 110 and 55 B. malayi proteins, respectively. 21 L. loa proteins were identified in 10 human plasma samples; 7 of these were present in 3 or more samples and spectral counts greater than 10. A L. loa protein with BmR1 homology was detected in 10 of 10 loiasis samples and a 14-3-3 zeta protein was found in 9 of 10 samples. Two 14-3-3 B. malayi homologs were detected in the gerbil (Bm4259 and Bm10299). This finding supports the idea that results obtained with L. loa can help to identify biomarkers for other filarial species. From these experiments, it is shown that vesicles can be detected in plasma from patients with high infection of parasite. With this, new biomarker candidates for both LF and loiasis have been identified and will be explored in future work.

7018

TOWARDS IMPROVED ONCHOCERCIASIS DIAGNOSTICS: CHARACTERIZATION OF A MAJOR ANTIGEN OF ONCHOCERCA VOLVULUS IDENTIFIED FROM THE PLASMA OF INFECTED INDIVIDUALS

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Onchocerciasis is a neglected tropical disease (NTD) caused by the filarial worm Onchocerca volvulus that infects people living in tropical regions with an estimated 220 million people at risk of infection. The World Health Organization targets onchocerciasis for elimination in the NTD roadmap and aims to stop mass drug administration (MDA) and/or interrupt transmission in most endemic areas by 2030. Several countries have eliminated the disease with repeated rounds of ivermectin MDA, prompting increased confidence in the feasibility of global elimination. Improved diagnostics tools that aid surveillance are critical to achieving this objective. Using direct proteomics and mass spectrometry, we previously reported 19 O. volvulus proteins detected in human serum and/or urine as potential biomarkers. We report results from the characterization of OVOC11613, the top biomarker candidate as a serodiagnostic target. The protein is an orthologue of the kinetochore associated Ifi-1 protein of Caenorhabditis elegant and 2021 AA in length. Two fragments of OVOC11613 were expressed in pET100-D and pTrcHis-A expression systems in Escherichia coli. The protein's potential for antibody detection was evaluated using western blot with sera of infected and uninfected subjects. Purified recombinant protein was used for production of antibodies in mice and rabbits to design antigen capture assays and for immunolocalization. 60% of subjects from Uganda infected with O. volvulus had IgG4 antibodies reactive with the recombinant antigen and the specificity with sera from subjects with no travel history to endemic regions was 100%. However, there was cross-reactivity with Loa loa, Wuchereria bancrofti or Brugia malayi patient-infected sera. Immunohistological studies with sections of onchocerca nodules containing adult worms and microfilariae showed strong labeling of all worm tissues except the cuticle, supporting the essential function of the protein in all cell types. These results support the abundance of OVOC11613 and potential as a biomarker for onchocerciasis that could be valuable for surveillance and monitoring in elimination programs

7019

THE POLY-LYSINE PEPTIDE AS A BROAD-SPECTRUM ANTIPARASITIC, AND EFFECTIVE AGAINST FILARIAL AND MALARIA PARASITES

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Tremendous efforts have been made to control and eliminate neglected tropical and tropical diseases. Filarial worms cause multiple neglected tropical diseases that have a debilitating effect on the worldwide population. One of them is Onchocerca volvulus which causes river blindness. Currently, there are no effective drugs against filarial worms that cause river blindness. There is a therapy against killing larvae (microfilariae), but there is no effective drug against the adult parasite (macrofilaricides) which survive and reproduce in the host for a long time. Similarly, Plasmodium falciparum, the causative malaria parasite, is globally the primary source of parasite infection-related deaths. The current treatment of choice is artemisinin-combination therapy, but due to the development of the parasite's resistance to existing drugs, there is an increased need for new therapies. Here we show that a feature of the P. falciparum proteome - runs of poly-lysine residues found primarily in adhesion and pathogenicity-related proteins - can be used as a successful peptide treatment against multiple human parasites. Our data indicate that a single dose of poly-basic peptides can successfully reduce P.falciparum parasitemia in human erythrocytes in vitro with a favorable low or no toxicity. The treatment efficiency of 30 lysine residues, in L and D form (PKL30 and PDL30, respectively), is sufficient for the complete clearance of the parasites in erythrocytes at nanomolar concentrations. In a similar experimental set-up, we used poly-lysine peptides to treat Burghia pahangi, similar species to O. volvulus and filarial worm model for animal infection. We used Brugia pahangi as a primary screen species and animal infection model to do poly-lysine peptide drug screens against Brugia adults. Assaying motility inhibition, we show 100% inhibition of worm motility in a single day with a dose value of 317nM for both peptides PKL30 and PDL30. These values for poly-lysine peptide-based compounds show promising results against filarial worms and potential for new drugs with the lowest effective dose tested until now.

7020

ASSOCIATION BETWEEN BLOOD LOA LOA MICROFILARIAL DENSITY AND PROTEINURIA LEVELS: A POPULATION-BASED CROSS-SECTIONAL STUDY IN A RURAL AREA OF THE REPUBLIC OF CONGO

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Case-reports hypothesized that proteinuria, sometimes with glomerulopathy or nephrotic syndromes, may be associated with loiasis. No specific study has ever been conducted to assess this association. We conducted a cross-sectional study to assess the relationship between Loa loa microfilarial densities and level of proteinuria in a rural area of the Republic of Congo. For each microfilaremic individual, 2 individuals without L. loa microfilaremia were matched on age, sex and place of residence. Among the 990 participants (62·5% were male, 35·6% were L loa microfilaremic), the prevalence of traces of proteinuria (< 300 mg/24h), light proteinuria (300 - 1 g/24h) and high proteinuria (> 1 g/24h) was, respectively, 37·5%, 50·6% and 71·4% among microfilaremic individuals and 62·5%, 49·4% and 28·6% among amicrofilaremic individuals. Individuals with high proteinuria had significantly higher L loa MFDs ($p < 0{\cdot}001$): mean ± SD mf/ml were 1595 ± 4960, 2691 ± 7982, 3833 ± 9878 and 13 541 ± 20 118 among individuals with no, traces, light and high proteinuria, respectively. Individuals with 5000 - 14 999 mf/mL and individuals with ≥ 15 000 mf/mL were respectively 5·39 and 20·49 more likely to have a high proteinuria than individuals with no microfilaremia. The risk of proteinuria increases with L loa microfilaremia. Further studies are needed to identify renal disorders (tubulopathies, glomerulopathies or nephrotic syndromes) responsible for loiasis-related proteinuria.

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ASSOCIATION BETWEEN ARTERIAL STIFFNESS AND LOA LOA MICROFILAREMIA: A POPULATION BASED CROSS-SECTIONAL STUDY IN A RURAL AREA OF THE REPUBLIC OF CONGO

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Loa loa filariasis (loiasis) is considered a benign disease. However, recent epidemiological data suggest an increased mortality in L. loa infected individuals, underscoring the importance of studies on the possible morbidity associated with loiasis. Chronic inflammation due to the host response to L. loa microfilaremia and the chronic exposure of vessel walls to the microfilariae (which may involve dysregulation of the structure of the vessel walls) may result in arterial stiffness. We conducted a cross-

sectional study in May-June 202 of 991 individuals living in rural areas of the Republic of the Congo and matched for age, sex, place of residence and microfilaremia to assess if L. loa microfilariae (mf) density in the blood is associated with arterial stiffness. Arterial stiffness and peripheral arterial disease (PAD) were assessed using a point-of-care device (pOpmètre®) allowing the measurements of the pulse wave velocity (PWV), the ankle-branchial index (ABI) and the pulse pressure (PP). Among 982 and 976 individuals included in the PWV and ABI analysis, 159 (16.2%) had a PWV considered off-limit and 137 (14.0%) had an ABI considered off-limit, respectively. Factors significantly associated with off-limit PWV measurements were: male sex, younger age, high mean arterial pressure, high pulse rate, high creatininemia, and L. loa microfilaremia (especially for the densities ≥ 10 000 mf/mL of blood). Factors significantly associated with PAD presence were: older age, high pulse rate, high body mass index, smoking, and L. loa microfilaremia. Compared to subjects without mf in the blood, those with more than 10,000 mf/mL were 2.99 times more likely to have an off-limit PWV (P < .001). There appears to be a strong association between L. loa microfilaremia and arterial stiffness, which can lead to cardiovascular diseases and mortality. It is essential to carry out further studies on this subject in order to investigate this association.

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EFFICACY AND FEASIBILITY OF SHORT-STRETCH COMPRESSION GARMENTS ENABLED BY THREE-DIMENSIONAL INFRARED IMAGING FOR STAGE 3 FILARIAL LYMPHEDEMA IN SRI LANKA

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Standard of care (SOC) for filarial limb lymphedema includes a WHO-recommended hygiene regimen of daily limb washing, exercises, and elevation. Further benefits have been observed with complete decongestive therapy (CDT), which includes compression bandaging applied by trained therapists. Unfortunately, CDT is not available for most individuals in low- and middle-income countries (LMIC) due to a lack of access to durable compression garments and trained therapists. Given the recent availability of inelastic, self-adjustable, short-stretch compression garments (SSCG), employable with minimal patient training, we sought to determine whether SSCG, enabled by portable, three-dimensional, infrared imaging (3DII) in addition to SOC is effective and feasible in LMIC settings. We conducted a six-week, interventional, single group, open-label, pilot study in nine adults (five female) with Dreyer stage 3 lymphedema. A four-week lead in period of SOC hygiene was followed by a two-week intervention SSCG period. Subjects were a median age of 74 years with affected mean leg volumes of 3052 mL (SD 454). Adherence to SOC measures alone resulted in a small but significant lower limb volume reduction (mean reduction 189 mL, SD 128, p=0.02), while two weeks of SSCG resulted in a marked additional reduction (mean reduction 296 mL, SD 241, p=0.006). Only 2/9 participants achieved goal usage of SSCG for ≥23 hours/day, while 9/9 reported >21 hours/day of use. There was a non-significant reduction in WHO-Disability Assessment Schedule scores between enrollment and study end (18.7, SD=9.5 vs. 17.5, SD=8.1, p=0.30). Garment acceptability was high throughout the study and qualitative interviews demonstrated satisfaction, ease, and willingness to use SSCG during the study and thereafter. In this study, CDT using SSCG was effective in reducing lower limb volume as well as being reported as comfortable and well accepted by participants. These results provide proof of concept for 3DII-enabled SSCG in LMIC where trained therapists for filarial lymphedema may not be available.

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IDENTIFICATION OF NOVEL POTENTIAL BIOMARKERS FOR BANCROFTIAN FILARIASIS

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Wuchereria bancrofti is responsible for 90% of the world's burden of lymphatic filariasis (LF). The Global Programme to Eliminate LF relies on rapid diagnostic tests that detect a circulating filarial antigen (CFA) to monitor for active filarial infections, and to monitor progress towards elimination. Unfortunately, clearance of CFA can persist up to five years following clearance of microfilaremia, making CFA a suboptimal way of monitoring for transmission potential. Development of antigen or serologic assays for W. bancrofti that more accurately reflect active transmission is a priority for LF elimination programs. To identify novel antigen biomarkers for W. bancrofti, we used a proteogenomic approach to examine 17 plasma samples from W. bancrofti-infected individuals from Cote d'Ivoire (4 samples) Papua New Guinea (5 samples), and Sri Lanka (8 samples) and 7 non-endemic controls (from St. Louis, USA) for the presence of W. bancrofti antigens. Filarial antigens were immunoprecipitated by one or more of following methods: immune complex (IC) precipitation with polyethylene glycol, monoclonal antibody DH6.5, which recognizes an abundant glycan moiety on many filarial glycoproteins, or polyclonal antibodies against Dirofilaria immitis or Brugia malayi. For 3 of the IC samples, deep scale fractionation was performed, and the generated hits were validated by comparison with stable isotope-labeled heavy peptides run under the same conditions. Seventy-six W. bancrofti proteins were detected in one or more infected samples, including 16 proteins with minimal human homology. We selected 4 for further development based on their relative abundance of detection. To date we have generated polyclonal sera to the leading candidate, a homologue of Brugia major allergen and validated its specificity by immunohistochemistry on female and male B. malayi worm sections. Ongoing work will determine the validity of these markers in detecting active filarial infections.

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PLASMA PENTRAXIN 3 AND ANGIOPOIETINS ARE ELEVATED IN LYMPHATIC FILARIASIS LYMPHEDEMA PATIENTS WITH ESSENTIAL HYPERTENSION

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Essential hypertension is one of the comorbidity features in lymphatic filariasis lymphedema (LE). Close connections between inflammation and development of hypertension have been described. But whether inflammation induced by filarial worms impairs blood pressure (BP) homeostasis, and consequently enhance clinical severity among LE patients is not established. This study aimed to examine the distribution of plasma pentatraxin (PTX)-3, angiopoietin (Ang)-1 and angiopoietin (Ang)-2 and their relationship with blood pressure homeostasis in LE participants with essential hypertension. Two hundred and twenty-two LE patients and 56 non-LE participants were enrolled in the study. LE patients were divided into hypertensive (n=111) and normotensive (n=111) based on clinical diagnosis of hypertension. Non-LE participants were normotensive and served as controls. Blood samples were taken and levels of inflammatory and angiogenic markers were determined by standard ELISA techniques. The results showed that plasma PTX3 and Ang2 and not Ang1 are significantly increased in LE patients with essential hypertension compared to controls (p=0.002, 0.015, respectively). However, we did not observe any significant difference in PTX3, Ang1 and Ang2 between LE patient with

essential hypertension and those without essential hypertension (p>0.05). Interestingly, LE patients with hypertension had significantly higher alanine transaminase (ALT) and gamma-glutaryl transferase (GGT) levels compared to normotensive LE patients (p=0.008, 0.001, respectively). PTX-3, Ang1 and Ang2 did not show significant correlation with each other and BP homeostasis within each group of comparison. In conclusion, elevated plasma PTX3 and Ang2 are significantly associated with LE. Increased levels of ALT and GGT are characteristics of LE with hypertension.

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FIELD EVALUATION OF STANDARDTM Q FILARIASIS ANTIGEN TEST FOR LYMPHATIC FILARIASIS DURING A PRE-TRANSMISSION ASSESSMENT SURVEY IN SIERRA LEONE, 2022

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As part of a multi-country evaluation, the SD Biosensor STANDARDTM Q Filariasis Ag Test (QFAT) was compared with (the currently used test) the Abbott BiolineTM Filariasis Test Strip (FTS) for classifying lymphatic filariasis (LF) prevalence at a population level and for ease of use in field conditions in Sierra Leone. The evaluation was done in two districts, Bombali and Karene, where repeat pre-transmission assessment surveys (pre-TAS) were planned. Two sites with high LF antigen prevalence in 2020 (4.1% in the village of Kagbo and 7.7% in the village of Makorba Yelimi) were chosen. Convenience sampling was used to recruit 350 community members ≥5 years in each site. Blood was collected by fingerstick (20µl for QFAT and 75 µl for FTS). The reading time of the result for both tests was 10 minutes. For all positive or invalid results, a repeat test was performed for both tests. In total, 728 participants (5 -91 years) were tested by QFAT and FTS. The positive rate was 4.8% (17/357) and 3.5% (13/367) for FTS and 3.4% (12/357) and 4.1% (15/367) for QFAT in Kagbo and Makorba Yelimi, respectively. All participants testing positive for FTS or QFAT underwent further testing of mid-night blood smear to detect microfilariae using microscopy. None of the positive participants had circulating microfilariae. Nearly half (14/30) of those who tested positive with FTS during this survey also tested positive with FTS in re-pre-TAS in 2020. Four FTS and three QFAT samples were indeterminate (meaning a positive result followed by a negative result). In field conditions, QFAT was easy to handle and recorded zero invalid tests compared to FTS (six invalids). Using the FTS results as a reference standard, the sensitivity and specificity of the QFAT was 78.6% and 99.4% respectively. The concordance between FTS and QFAT was 0.81 (Cohen's Kappa). The discrepancy found between the two tests in terms of positive tests was not statistically significant (P value=0.78). The results suggest that the QFAT is a credible LF diagnostic test when compared to the routinely used FTS; use of either test would result in the same program decision. Page | 1

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EFFECT OF SEASONALITY AND HYGIENE ON THE INCIDENCE OF ACUTE FILARIAL ATTACKS IN PATIENTS WITH LYMPHEDEMA IN MALI

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Lymphatic Filariasis can cause disfiguring swelling of the limbs (lymphedema or elephantiasis for advanced stages) and/or damage to other organ systems including the genital-urinary system (e.g., hydrocele or vulvar disease). Current research has indicated that filarial lymphedema patients not only face severe social stigma and prejudice but also frequently undergo acute filarial attacks marked by limb swelling, fever, skin blistering and excoriation. Furthermore, there is little empirical data on the extent to which seasonal variations affect filarial attacks in lymphedema patients. To this end, we used data from a double blinded placebo-controlled study on the utility of doxycycline/placebo to improve lymphedema in Wuchereria bancrofti infection (in Mali) to investigate the incidence and effect of seasonal variation (rainy/wet and dry seasons) on acute filarial attacks. Using data from the 200 patients (87% female) all of whom received limb hygiene (with lymphedema followed for 24 months) We found that study participants experienced filarial attacks equally frequently during both the dry and wet seasons. In contrast, the incidence of filarial attacks differed depending on the season (11.11 per person-month in the dry season) compared to 54.67 per person-month in the wet season) The difference in attack means between rainy/wet and dry seasons was statistically significant (P=0.0068). Doxycycline administration was not associated with alterations in the frequency of acute attacks (no statistical difference between doxycycline/placebo). Over the 24-month course of the study, there was a statistically significant decrease in the frequency of acute attacks for each arm of the study (chi-square trend for the doxycycline group was 7.20; p=0.007) and 17.76 p<0.0001 for placebo group), but the 2 groups did not differ from each other. Our data suggest that the frequency and the incidence of filarial attacks is significantly increased during the rainy season compared to the dry season and that hygiene (rather than doxycycline) was the major driver of progressive decrease in the frequency of filarial attacks over the 24 months of the study.

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THE CLINICAL SPECTRUM OF LYMPHATIC FILARIASIS. A CASE OF PROTEIN-LOSING ENTEROPATHY

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Populations from endemic areas of Lymphatic Filariasis (LF) usually remain asymptomatic or develop chronic manifestations, while the acute form typically occurs in travelers to filariasis-endemic regions. Therefore, cases of imported chronic filariasis are rare. Our goals were to illustrate the complexity of the diagnosis of a chronic form of LF in a patient with a remote history of travel to an endemic area; and to know some significant clinical manifestations.The patient, 76-year-old, of the Garcia Orcoyen Hospital (Spain, Europe) was a retired military man. His personal history included arterial hypertension, former smoker, atrial fibrillation anticoagulated with edoxaban, and duodenal lymphangiectasias described in several upper gastrointestinal endoscopies performed in 2019 and 2020 for study of iron deficiency anemia. He was admitted to the Internal Medicine unit for study,

with edema in the lower limbs and at the scrotal level of approximately 6 months of evolution, together with dyspnea on moderate exertion. The patient also exhibited lymphopenia with a normal CD4/CD8 ratio, serositis, and hypoproteinemia, all compatible with protein-losing enteropathy (PLE). This was confirmed by performing a scintigraphy with labeled albumin. Considering PLE as the main cause of the patient's clinical picture, a broad differential diagnosis was carried out. Celiac disease, Whipple's disease, solid tumors, hematology or paraneoplastic syndrome were ruled out. Since the patient spent part of his youth, as a military man, in the Sahara area, a study of imported diseases such as LF was performed, obtaining a positive serology (IgG and IgG4) for Wuchereria bancrofti, with absence of microfilariae in the examination of the peripheral blood smear. After ruling out the presence of other filariae (Loa loa and Onchocerca volvulus) before starting specific treatment, due to the high risk of microfilaricidal activity, Albendazole 400mg/12h/21 days and Doxycycline 100mg/12h/6 weeks were administered.

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SHIFT IN THE SKIN MICROBIOME AMONG INDIVIDUALS PRESENTING WITH FILARIAL LYMPHEDEMA COMPARED TO NON-FILARIAL HEALTHY INDIVIDUALS IN GHANA

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Lymphatic filariasis (LF) is a debilitating neglected tropical disease that remains a major public health challenge in endemic countries. In addition to providing mass drug administration (ivermectin, albendazole, and diethylcarbamazine) to reduce parasite burden, there is also a need to mitigate the challenges associated with lymphedema progression. Filarial lymphedema is known to be complicated by secondary bacterial infections; however, this has yet to receive considerable attention in LF-endemic communities in rural Ghana. Thus, the focus of this study was to understand the skin microbiome of individuals presenting with filarial lymphedema over time. This longitudinal study employs culture and Matrix-Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) to characterize the microbiota of filarial lymphedema lesions over 24 months of follow-up and how it differs non-filarial individuals outlined in literature. The results reveal four marked phyla with varying distributions in the filarial lymphedema lesions relative to healthy skin: Firmicutes (69.7%), Proteobacteria (16.6%), Actinobacteria (13.3%), and Bacteroidetes (0.3%). Propionibacterium and Corynebacterium, which are usually resident and abundant in healthy skin, are underrepresented in the skin from lymphedema lesions. Most of the taxa found in the skin from lymphedema lesions are not the typical organisms found on human skin; instead, they are potentially pathogenic, with the Streptococcus, Acinetobacter, Klebsiella, Pseudomonas, Bacillus, Corynebacterium, Micrococcus, Enterococcus, Proteus, and Staphylococcus genera being the most common isolates. Our data reveals a significant shift in the bacterial population with the introduction of potentially pathogenic bacteria that compete with the healthy skin resident microbiota during LF infection.

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DETECTION AND DISCRIMINATION OF ONCHOCERCA VOLVULUS AND O. OCHENGI FROM BLACKFLY POOL DNA USING A NOVEL POLYMERASE CHAIN REACTION - RESTRICTION FRAGMENT LENGTH POLYMORPHISM (PCR-RFLP) TECHNIQUE

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The WHO has approved the O150 PCR-ELISA in blackflies, a molecular xenomonitoring technique, as part of the Onchocerciasis Elimination guideline. However, the high cost, non-availability, and delay of the ELISA component make its application difficult in resource-limited settings. Therefore, this study focused on developing a PCR-RFLP assay to detect and discriminate O. volvulus and O. ochengi in blackflies. The speciation assay was designed based on the genetic difference between the COX1 mitochondrial gene of O. volvulus and O. ochengi, which identified HaeIII as a unique restriction enzyme for O. volvulus only. The assay validation was performed with archived blackflies (S. damnosum sensu lato) collected in 2011 from Agbelekeme, an endemic onchocerciasis community. Triplicates of 50 and 100 Blackfly pools were performed separately for heads and bodies. Blackfly pool DNA was extracted, and the Onchocerca-DNA was captured with the Onchocerca-COX1 probe and magnetic beads. The PCR-RFLP assay was applied to the Onchocerca-captured samples, after which the PCR products were sequenced and analyzed. Of the three 50 blackfly head pools, only 1 (1/3) carried infective O. ochengi L3. All three 100 blackfly head pools (3/3) carried infective O. volvulus L3. However, two of the three 100 blackfly body pools (2/3) were infected with O. ochengi. Only one of the two infected 50 blackfly body pools carried both O. volvulus and O. ochengi. After the DNA sequence analysis, the enzyme-restricted samples showed high homology with O. volvulus, whereas the unrestricted ones were highly homologous to O. ochengi. The novel PCR-RFLP assay has demonstrated its effectiveness in detecting and discriminating between O. volvulus and O. ochengi in blackflies. With zoonotic onchocerciasis in sight in some parts of the world, this tool will be useful for the early detection of potential zoonotic transmission of the bovine onchocerciasis in the human population.

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ANTIBIOTIC RESISTANCE AND MECA CHARACTERIZATION OF STAPHYLOCOCCUS HOMINIS FROM FILARIAL LYMPHEDEMA PATIENTS IN THE AHANTA WEST DISTRICT, GHANA: A CROSS-SECTIONAL STUDY

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Filarial infections affect over 150 million people in the tropics. One of the major forms of filarial pathologies is lymphedema; a condition where the immune response is significantly altered, resulting in changes in the normal flora. Staphylococcus hominis, a human skin commensal, can also be pathogenic in immunocompromised individuals. Therefore, there is the possibility that S. hominis could assume a different behavior in filarial lymphedema patients. To this end, we investigated the levels of antibiotic resistance and extent of mecA gene carriage in S. hominis among individuals presenting with filarial lymphedema in rural Ghana. We recruited 160 individuals with stages I-VII lymphedema, in a cross-sectional study in the Ahanta West District of the Western Region of Ghana. Swabs from lymphedematous limb ulcers, pus, and cutaneous surfaces were cultured using standard culture-based techniques. The culture isolates were subjected to Matrix-Assisted Laser Desorption/Ionization Time of Flight (MALDI-TOF) mass spectrometry for bacterial identification. Antimicrobial susceptibility testing (AST) was performed using the Kirby-Bauer method. mecA genes were targeted by PCR for strains that were cefoxitin resistant. In all, 112 S. hominis were isolated. The AST results showed resistance to chloramphenicol (87.5%), tetracycline (83.3%), penicillin (79.2%), and trimethoprim/sulphamethoxazole (45.8%). Of the 112 strains of S. hominis, 51 (45.5%) were resistant to cefoxitin, and 37 (72.5%) of the cefoxitin-resistant S. hominis haboured the mecA gene. This study indicates a heightened level of methicillin-resistant S. hominis isolated among filarial lymphedema patients. As a result, opportunistic infections of S. hominis among the already burdened filarial lymphedema patients in rural Ghana may have reduced treatment success with antibiotics.

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GUIDELINES FOR SELECTION OF FIRST- AND THIRD-LINE COMMUNITIES FOR MONITORING AND EVALUATION DURING ONCHOCERCIASIS ELIMINATION MAPPING

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Since the era of OCP and APOC, control of onchocerciasis was achieved by treating individuals in 1st line (communities 5km from breeding sites - high-risk), and 2nd line (communities 10km away - medium-risk) excluding 3rd line (communities >=15km away - low-risk) to reduce microfilariae load and prevent blindness via infective blackfly bites. Currently, there is a paradigm shift from control to elimination with focus on onchocerciasis elimination mapping based on evaluating infections levels in the 1st line, 2nd line, and 3rd line communities. There are no structured protocols for accurately selecting these communities since a 3rd line community to a given breeding site may be a 1st line community to another breeding site. The purpose of this study is to develop guidelines for monitoring and evaluation of selected communities using blackfly breeding sites prospection and mapping. This study was piloted using the proposed guidelines in selecting six communities (three each from 1st and 3rd line). This involved initial mapping of proposed study area and prospecting for blackfly larvae. Three positive larval breeding sites about 15km apart were selected and blackfly collection points were set up. Maps were updated with data on breeding sites. This was followed with selecting three 1st and three 3rd line corresponding communities based on positive larval breeding sites such that no natural barrier existed between breeding sites and communities. Three concentric circles of radius 5km, 10km, and 15km from each selected breeding sites was drawn to show communities found within the transmission focus. Blackfly densities at 3rd line communities was significantly lower than in 1st line communities ($p < 0.01$) with no difference in forest and savannah blackfly species ($p = 0.42$). The results indicate that the guidelines used in selecting the 1st and 3rd line communities were appropriate and hence flies captured from the 3rd line communities migrated from the breeding sites within the first line communities. These guidelines tested will be useful in the current onchocerciasis elimination mapping in selecting communities for monitoring and evaluation.

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DEVELOPING A TRAP FOR AFRICAN CHRYSOPS SPECIES TO ACCELERATE ONCHOCERCIASIS ELIMINATION: PROOF OF CONCEPT IN CAMEROON

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Elimination of onchocerciasis is a challenge in areas co-endemic with loiasis as ivermectin causes severe adverse events in loiasis-infected individuals. With no safe treatment, developing and deploying a successful trap for loiasis vectors - Chrysops, represents a potential solution to address this challenge. We leveraged on the horizontal polarotactic characteristic of Chrysops to develop a trap for African Chrysops species. Shiny solid surfaces of various colours (black, brown and bordeaux), shapes (circle, triangle and square) and sizes (small, medium, and large) were used to create horizontally polarised light to attract Chrysops. These surfaces were placed at different heights from the ground (0m, 0.5m and 1m) and coated with glue to immobilise any flies that landed them. Three villages were selected in two Health Districts (HD) in South Region, Cameroon where three collection sites were identified based on community knowledge and fly abundance. Traps were deployed using a Latin square developed to capture various combinations. Data was collected from September-December 2022. Flies captured were counted, and only Chysops were morphologically identified and dissected. Descriptive statistics were presented both overall and by community, and Multivariable model to compare trap features.Overall, 693 (12.1%) Chrysops (C. dimidiata and C. silacea) were collected - 53.8% and 46.2% from Sangmelima and Djoum HD, respectively. Most flies were collected in December (524; 75.6%) corresponding to dry season, and from Djoum (320 out of 524). Peak capture was observed from 8am-10am. Multivariable model results showed lower catch-rates for brown than black traps (RR=0.70, 95%CI=[0.53, 0.91]) and for medium compared to large (0.70 [0.54, 0.91]). Differences across shape and height were not statistically significant (p=0.07 and p=0.11). While these results are not statistically supported for decision making in validation of this trap, the study provides preliminary data for trap features for various Chrysops species. Future research could investigate chemical attractants to increase Chrysops collection to optimise trap development.

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COMPARISON OF SPONTANEOUS VS IVERMECTIN-INDUCED CROSS-REACTIVE ANTIGENEMIA IN LOIASIS

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Circulating Loa loa antigens that cross-react with lymphatic filariasis (LF) rapid diagnostic tests (RDT) are often detected in individuals with high L. loa microfilariae (Mf) density, which poses a major challenge to LF mapping/elimination in co-endemic areas. To test the hypothesis that L. loa cross-reactive antigens (LCRAgs) are released by dying Mf, we enrolled two cohorts of loiasis infected individuals. Cohort 1 (spontaneous antigenemia group) included 86 heavily infected patients (median Mf count: 34,450 Mf/mL; IQR 22,860-54,720), 73 of whom had CRLAgs at enrollment. Cohort 1 participants were monitored quarterly for changes in CRLAgs over 15 months. Cohort 2 (induced antigenemia group) included 39 moderately infected loiasis patients (median Mf count: 8,600 Mf/mL; IQR 5,500-11,980) who were negative for CRLAgs at enrollment, treated with a single dose of ivermectin (150 µg/kg), and monitored over 7 days for release of CRLAgs. In cohort 1, there was no significant change in Mf counts over time (Chi-square=3.261; df=4; p-value=0.52152) and 17% experienced a status conversion (i.e. from positive to negative or vice versa). In cohort 2, Mf counts decreased ~75% by day 3 post-treatment in all participants, and 11 participants (28.2%) developed post-treatment CRLAgs detectable by RDT. Mass spectrometry (MS) detected many peptides belonging to the NAS-14 metallopeptidase family in all 50 tested samples in cohort 1, including the 13 samples where CRLAgs were not detected by RDT. However, MS detected NAS-14-derived peptides in only 7 (64%) of the 11 CRLAg positive samples. In cohort 2, the presence of post-treatment antigenemia was not significantly associated with baseline Mf count or Mf reduction (OR=1.0413; 95%CI:0.9805-1.10590; p-value=0.1873). Thus, although CRLAgs can be induced by ivermectin treatment, the antigen profiles of induced and spontaneous antigenemia are not identical, suggesting additional mechanisms contribute to the release of CRLAgs in heavily infected individuals.

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EFFORT TOWARDS ELIMINATION OF LYMPHATIC FILARIASIS IN CAMEROON: RESULTS OF THE LAST TRANSMISSION ASSESSMENT SURVEY IN TWENTY HEALTH DISTRICTS OF ADAMAOUA, CENTER AND FAR-NORTH REGION

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Cameroon is endemic for lymphatic filariasis (LF) in 144 of 200 health districts (HDs) in the country. The goal of Cameroon is to eliminate LF as a public health problem by 2026. Mass drug administration (MDA) using ivermectin and albendazole were implemented between 2008 and 2017 in all endemic HDs. The first transmission assessment survey (TAS-1) was conducted between 2014 and 2019 in 143 HDs and in 2021 in Akwaya HD, and as all HDs passed, MDA was stopped in all 144 endemic HDs. To date, 143 out of 144 districts have successfully passed TAS2, except Akwaya (due in 2023). Twenty HDs from Adamaoua, Far North and Central regions underwent TAS3 in 2022, in compliance with WHO guidelines. These HDs were grouped into 8 evaluation units (EUs) according to their epidemiological profiles and geographical locations. The Survey Sample Builder (SSB) was used to calculate the sample size and select the clusters. According to school enrolment rate, the survey was conducted in communities for the Adamaoua and Far North regions and in schools for the Centre region. The Filariasis Test Strip (FTS) was used to detect LF antigen and electronic data collection was used for this survey. Children testing positive were all confirmed by a second FTS test. Out of the 13,168 children in 249 clusters tested, 7 children tested positive by FTS. The number of positive children in each EU ranged from 0 to 4 and was below the critical cut-off value of 18-20 per EU. The results of the TAS3 confirmed the sustained interruption of LF transmission in these 20 HDs x to y years after stopping MDA, bringing the number of districts that have passed the second surveillance survey (TAS3) to 59 in Cameroon. The national program will establish a post validation surveillance system in HDs that have completed TAS3. Cameroon is well placed to submit the elimination dossier for validation by WHO in 2026.

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IMPLEMENTING THE LYMPHATIC FILARIASIS REPEAT PRE-TRANSMISSION SURVEY IN A CONTEXT OF INSECURITY IN TWO HEALTH DISTRICTS IN BURKINA FASO

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Lymphatic Filariasis (LF) was endemic in all 70 health districts (HDs) of Burkina Faso. Since 2019, LF transmission assessment surveys (TAS) have been postponed in some areas of the country due to insecurity. In December 2022, the National Neglected Tropical Disease Program (NTDP) conducted a repeat pre-transmission assessment survey (re-pre-TAS) in two insecure HDs: Fada N'gourma and Tenkodogo. These were the fifth pre-TAS in Fada and fourth pre-TAS in Tenkodogo; both most recently failed re-pre-TAS in 2020. The objectives were to assess the prevalence of LF and to test the feasibility of a new approach to implement surveys in a context of insecurity. The new strategy used local health center staff who were trained at the district level on survey methodology, use of filariasis test strips (FTS) and electronic data collection via ESPEN Collect. Mitigation measures were taken to ensure the security of interviewers and respondents. The study was conducted in 7 and 6 sentinel and spot check sites in Fada and Tenkodogo, respectively, from December 2022, to January 2023. Age, sex, treatment status, and blood samples for FTS and microfilaremia (mf) tests were collected from individuals ≥5 years. The NTDP conducted daily remote supervision to ensure quality data collection. Night blood samples from FTS-positive individuals were sent to the district laboratory for mf testing. Of the 4,403 people tested, over 92% reported having swallowed ivermectin and albendazole at least once. Former positives from the 2020 survey who were still FTS positive in 2022 and for whom treatment had been provided were excluded from the sample and current analysis. The filarial antigen prevalence was below 2% in 10 sites and between 2% and 4% in three sites. The program sought and obtained WHO advice to continue to TAS1 because most positives (49%) were over 15 years old and mf was negative in all positives in both HDs. The use of local health workers allowed for the successful completion of the re-pre-TAS surveys. Lessons learned will be used to develop similar approaches for conducting surveys in other insecure areas and the mf negative but FTS positive cases will be further investigated.

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EFFORTS TOWARD ELIMINATION OF LYMPHATIC FILARIASIS IN GUINEA: RESULTS OF TRANSMISSION ASSESSMENT SURVEYS IN ELEVEN HEALTH DISTRICTS

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Lymphatic filariasis (LF) is a major neglected tropical disease in Guinea. Mapping carried out from 2005 to 2013 identified 24 endemic health districts (HD) out of 36 requiring annual mass drug administration (MDA). MDA for LF started in 2014. By 2021, 11 HDs (Beyla, Boke, Dalaba, Dinguiraye, Forécariah, Guéckédou, Kérouané, Kindia, Mali, Mandiana and Telimélé) with baseline prevalence between 1.5% -14.4% completed five rounds of MDA with epidemiological coverage > 65%. These HDs conducted pre-transmission assessment survey in 2021-2022. The results showed prevalence below the 2% threshold in all sentinel and control sites, making all 11 HDs eligible to conduct the first transmission assessment survey (TAS1) in 2022. For TAS1, a cross-sectional survey, was conducted in 11 HDs corresponding to 11 evaluation units (EU). The survey sample builder was used to determine the sample size and to select clusters. In 11 EUs, the sample size per EU ranged from 1,500 to 1,695. A school-based survey strategy was used in four EUs (Boké, Dalaba, Guéckédou and Kindia) while a community-based strategy was used in seven EUs (Beyla, Dinguiraye, Forécariah, Kérouané, Mali, Mandiana and Telimélé) due to low school enrollment (<75%). Among the 343 clusters surveyed, the school-based survey strategy was used in 133 clusters in four EUs to test 6,709 children in first and second grade. A total of 17,719 children were tested in 343 clusters with 43% (7,554/17,719) of girls and 57% (10,162/17,719) of boys. Seven EUs recorded between 1 - 9 FTS positives, all well below the critical cut-off value for each EU. Four EUs did not record any positive FTS cases. All the EUs met the minimum sample size. These results indicate that after five rounds of annual LF MDA with sufficient epidemiological coverage, these 11 HDs have successfully reached the criteria to stop MDA and 4,031,909 people in Guinea are no longer in need of MDA. The 11 HDs

are now in the post-treatment surveillance phase, the national program will conduct the second transmission assessment survey (TAS2) in two years' time.

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EXAMINATION OF METABOLITE BIOMARKERS OF LOIASIS REVEALS PROMISING CANDIDATES PREDICTIVE OF MICROFILAREMIA

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Microfilaria (Mf) load is an essential indicator of the severity and transmissibility of filarial infections. Real-time Loa loa Mf load prediction using the LoaScope enables exclusion of those with high Mf counts from ivermectin treatment during mass drug administration permitting re-implementation of MDA for onchocerciasis and LF in loiasis-coendemic areas. However, the LoaScope is not commercially available, and alternative methods to quantify Mf load may lead to more efficient estimation. Rapid assays of Mf loads would also aid LF elimination by providing a direct measure of transmissibility, as opposed to current antigen detection tests that remain positive for months to years after clearance of microfilaremia. We sought to identify blood metabolite biomarkers predictive of microfilaremia using loiasis, which achieves very high Mf loads, as a model. For discovery, we used banked plasma samples from 62 microfilaremic and 40 amicrofilaremic individuals from an endemic area, as well as 15 non-endemic controls. Samples were analyzed by liquid chromatography-mass spectrometry using a Thermo ID-X high-resolution accurate mass instrument. Using a compositional data approach (DiCoVar) based on pairwise metabolite ratios, we identified multiple features correlated with microfilaremia. Targeted measurement of these features by LC-MS/MS identified two which were individually significantly associated with Mf-positivity: a mass of 363 Da ($p<2.22e-16$), and a mass of 179 Da ($p=3.2e-13$). Each of these features exhibited a significant linear association with L. loa Mf load. The 179 Da feature was confirmed to be N-acetyl-tyramine by comparison with a reference standard. The 363 Da feature (predicted formula C13H21N3O9 has not yet been determined. Model optimization and validation against an independent set of patient samples is ongoing. Further work will determine whether these molecules can be developed as viable quantitative biomarkers for microfilarial load.

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EXAMINING THE OVERLAP IN LYMPHATIC FILARIASIS PREVALENCE AND MALARIA INSECTICIDE-TREATED NET ACCESS AND USE IN AFRICA

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Eradication and elimination strategies for lymphatic filariasis (LF) primarily rely on multiple rounds of annual mass drug administration (MDA), but also may benefit from vector control interventions conducted by malaria vector control programs. We aim to examine the overlap in LF prevalence and malaria vector control to identify potential gaps in program coverage. We used previously published geospatial estimates of LF prevalence as well as publicly available insecticide-treated net (ITN) access and use estimates among the total population, and malaria Plasmodium falciparum parasite rates (PfPR) from the Malaria Atlas Project (MAP). We overlaid the LF prevalence estimates with ITN estimates and malaria PfPR at the 5km2 level for 38 LF and malaria-endemic locations in Africa. In this analysis, almost half of the locations (47.1%; 82/174 of IUs) with the highest LF prevalence (>5%) had at least 50% coverage with ITN access and use. Among high prevalence LF areas low ITN use largely corresponded to areas with low access, with 84.8% (78/92) of these IUs having both access and use estimates under 50%. Additionally, when classified using malaria PfPR, some (27.2%; 25/92) of these low ITN coverage, high LF prevalence locations were also considered high burden for malaria. Among areas with lower LF prevalence (<5%), the majority (44.6%; 2313/5182) had low ITN access, while only 1.78% (92/5182) had low use, and 1.51% (78/5182) had both low access and use. These results illustrate the degree that malaria control programs have achieved access to and use of ITNs in LF-endemic areas. As LF can be transmitted by multiple vector species, the impact of ITNs on LF prevalence may vary depending on the predominant vector species and vector biting patterns. Furthermore, location differences in MDA coverage, ITN implementation, and other factors will also affect ITN impact. Spatial analyses like these can be combined with other context-specific knowledge to help inform future elimination and control strategies.

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LYMPHATIC FILARIASIS TREATMENT STUDIES: THE CASE FOR AN INDIVIDUAL PARTICIPANT-LEVEL DATA PLATFORM

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Lymphatic filariasis (LF) causes a huge public health burden through chronic disability. Several treatment regimens have been trialled and implemented in mass drug administration, most recently the combination therapy utilising ivermectin, diethylcarbamazine (DEC), and albendazole. We conducted a systematic review to identify the level of evidence supporting current treatment recommendation and assess the possibility of building a global data repository of LF trials aiming at conducting individual patient data meta-analyses to improve therapeutic and preventive approaches. We undertook a feasibility assessment by scoping published literature in 12 databases by designing a search strategy to retrieve all prospective studies assessing LF treatment and morbidity management and disability prevention (MMDP) with a follow-up. Inclusion and exclusion criteria identified studies where individual participants were tested or diagnosed, treated, and tested post-intervention or had safety data collected. We found 134 eligible studies from 22 countries published between 2000 and 2021, with approx. 30,000 participants for whom data on safety and/or outcome of treatment was collected. Eight drugs or combinations were the most frequently administered, including DEC, albendazole, ivermectin, as well as doxycycline in various combinations. For efficacy calculations, we estimate ~8000 IPD have been generated where microfilarial levels were measured at baseline and after treatment, commonly after six months to two years, with some follow-ups to ten years. 29 studies of MMDP interventions, with an estimated ~6000 participants, were retrieved. The lymphatic filariasis treatment trial landscape is heterogeneous, but building a global IPD repository suitable and available for pooled analysis is feasible. Such a global IPD platform would allow answering previously unresolved questions such as factors leading to heterogeneity in treatment outcomes across geographies and underrepresented groups.

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MOVING TOWARD PERSON CENTERED CARE FOR NTDS INTEGRATION OF MENTAL HEALTH WITHIN CASE MANAGEMENT NTDS IN LIBERIA

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Progress toward eliminating NTDs continues, but many persons will experience lifelong impacts including stigma, and mental health consequences. Health system gaps, and a historic focus on disease control have meant affected persons often lack access to effective services resulting in physical and psycho-social consequences, complex treatment journeys, and catastrophic socio-economic impacts. Yet effective care for people with NTDs is critical in reaching elimination targets. Integrated health system approaches to managing skin NTDs are a key solution to addressing equity and effectiveness challenges. Liberia is one of the first countries globally to develop a national integrated approach to managing skin NTDs, but evidence on optimal approaches for quality service delivery integrating mental health at scale is limited. To address this, we use person-centered approaches to co-develop and adapt health systems interventions, integrating mental health, for the management of people affected by skin NTDs in Liberia. We worked with Ministry of Health officials, health workers, informal health providers, and affected persons drawing on a diverse range of participatory research methodologies to identify strategies to detect, refer, treat and support people living with skin NTDs. We developed and are piloting a comprehensive intervention manual to support the integrated management of skin NTDs, including mental health. We found that mid-level health workers appreciated training approaches and that new knowledge facilitated better patient care, including improved understanding of causes of NTDs, combatting myths and stigma. They commit to implement new knowledge and have plans to raise awareness about NTDs and to counsel patients based on new skills gained. After training, persons affected have increased awareness of the physical cause for their condition and expressed plans to seek care from facility, instead of informal providers. They described new knowledge of how to care for themselves, feeling braver and proud to join their friends again. Integrating mental health and NTDs requires a collaborative cross-sectoral approach.

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THE IMPACT OF INDEPENDENT MONITORING (COVERAGE SURVEY) AGAINST THE 2019 MASS DRUG ADMINISTRATION DATA: THE USE OF IVERMECTIN AND ALBENDAZOLE IN LIBERIA

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Liberia is endemic for Lymphatic Filariasis in 13 of the 15 counties. The country began implementing the annual Lymphatic Filariasis mass drug administration since 2012 with Ivermectin and Albendazole but had to suspend the program in 2014/15 due to the Ebola Virus outbreak. In October -November of 2018, the Neglected Tropical Diseases program in Liberia implemented Mass Drugs administration (MDA) in all endemic counties. To verify the 2018 mass drugs administration data, a coverage survey was conducted in nine counties (Bong, Grand Bassa, Grand Cape Mount, Grand Kru, Lofa, Margibi, Maryland, Montserrado, and Nimba) to verify the reported coverage of Ivermectin and Albendazole from the target population using a community Lot Quality Assurance Sample (LQAS) methodology. This allows the program to determine if a county (supervision area) has achieved the goal of 80% coverage. There were fourteen (14) supervision areas with two hundred and sixty- six (266) samples interviewed. The survey targeted all population older than 5 years during the campaign who lived in the selected counties. Communities were selected using proportional probability of size using the 2018 mass drug administration dataset as a reference. From the 14 supervision areas, 4 supervision areas had unacceptable coverage according to LQAS analysis (93% certain they are below 80%). The analysis further indicated the following: Bong with a coverage of 79%, Grand Bassa 57%, Grand Cape Mount 80%, Grand Kru 78%, Lofa 80 %, Margibi 83%, Maryland 80%, Montserrado 35% and Nimba 82% for 2019. Coverage for Ivermectin and Albendazole has met the target for the 9-counties area surveyed (weighted coverage 81%). The results from 2018 coverage shows Grand Bassa with a coverage of 54%, Lofa 75% and Maryland 42%. This result shows Grand Bassa failed both rounds of coverage scoring below 65% followed by Montserrado and the program should investigate sentinel sites techniques and also considered changing strategies towards MDA in those counties.

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INTEGRATED SEROLOGICAL SURVEILLANCE FOR MULTIPLE INFECTIOUS DISEASES IN VANUATU

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Vanuatu's population is at risk of infection with neglected tropical diseases (NTDs), vaccine-preventable diseases (VPDs) and other infectious diseases due to low vaccine coverage, climate change, remote locations, and poor access to water and sanitation. Serological surveys that measure the prevalence of antibodies (seroprevalence) are a strategy for monitoring current or past exposure to infectious pathogens. Integrated sero-surveillance using novel multi-bead assays that can detect ~100 different disease-specific antibodies from a single dried blood spot (DBS) has the potential to establish nationally representative programs. We conducted an integrated serological survey to assess the seroprevalence of antibodies against multiple NTDs, VPDs and other infectious diseases. Between 2021 and 2023, we conducted cross-sectional serosurveys in 92 villages in Tafea, Sanma, and Shefa provinces, Vanuatu. After seeking informed consent, approximately 2000 participants aged >1 year of age provided a finger prick blood sample to prepare a DBS that was analysed using the Luminex technology. At the time of writing, we are finalising the collection and analysis of samples. We will estimate the prevalence of antibodies against the following diseases/agents: NTDs (including trachoma, yaws, lymphatic filariasis, strongyloidiasis and dengue), VPDs (measles, rubella, diphtheria, pertussis, tetanus, mumps and varicella-zoster virus), additional arbovirus (zika and chikungunya), as well as malaria, COVID-19, cryptosporidiosis, giardiasis, amoebiasis, taeniasis and cysticercosis. Our results will provide a measure of effective population-level immunity or exposure to multiple infectious diseases, with the added advantage of being cost-effective, scalable, acceptable, and able to target hard-to-reach and high-risk populations. These data can complement other surveillance mechanisms, including case-based reporting and vaccine coverage estimates obtained from electronic or paper-based records and household surveys for VPDs and parasitological surveys for NTDs and other infectious diseases

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LESSONS LEARNED FROM DEPLOYING ELECTRONIC DATA COLLECTION AS PART OF MASS DRUG ADMINISTRATION CAMPAIGNS IN SOUTH SUDAN

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Public health programs require the collection and analysis of data from remote locations. In many countries, programs continue to conduct a large percentage of their programmatic data collection using paper. This is especially true among neglected tropical disease (NTD) programs given the remote nature of the work. Increasingly NTD programs are exploring the use of electronic data collection. The Enhancing the 'A' in SAFE (ETAS) study, a randomized control trial (NCT05634759), was designed to understand the cost, feasibility, and acceptability of enhanced mass drug administration (MDA) interventions for trachoma. As part of this trial, 2 different electronic data collection systems were incorporated into MDA activities between

April and November 2022 in Eastern Equatoria State, South Sudan. The interventions for this trial included 2 enhanced MDA strategies in South Sudan: 1) community-wide MDA followed by 2 additional rounds of MDA targeted to children ages 6 months to 9 years in quick succession; and 2) biannual community-wide MDA. As part of the research, software that was designed for longitudinal analysis and the ability to track multiple treatments across the same population was primarily used for a baseline census and tracking multiple MDA treatments in study villages. A second software was used for the purposes of conducting MDA community awareness surveys and as part of an MDA treatment validation activity. Some of the advantages of using electronic data collection included: a clearer denominator, tailored lists of individuals that had been missed during the MDA and needed to be targeted as part of mop-up, and the ability to determine an accurate MDA coverage rate. Disadvantages included the additional time taken within the villages to locate individual names before treatment, keeping phones charged in areas without electricity, and keeping data synced across teams. Experience from using these 2 platforms showed that there were both advantages and disadvantages that should be considered by NTD programs working in resource-poor and remote locations.

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COMMUNITY ENGAGEMENT TO ACCELERATE ONCHOCERCIASIS ELIMINATION IN CAMEROUN

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Onchocerciasis is a vector-borne parasitic disease that is endemic in Cameroon, affecting all ten regions of the country. An estimated 60% of the population is at risk of the infection, and around six million people are currently infected. The Community-Directed Treatment with Ivermectin (CDTI) strategy, which promotes the empowerment of communities by involving them in mass drug administration (MDA) organization and delivery was implemented in Cameroon in 1998 by the Ministry of Public Health. After more than two decades of uninterrupted annual delivery of ivermectin, the prevalence of microfilaria has significantly declined in most of the foci throughout the country, while the infection was found to persist in some hotpots foci, thus hindering the progress towards elimination. The persistence of the infection may be due to inadequate therapeutic coverage and low participation. To address these challenges, it is essential to identify barriers to the implementation of CDTI activities at the community level. We therefore aim to investigate community views and perspectives towards MDA with ivermectin. To this end, a cross-sectional mixed study was conducted in 32 communities in four regions of Cameroon, selected based on their treatment coverage levels. All individuals, aged 21 years and above, and living in the targeted communities were eligible to this study. Enrollees were interviewed about onchocerciasis and CDTI using a structured questionnaire and focus group discussions. A total of 140 individuals were interviewed, and 32 focus group discussions were conducted. Overall, population interviewed was exhibited higher level of knowledge in areas with the highest treatment coverage 50%. Regarding CDTI, the consumption of alcohol after ivermectin intake was reported in all the regions, and was reported as a potential reason of non-participation to MDA. These findings bring additional insights and open new avenues to increase awareness about onchocerciasis and better engage communities to improve participation acceptance and adherence to CDTI.

7045

NTD AMBASSADORIAL ENGAGEMENTS: STRATEGY FOR HIGH-LEVEL DECISION MAKING AND ADVOCACY TOWARDS RESOURCE MOBILIZATION FOR THE CONTROL AND ELIMINATION OF NTDS IN GHANA

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Achieving the elimination targets set in the WHO 2030 Road map for neglected tropical diseases (NTDs) requires embedding multisectoral collaboration as a strategic priority to identify synergies for mainstreaming NTDs. Leveraging the health and socioeconomic impacts of NTDs to build strong partnerships, Ghana has eliminated three NTDs and reduced the overall NTD burden in the country. The NTD Ambassador champions the Ministry of Health NTD Program's (MOH-NTDP) efforts to engage key decision-makers across sectors and build buy-in for sustainable, multisector collaboration to control and eliminate the 14 endemic NTDs. Supported by World Vision through USAID's Act to End NTDs | West Program, the NTD Ambassador and MOH-NTDP implemented high-level stakeholder engagements to raise awareness, foster political commitment, and build momentum for mainstreaming NTDs. These included a national-level meeting to solicit support for sustainable interventions in alignment with the Ghana Beyond Aid Agenda, a regional townhall to mobilize local ownership of NTD priorities within decentralized structures, and cross-ministerial strategic discussions based on recommendations from the engagements. As a result, the Ministry of Local Government, Decentralization, and Rural Development (MLGDRD) and the Ministry of Education (MOE) joined the MOH as champions for cross-sector coordination, identifying joint goals for sustainable development and a Ghana free of NTDs. The MLGDRD committed to champion NTDs in the Parliamentary Select Committee on Health, identifying a representative to advocate for NTD priorities and sustainable resource mobilization. The MOE established an NTD desk to coordinate programming such as routine school deworming, the Ghana Education Service-Ghana Health Service partnership through the School Health Education Program, and championing joint advocacy efforts with education stakeholders to promote NTDs education and positive WASH practices at the community level. These commitments are leading to program and policy changes which create an environment that fosters institutionalized multisector collaboration.

7046

KNOWLEDGE, ATTITUDE, AND PRACTICE OF MOTHERS TOWARD CHAGAS DISEASE IN LA GUARDIA, SANTA CRUZ DEPARTMENT, BOLIVIA: A CROSS-SECTIONAL STUDY

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Chagas disease(CD) is a NTDs, caused by the protozoa T.cruzi and transmitted by the triatomine bug. The disease is endemic in rural areas of Latin America. There are other transmission routes including blood transfusion and trans-placental vertical transmission. Based on the annual reports indicating low rate of coverage in Bolivia, this study's general objective was to estimate the coverage of serologic test for T. cruzi during the antenatal period and its relevant factors among Bolivian mothers who delivered children younger than two years old in La Guardia region where Chagas is endemic. Specific objectives were assessment of KAP the mothers against CD to identify factors influencing Coverage of Chagas test, and to suggest possible strategies to overcome barriers for pregnant mothers to access more efficient medical care. Method is quantitative, structured interview-based, cross-sectional study conducted in four public health centers in La Guardia, from September to October 2022. Eligible mothers were recruited from those older than 18 years with a child under two years of age by home visits. Analysis was performed using Stata17

for descriptive, univariate and multivariate levels. A total of 634 participants were recruited in the study. 74.5%(N=472) reported having been tested for CD during pregnancy or at the time of delivery of their recent child. This KAP study clearly concluded that higher levels of mothers' knowledge, attitude and practice factors were strongly associated with mothers who claimed to experience Chagas test. And 6 significant factors influenced the experience of Chagas test were educational history, Maternal and child handbook, Knowledge of newborn test, Knowledge of National Chagas program, necessity of family member's test, and Experience of treatment. Conclusion is the study estimated that 74% of the participants performed serologic test. Those who have high knowledge, attitude, and practice are strongly associated with CD testing. That raises more responsibilities for not only the health care providers but also the community to make mothers aware of the importance of screening tests in endemic areas.

7047

PORTABLE SMARTPHONE-BASED MOLECULAR TEST TO SUPPORT THE ELIMINATION PROGRAM OF LEISHMANIA DONOVANI

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New emerging diseases are a threat to public health systems worldwide. Low- and middle-income countries are facing additionally the burden of ancient pathogens, which were and still are circulating in human and animal populations. To control these diseases, the World Health Organization (WHO) created a list of so-called neglected tropical diseases (NTDs) together with a program to eliminate these pathogens. One of the NTDs is Leishmaniasis, caused by the parasite Leishmania donovani (LD). LD is a huge problem in different countries in Asia and Africa causing kala-azar (visceral leishmaniasis, VL) and Post kala-azar dermal Leishmaniasis (PKDL). Accessibility to accurate diagnostic methods is the essential first step to achieve the elimination goals. There is a need for sensitive, affordable and portable diagnostic systems for the field. The aim of this study was to test the accuracy of a handheld Minoo device connected to a smartphone for the detection of LD. It is based on isothermal DNA amplification and fluorescence detection in less than 20 minutes. Kassandra, a Phyton-based algorithm, is utilized for fluorescence signal analysis, including data processing, feature extraction and result classification.Limit of detection (LOD) was determined using a ten-fold dilution range of whole LD genome and LD molecular standard. Pathogens considered for differential diagnosis were tested to identify possible cross-reactivity. For clinical performance, 170 human samples from India and Bangladesh were screened. DNA extracted from peripheral blood (n = 98) and skin biopsies (n = 72) was tested. As control all samples were simultaneously examined with real-time PCR.The Minoo devices detected down to 11.2 genome equivalences and 134 copies of the molecular standard per reaction. Other Leishmania species were detectable, while no other pathogens were identified. In total, the evaluated clinical sensitivity was 88% while the specificity was 91%. Minoos can offer a convenient, sensitive, cheap alternative to real-time PCR. The devices are easy to handle and ideal for regular testing in low resource settings to monitor the progress of elimination.

7048

REACHING THE LAST MILE IN ONCHOCERCIASIS ELIMINATION IN MALI: RESPONDING TO PRE-STOP FAILURE

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Onchocerciasis is a parasitic disease caused by the filarial nematode Onchocerca volvulus and transmitted by the bites of black flies of the genus Similium. In Mali, the impact of mass ivermectin administration has shown progress in onchocerciasis elimination in all operational transmission zones except the KA05. The aim of this study is to accelerate onchocerciasis elimination using an implementation research approach to understand the complexity and socio-economic barriers that hinder the elimination process in KA05 which failed the pre-stop survey. We conducted a mixed methods study with community cross-sectional surveys, community mapping, focus group discussions (FGDs) and in-depth interviews (IDIs). Community mapping took place with stakeholders and community leaders to highlight patterns of migrations in/out of communities, geographic features and notable landmarks. A questionnaire was administrated to understand perceptions of mass drug administration (MDA) and other health interventions at the community level, reasons for missing out health campaigns, preferences and intent to participate in future MDA. 921 persons participated in the survey; 10 FGDs and 24 IDIs were conducted concurrently. Farmers (66.4%), gold miners (15%) and daily workers (6.1 %) represented the main occupations of survey respondents. 41.6 % of respondents reported participation in the most recent MDA campaign. 51.1% of respondents reported not remembering the most recent MDA campaign. Reasons for nonparticipation in the most recent MDA included lack of information about the campaign and distrust of drugs. In some areas, there were insufficient community drug distributors (CDD) to cover all villages and hamlets. As a result, CDDs did not have enough time or resources to cover all sites. This study highlights the possibility that populations miss multiple MDA rounds hampering elimination efforts. Reasons include low CDD numbers, multiplicity of difficult-to-access and remote hamlets, frequent movement of populations in the area and poor social mobilization. Identifying and addressing these challenges will aid NTD elimination efforts in Mali.

7049

DIGITAL INNOVATION FOR EFFECTIVE MANAGEMENT OF NEGLECTED TROPICAL DISEASE PROGRAMME DATA: LESSONS AND CHALLENGES

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Neglected tropical diseases (NTDs) affect over a billion people globally. The strategies for the control and elimination of NTDs requires collection and managing a high volume of data to facilitate decision-making. In the past, data collection in NTDs programmes has been mostly paper based. In recent years, the use of digital health technology offers several advantages, such as real-time data capture, automated data processing and analysis. The Nigeria NTDs elimination programme had reported disparity between reported and actual drug coverage in several contexts. This has resulted in over or under utilization of medicines, medicine wastages, and delay or premature implementation of disease assessment. This paper shares learning and challenges of piloting a digital health tool to manage NTD intervention data across four states in Nigeria. As part of a comprehensive project to advance onchocerciasis elimination, CBM trained Front Line Health Workers (FLHWs) to pilot two digital systems - a mass drug administration treatment reporting tool and a real-time supportive supervisory system based on national forms. The tools are designed to monitor treatment coverage, inclusion in terms of age, gender and disability and drug management. Both tools were built on KoboToolbox and piloted during the 2022 MDA in Bayelsa, Ogun, Oyo and Rivers States. Despite being the first time the level one summary forms were digitalized, 1.7million data points were collected across the four states and an average of 29% of treatment data reported immediately after MDA was completed. Similarly, supervisor's locations were tracked using GPS-enabled devices and

superimposed on implementation areas to track supervisory coverage. The success of this pilot has demonstrated that digitalizing MDA reporting forms is an innovation that offer significant potential for improving the availability of reliable and timely data for decision making, however, concerted efforts to overcome the challenges and ensure equitable access to these technologies is required.

7050

LESSONS LEARNED ON FINGER-INKING AS A MEANS OF COVERAGE VERIFICATION FOR MASS DRUG ADMINISTRATION FOR NEGLECTED TROPICAL DISEASES

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When we think of finger-inking, most associate this with elections or when children are given polio drops. To independently verify the coverage of mass drug administration <MDA> campaigns for neglected tropical diseases <NTDs>, coverage surveys rely on self-reported responses from eligible individuals to report whether they took the drugs administered during the MDA. While this has been the standard approach followed widely by various governments and donors administering and funding MDAs globally, in a recent project, the Accelerate Resilient, Innovative, and Sustainable Elimination of NTDs across four countries Tanzania, Uganda, Kenya and Mozambique, finger-inking was introduced as part of the MDA activities. Eligible individuals who received drugs subsequently had their fingers inked. The independent coverage survey administered after the MDA captured information on self-reported coverage (where individuals self-report whether they took the drug) and verified coverage (where individuals who report taking the drug have their fingers checked for visible finger ink marking). The study provides valuable insights into the differences between self-reported and verified coverage, the operational challenges in applying finger inking during MDAs, the cost implications for MDAs, the acceptability of finger inking among different target beneficiaries (e.g. women, men, youth, and children) and what this means for future MDAs for NTDs.

7051

THE JOURNEY OF NTD DATA FROM LOCAL FRAGMENTED DATABASE SYSTEMS INTO STABLE AND SECURE HEALTH MANAGEMENT INFORMATION SYSTEMS

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NTD Programs operate to eliminate or control diseases such as LF, Trachoma, OV, SCH and STH, in endemic countries around the world. Such programs collect routine monitoring and outcome data in relation to their Mass Drug Administrations and Disease Specific Assessments to assist with programmatic decision making, to inform program progress, to report to donors and funders and to provide an evidentiary basis when submitting elimination dossiers to WHO. It is essential that countries have stable and secure database systems with complete current and historical NTD data to protect investments in elimination and control programs. Despite this, many countries continue to use siloed Excel sheets for the day-to-day management of NTD program implementation, a situation which is fraught with numerous challenges including: lack of a shared single database across all diseases, lack of ability to access the database by multiple users simultaneously in a network-based setting to eliminate data divergence, lack of built-in data security mechanisms (password, virus protection, and regular back-ups), and limited NTDP personnel capacity to update and maintain the data systems over time. Typically, Ministries of Health employ HMIS - often but not always based on DHIS2 software - as a central repository for all health-related data, spanning programs relating to Malaria, TB, HIV-AIDs, etc. However, NTD data are often not included as part of such systems and the NTD programs are left to manage their own data systems independently. In recent years, however, there has been a push to integrate NTD data into centralized HMIS because of the obvious benefits, and countries are slowly moving in that direction - starting with integrating data relating to a handful of NTD indicators only. The movement towards full integration of all NTD data into existing HMIS is essential to ensuring a sustainable path forward as countries move towards full self-reliance in relation to the management of these debilitating diseases. This poster explores a diverse set of attempts towards integration of NTD data into HMIS across USAID's Act to End NTDs West portfolio of countries in West Africa.

7052

CHAGAS DISEASE SCREENING OF MATERNAL DONORS IN PUBLICLY BANKED UMBILICAL CORD BLOOD IN NORTH CAROLINA, UNITED STATES 2007-2022

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Trypanosoma cruzi antibody screening in the perinatal setting has the dual benefit of identifying cases of Chagas Disease in women for whom treatment could reduce morbidity and providing opportunity for early intervention in the case of vertical transmission to infant. North Carolina (NC) has had substantial growth in population from Chagas endemic regions. Routine screening for T. cruzi is not performed in NC. However, T. cruzi antibody testing is performed on all donated umbilical cord blood by the largest public cord blood bank in NC, the Carolina Cord Blood Bank (CCBB). We aimed to identify the prevalence of positive T. cruzi screening serology within a cohort of donated umbilical cord blood. We performed a retrospective review of positive screening serology for T. cruzi in all cord blood samples donated to the CCBB in NC from 7/1/2007–9/30/2022. Screening was performed using chemiluminescent microparticle immunoassay for the qualitative detection of antibodies to T. cruzi. Descriptive statistics including T. cruzi serology, maternal race/ethnicity, and delivery site were tabulated. Among 25,706 cord blood donations screened over a 15-year period, 45 samples (0.18%) had a positive T. cruzi antibody screen. Among the 3,576 donations from patients identifying as Hispanic (13.9% of the entire cohort), 12 (0.34%) had a positive screen. Of the 45 mothers with a positive screen, 23 identified as Caucasian, 12 as Hispanic, 5 as Black, 3 as multiracial, and 2 were unknown. 35.5% of positive screens occurred at a single donation site and 75% of mothers with a positive screen delivered within three neighboring counties. The prevalence of a positive T. cruzi screen in donated cord blood was 1.7 per 1000 cord blood donations. A higher proportion of positive screening was seen in Hispanic mothers, suggesting a role for screening for T. cruzi in the perinatal period, potentially in targeted populations or regions that are associated with higher proportions of positive screening found in this study. Further evaluation is needed to determine the rates of positive confirmatory testing and linkage to care for those with a positive screening test in this cohort.

7053

TSETSE FLIES INFECTED WITH TRYPANOSOMES IN THREE ACTIVE HUMAN AFRICAN TRYPANOSOMIASIS FOCI OF THE REPUBLIC OF CONGO

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Human African trypanosomiasis (HAT) is a neglected tropical disease still endemic in the Republic of Congo. Despite the continuous detection of HAT cases in the country, there is still not enough data on trypanosome infections in tsetse flies, trypanosome species and tsetse flies' species distribution in endemic foci. The present study was intended to fill this gap and improve understanding of trypanosome circulation in three active foci in the centre and south of Congo. Pyramid traps were set in various places

in villages to collect tsetse flies both during the rainy and dry seasons. Once collected, tsetse flies were identified using morphological keys. DNA extracted from flies was processed by PCR for species identification and for detection of trypanosome presence. A second PCR was run for different trypanosome species identification. A total of 1291 tsetse flies were collected. The average apparent density of flies per day was 0.043 in Mpouya, 0.73 in Ngabé and 2.79 in Loudima. Glossina fuscipes quazensis was the predominant tsetse fly collected in Ngabé and Mpouya, while Glossina palpalis palpalis was the only tsetse fly found in Loudima. A total of 224 (17.7%) flies were detected infected by trypanosomes; 100 (7.91%) by Trypanosoma congolense savannah, 22 (1.74%) by Trypanosoma congolense forest, 15 (1.19%) by Trypanosoma vivax, 83 (6.56%) by Trypanosoma brucei (s.l.) and 2 (0.16%) undetermined species. No T Trypanosoma brucei gambiense was found. A total of 57 co-infections between T. brucei (s.l.) and T. congolense savannah or T. brucei (s.l.) and T. congolense forest were found only in G. p. palpalis. Loudima recorded the highest number of infected tsetse flies. The study provided updated information on the distribution of tsetse fly populations as well as on Trypanosoma species circulating in tsetse flies in the different active HAT foci in Congo. These data suggested a high risk of potential transmission of animal trypanosomes in these foci, thus stressing the need for active surveillance in this endemic area.

7054

RESULTS FROM PATIENT INSIGHTS RESEARCH EXPLORING DISEASE AWARENESS, PATIENT JOURNEY, AND CURRENT MANAGEMENT OF VISCERAL LEISHMANIASIS IN BIHAR, INDIA

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Visceral leishmaniasis (VL) is a neglected tropical disease, lethal if untreated, with 50 000- 90 000 cases per year worldwide. India is one of the most affected endemic countries. As VL affects almost exclusively an underserved population with limited healthcare access, there is a major gap in understanding patient perspectives. The ongoing research seeks insights from patients' life experiences. Given the high illiteracy rate in VL patients, oral interviews with patients and caregivers of pediatric patients were held in Hindi, in Bihar, India. The objectives were to evaluate patient disease awareness, to determine drivers and barriers to seeking health care, and to understand the impact of the disease on patient's lives. Participants were asked their understanding about VL, including symptoms, diagnosis, treatment and measures to prevent infection. Their insights regarding barriers to diagnosis and treatment and their experiences of the treatment process were collected. In order to inform the clinical development of a new, oral therapy, opinions on a potential new treatment were gathered. Recruitment of the planned 30 participants is ongoing. Preliminary results from the first six participants show a poor understanding of the disease, and of its transmission, even after being treated for VL. The time from symptom onset to diagnosis varies amongst participants (from several days up to one month), resulting in delays to effective treatment for VL. In the short-term, the impact of disease is reported as greatly affecting participants' daily social and practical lives, their finances and their emotional well-being. Patients received intravenous and oral therapies in hospital settings to treat their disease. An oral therapy, given in an outpatient setting, was viewed as a preferable treatment option. Full results from all interviewed patients and caregivers will be presented in the poster. This research aims to improve understanding of patient needs and expectations, in view of a patient-centric clinical development program, for a potential new oral treatment.

7055

SEROPREVALENCE AND RISK FACTORS OF TOXOPLASMA GONDII IN WOMEN OF REPRODUCTIVE AGE (15-44 YEARS) — NIGERIA, 2018

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Toxoplasmosis is caused by an obligate intracellular protozoan, Toxoplasma gondii which may cause illness in infants born to mothers who become newly infected during or just before pregnancy. Infection can also occur via contaminated food or water. The nationally representative 2018 Nigeria HIV/AIDS Indicator and Impact Survey included blood specimen and survey data collection. Blood specimens were tested by multiplex bead assay (MBA) for antibodies against antigens such as SAG2A from T. gondii. We evaluated seropositivity to SAG2A (defined as median fluorescent intensity >211) in a sample of 9,752 women of reproductive age (WRA) aged 15-44 years. Bivariate logistic regression was performed to identify potential risk factors. Anti-SAG2A seropositivity overall was 27.4% (95% CI 26.1-28.7%) and was lower in 15-24-year-olds (21.9%, 95% CI 20.3-23.6%) than 25-44-year-olds (31.8%, 95% CI 30.9-33.5%). A similar proportion of pregnant (24.6%, 95% CI 21.5-28.0%) and non-pregnant women (27.5%, 95% CI 26.2%-28.9%) were seropositive. WRA from all states had evidence of T. gondii exposure; seroprevalence ranged from 7.4% (95% CI 3.6-14.7%) in Yobe to 70.3% (95% CI 58.1-80.1%) in Bayelsa. Lower seroprevalence was associated with owning livestock (OR 0.66, 95% CI 0.58-0.75) and being Muslim (OR 0.62, 95% CI 0.54-0.72) compared to being Christian. Those in higher wealth quintiles had greater odds of seropositivity (OR 2.51, 95% CI 2.07-3.05) compared to the lowest. Unimproved sanitation and drinking water sources were not associated with a difference in odds. This is Nigeria's first population-based estimate of T. gondii exposure in WRA, obtained by leveraging MBA to test specimens from a prior survey. However, data on specific risk factors were not collected, limiting interpretation. Women who have been exposed to T. gondii (i.e., seropositive) before pregnancy have minimal risk of transmitting the infection to their fetus in subsequent pregnancies. Among this sample, almost 75% of WRA are at risk of congenital transmission. Future studies should further investigate potential risk factors to inform development of effective prevention measures.

7056

CLINICAL IMPLICATION OF REGIONAL LEISHMANIA SPECIES DISTRIBUTION IN ECUADOR: A CROSS-SECTIONAL STUDY

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Among the cutaneous leishmaniasis (CL) causing Leishmania species in Ecuador, Leishmania guyanensis and L. braziliensis are dominant. Earlier studies on CL species in Ecuador focused on the Pacific areas, included only few patients from the Amazon region, and did not study patient characteristics. The resulting lack of knowledge impairs a region specific diagnosis and therapy for CL possibly leading to treatment delay and patient suffering. Patients were included by private and public primary health care centers and hospitals in the Pacific part of the Pichincha province and in the Amazonian Napo, Pastaza, and Morona Santiago provinces. All patients were subjected to a microscopic smear slide examination of a skin lesion suspected for CL in the participating centers. A skin scraping and filter paper imprint sample was taken from the border of the lesion for

smear slide microscopy and qPCR. Leishmania species was determined by Cytochrome B sequencing. Additional patient and geographic variables were collected. Presence of Leishmania parasites was confirmed with PCR and/or microscopy in 245 patients who were included for this study. 154 patients (63%) were infected in the subtropical Pacific region and 91 (37%) in the Amazon. Infecting Leishmania species could be determined in 135 (73%) patients. L. guyanensis was the main CL causing species (93%) in the subtropical Pacific, but more than half of the patients with species determination from the Amazon was either infected by L. braziliensis (46%) or L. lainsoni (13%). Patients infected in the Pacific region had significantly higher concentrations of Leishmania DNA in the samples. Median health seeking delay for patients infected in the Amazon was 1 month longer. Lesion type and number of lesions was not significantly different across regions. L. guyanensis was the dominant species in CL patients in the Pacific region and health seeking delay was relatively short leading to a low risk of mucosal leishmaniasis (ML). The majority of CL lesions in the Amazon was caused by L. braziliensis (causative agent of ML) or L. lainsoni, health seeking delay was longer.

7057

THE ASYMPTOMATIC DOG WITH VISCERAL LEISHMANIASIS: IS THIS THE "REAL BAD DOG"? A SYSTEMATIC REVIEW

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The case of the asymptomatic canine visceral leishmaniasis (aCVL) has drawn attention because its epidemiological role in the persistence of visceral leishmaniasis in urban areas is not yet well understood. With that in mind, we conducted a systematic review of epidemiological reports on aCVL. We used the descriptors "asymptomatic" and "canine visceral leishmaniasis." We retrieved 365 articles in Pubmed and 504 in ScienceDirect. After reading the abstracts and full articles, we selected 49 that met the criteria for the epidemiological aspects of aCVL. 55.2% (27) were cross-sectional studies, 22.4% (11) were experimental, 16.4% (8) were diagnostic evaluations, 4.1% (2) were mathematical models, and 2.1% (1) were cohort studies. The proportion of aCVL in cross-sectional studies ranged from 4 to 60% in countries from the Global South, such as Brazil and Iran. The experimental studies showed that aCVL dogs can infect the vector and have amastigotes identifiable in blood, skin, liver, lymph nodes, and bone marrow. The development of new diagnostic techniques focused on the ability to identify asymptomatic dogs. Also, 2 studies (1 cross-sectional and 1 cohort) indicated that the owner profile of an aCVL dog is middle to upper-class. Two mathematical models considered that intervention in aCVL could have a positive impact on the transmission ratio in a given area, and showed that the presence of aCVL must be taken into account when developing strategies for disease control. The burden of aCVL can be heavy, and infected dogs can continue to transmit for a long time before developing symptoms and receiving adequate interventions. The analyzed studies revealed that the owner profile of aCVL dogs is mostly wealthy, and they also tend to not adopt particular measures against visceral leishmaniasis with their dogs. Therefore, emphasizing this owner profile and encouraging them to take the necessary precautions could be an effective approach to help achieve disease control.

7058

ADDRESSING AFRICAN SLEEPING SICKNESS TRANSMISSION THROUGH STREET THEATRE

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Human African Trypanosomiasis, or African sleeping sickness, is caused by the parasite Trypanosoma brucei which is transmitted by the Tsetse fly. Community engagement surrounding this disease and education in methods of control and elimination of the insect vector has proved lacking in endemic regions. Mistrust in research in sub-Saharan African regions also poses a barrier to intervention methods. This mistrust can often be traced to the ebola outbreaks of the past decade and can lead to a hostile environment. Beliefs, fears, and unsubstantiated rumours such that healthcare workers and researchers were responsible for disease spread, have resulted in the injury and death of scientific and medical field workers. Trust in scientists is crucial in working toward the World Health Organization's target of eliminating sleeping sickness transmission by 2030.Our innovative project has addressed these barriers through a unique method of community engagement and epidemiological data collection: street theatre. The project provides a model for stirring the public's interest in science, breaking down trust barriers and involving the community in developing strategies that can reduce transmission. This project is readily transportable and accessible across geographical and language boundaries. The performance was developed by a diverse team of Malawian and Scottish scientists, performers, and health officials, and was performed both in Glasgow and throughout the Rumphi and Nkhotakota regions in Malawi, which has brought an important educational component to underserved communities but also demonstrates the value of and enhances the trust in, scientific research.This unique community engagement project, and the methodology behind its development, have provided a platform for future artistic and theatrical endeavours that can be adapted to other parasite-driven diseases – such as malaria, schistosomiasis, and leishmaniasis. Our process and outcomes now serve as a toolkit to support the development of future collaborations and interactive performances in local communities, resulting in a strong legacy for the project for years to come.

7059

EPIDEMIOLOGY OF SPOTTED FEVER GROUP RICKETTSIA AND CHAGAS DISEASE INFECTION IN A RURAL COMMUNITY IN BOYACÁ, COLOMBIA

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Neglected tropical diseases (NTD) are described by the World Health Organization (WHO) as a group of communicable diseases that occur mostly in tropical and subtropical regions affecting people in under-resourced areas. The WHO has recognized twenty conditions as NTDs, such as Chagas disease (CD); however, there has been debate on adding other diseases to the list. Rickettsial infections are a group of vector-borne bacterial pathogens prevalent in tropical and subtropical regions that affect mostly poor communities, and despite not being included in the WHO's NTDs list, are understudied and remain a blind spot for public health efforts. Among rickettsioses, spotted fever group Rickettsia (SFGR) are of public health importance due to the wide species distribution, with R. rickettsii being a highly pathogenic species. Colombia is affected by these infections that require simultaneous efforts: Chagas disease is a notifiable disease that requires public health interventions due to the emergence

of vector species that circumvent previous vector-control strategies, and gain terrain in areas where the primary species was eliminated; on the other hand, SFGR infections are non-reportable, and despite growing emergence globally, local epidemiological factors that are driving its emergence still remain unknown. A collaboration with the Boyacá Health Department revealed concerns about the underdiagnosis and thus lack of treatment among patients exposed to those infections, especially in rural communities. A serosurveillance study was performed between 2021-2022 in the municipality of Miraflores, Boyacá evaluating human and canine serological samples, to better understand the epidemiology of these infections. Despite different ecology and epidemiology, both infections require adequate evaluation and understanding to reduce the risk they pose for the community. Our presentation will bring the first evidence of SFGR exposure in the department of Boyacá and will discuss the results of the cross-sectional serological survey evaluating Chagas disease and SFGR exposure.

7060

MODELLING SLEEPING SICKNESS AT DIFFERENT SPATIAL SCALES: A HEALTH AREA ANALYSIS

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The intensification of control and surveillance activities relating to gambiense human African trypanosomiasis in the last two decades has led to a large decline in the number of annually reported cases. However, while the disease moves closer to achieving the ambitious target of elimination of transmission, pockets of infection remain. The distribution of cases is highly heterogeneous and dependent on many factors, such as the density of the disease vector, the tsetse, and access to diagnostics and treatments and health facilities.We present a stochastic mathematical model for gHAT in the Democratic Republic of Congo (DRC) that captures the dynamics at the health area level, a finer scale than previous modelling studies, to better understand the geographical variation in case numbers. All fitted parameters of the model are matched to health area data and the stochastic properties allow us to better quantify the uncertainty in our results. The model allows greater flexibility in simulating projections to target specific regions for control interventions and we are working with PNLTHA-RDC to tailor our modelling strategies to realistically match planned activities, as well as the plausible alternatives. The analysis focusses on the 16 health areas of Mosango health zone as a case study, with the ability to scale up this method to approximately 1200 analysable health areas within the DRC. The modelling approach in Mosango highlights the benefit of using smaller scales, since approximately one third of cases in the health zone come from a single health area. And this is reflected in the modelling results, where in this health area, Kinzamba II, we predict a later expected year of elimination of transmission, under the current intervention strategies. Aggregating all our health area results to the larger spatial unit of the health zone, accurately recovers the results of earlier analyses, but fine spatial scale models could be pivotal in understanding exactly where remaining transmission is occurring.

7061

FROM THE PLAINS TO THE MOUNTAINS: A NEW FRONTIER FOR LEISHMANIASIS IN NORTH INDIA

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Leishmaniasis, a disease traditionally endemic to Bihar, Jharkhand, West Bengal, and Eastern UP, has recently been observed in Northern Himalayas. To investigate this trend, we conducted a retrospective analysis of all cases of Leishmaniasis that presented to a tertiary care hospital in this region. Our study included 14 patients, all of whom had Visceral Leishmaniasis (VL) and presented with fever. Vomiting, malaise, weight loss, and abdominal pain were other frequently reported symptoms. Hemophagocytic lymphohistiocytosis (HLH) was the most common complication, occurring in 71.4% of patients. All patients were pancytopenic, had deranged liver function tests, and had splenomegaly. The diagnosis was made based on rk39 antigen detection or LD bodies on bone marrow aspiration or both. We identified several risk factors for VL, including living in rural areas and organic matter around the household being the most common, followed by the presence of peri-domestic animals, precarious living conditions, sleeping outside or near vegetation, dense vegetation cover, contact with people from endemic areas, presence of nearby water bodies, and nearby construction work. Low educational status, proximity to households of VL patients, and travel to endemic regions were less commonly reported risk factors. Treatment with conventional or liposomal Amphotericin B or a combination of both was effective, with only one septic patient being unable to receive treatment. Three patients (21.4%) died. Our findings suggest that diagnosing VL in non-endemic areas can be challenging, particularly when it occurs with HLH. The recent increase in cases in the mid-Himalayan range of North India is likely due to the area's ecological similarities to endemic regions, allowing the sandfly to move up the Ganges river. Therefore, our study highlights the need for a reassessment of endemicity in the mid-Himalayas region of North India and the importance of early diagnosis and treatment of VL in non-endemic areas.

7062

EPIDEMIOLOGICAL, SEROLOGICAL, AND ENTOMOLOGICAL ASPECTS OF VISCERAL LEISHMANIASIS IN SUSPECTED NEW VISCERAL LEISHMANIASIS FOCI IN BANGLADESH

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The study aimed to explore epidemiological, serological, and entomological aspects of visceral leishmaniasis (VL) in suspected new VL foci and assess the knowledge, attitude, and practices of the community living in the alleged new VL foci. The study investigated new VL cases reported between 2019 and 2020 in four sub-districts where we tested 560 members using the rK39 rapid test and conducted vector collections in six neighbouring houses of the index to assess sandfly density and distribution, examined sandflies' infection, and determined the spatial relationship with VL infection. Furthermore, we highlighted the importance of early detection, community awareness, and targeted interventions in controlling the spread of the disease. The study screened 1078 people from 231 households in four upazilas for fever, history of VL, and PKDL-like skin lesions. Savar's rK39 rapid test positivity rate was the highest (3.51%). The sandfly was present across all areas except Dharmapasha, but all 21 collected female P. argentipes sandflies were negative for the Leishmania parasite DNA. We found that one person from Islampur with a history of VL, and one from Islampur and Savar had PKDL-like lesions. After the awareness intervention, more people became familiar with VL infection (91.27%), and the knowledge of the participants concerning sandflies being the vector of the disease and the risk of having VL increased significantly (30.14%). The study found no active case in the new foci, but some asymptomatic patients. As sandfly vectors exist, the National Kala-azar Elimination Programme (NKEP) should consider these areas as kala-azar endemic and start the control activities as per national guidelines.

7063

MODELING THE RELATIONSHIP BETWEEN PRECIPITATION AND TEMPERATURE ON THE INCIDENCE OF CUTANEOUS LEISHMANIASIS IN NORTHERN MOROCCO

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Leishmaniasis is a Neglected Tropical Disease of global epidemiological importance due to its causation of large open wounds during infection, which lead to severe social stigmatization. Cutaneous leishmaniasis (CL), caused by Leishmania species, is endemic in Morocco and is associated with high levels of geographic and secular variation. Because CL is transmitted by dipteran vectors who are poikilotherms, we hypothesize that environmental factors play a key role in its transmission. Therefore, we examined historical associations between rainfall and temperature patterns and CL due to Leishmania tropica incidence in four northern provinces of Morocco and fitted time series models using meteorological covariates to predict CL cases in those provinces from 1995 to 2014. The regression models showed that the level of rainfall most strongly predicted CL incidence after a time lag of 4 months, 3 months, 1 month, and 4 months, respectively, in Moulay Yacoub, Sefrou, Taounate, and Taza Provinces; and that temperature most strongly predicted CL incidence after a time lag of 5 months, 4 months, 6 months, and 5 months, respectively, in Moulay Yacoub, Sefrou, Taounate, and Taza Provinces. Taza Province had the highest rate of CL incidence during the final three years of the study, but the highest CL incidence rate over the course of the study was in Moulay Yacoub in 2000 (55.71/100,000). Changes in temperature, precipitation patterns, and humidity due to climate change will likely have a significant influence on future CL transmission patterns in endemic regions. These models provide evidence that meteorological data can be used to predict future CL incidence.

7064

HAEMOGLOBIN DYNAMICS FOLLOWING TREATMENT OF VISCERAL LEISHMANIASIS: AN INDIVIDUAL PATIENT DATA META-ANALYSIS USING THE INFECTIOUS DISEASES DATA OBSERVATORY DATA PLATFORM

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Anaemia is the most common haematological manifestation of visceral leishmaniasis (VL). However, the evolution of different haematological characteristics following treatment remains poorly understood. An individual patient data meta-analysis (IPD-MA) was undertaken to explore the haemoglobin measurements at baseline and following treatment using the Infectious Diseases Data Observatory (IDDO) VL data platform. Anaemia and severe anaemia were defined using the WHO definitions. Mixed effects logistic regression models were fitted in one-stage IPD-MA to identify risk factors associated with severe anaemia at presentation; between study clustering was considered using random intercepts for study sites. Thirty-four studies (31 published; 3 unpublished; 2000-2019) from the IDDO VL data platform were included in the IPD meta-analysis. Of the 9,207 patients enrolled in these studies, 5,778 (62.8%) were from the Indian sub-continent (ISC), 2929 (31.8%) were from Eastern Africa (EA), 377 (4.1%) from Brazil and 123 (1.3%) were from Greece. Of the enrolled, 664 (7.2%) were <5 years old, 3,402 (37.0%) were 5-15 years old, 5,129 (55.7%) were aged 15 or older and age was missing in 12 (0.1%). Miltefosine was administered in 2,109 (22.9%), pentavalent antimony in 1,912 (20.8%), amphotericin B (non-liposomal) in 1,213 (27.3%), liposomal amphotericin B (L-Amb) in 485 (5.3%), paromomycin in 900 (9.8%), combination drugs in 1,283 (13.9%), and placental extract in 5 (0.1%) patients. At presentation, 98% of the patients were anaemic and 48% had severe anaemia. In univariable analysis, young age and female sex were associated with an increased risk of severe anaemia. Multivariable analysis was undertaken by controlling the following predictors: age, sex, geographical region, and calendar year. In the multivariable model, age 15+ years had lower odds of severe anaemia compared to <5 years (odds ratio (OR): 0.65; 95% confidence interval (CI): 0.50-0.84]), and males had lower odds compared to females (OR=0.56; 95% CI: 0.50-0.62). Further analysis is ongoing to delineate the role of covariates and to characterise the longitudinal haemoglobin profile.

7065

SYSTEMATIC REVIEW OF CHAGAS DISEASE IN ENDEMIC COUNTRIES, 1980 - 2019.

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Chagas disease (CD) is a neglected tropical disease endemic to Latin American countries. It is transmitted by triatomine insect vectors, mostly in rural and poor areas. Our objective is to describe the available CD seroprevalence data in Latin America. We conducted a systematic review of CD seroprevalence from 1980 through 2019. We included CD seroprevalence studies in humans in endemic locations, using PubMed and reference mining. We included surveys from representative populations or censuses, using two or more diagnostic methods, unless the single method was ELISA or ICT (per WHO guidelines). The systematic review protocol was published in Open Science Framework (DOI 10.17605/OSF.IO/USWC3). This review is currently being updated through 2021, as described in a separate protocol (PROSPERO ID CRD42022368900). We found 3,723 papers in this search. During the title and abstract screening, we included 439 papers. 307 papers were excluded because they were not retrievable (18) or did not meet inclusion criteria (289). 132 studies were included in the final analysis, comprising 189 location- years of data. We found studies from 17 of the 20 endemic countries. There were 38 studies with data from the 1980s, 47 from the 1990s, 62 from the 2000s, and 12 from the 2010s. No data were available for 10 of the 20 countries after 2010. Most of the studies were conducted in highly endemic, rural areas. Diverse levels of endemicity made it difficult to compare prevalence across countries and years without adjusting for the population at risk. CD data are sparse, and many endemic countries have little or no recent published seroprevalence data. Most seroprevalence studies were conducted in rural areas, but migration from rural to urban areas in Latin American countries and the chronic nature of CD make it challenging to estimate the true total prevalence from these data. The small number of recent studies demonstrates the need for new surveys. Additional data on seroprevalence in large urban areas would help to quantify the effect of rural-to-urban migration on CD epidemiology.

7066

FIRST MOLECULAR DOCUMENTATION OF LEISHMANIA MAJOR IN THE PHLEBOTOMINE SAND FLY, AL AHSA, EASTERN REGION, SAUDI ARABIA

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Cutaneous Leishmaniasis (CL) is considered an overlooked public health threat in Saudi Arabia. Many Saudi regions are highly endemic including Al Ahsa. No previous published species identification of Leishmania parasite in the vectors in Al Ahsa. This study aimed to molecularly identify Leishmania species from sand flies collected from Al Ahsa, Eastern Region, Saudi Arabia. This is a cross-sectional study that was conducted in Al Ahsa from July 2020 to May 2021. Eastern and southern towns were the targeted areas of collection that considered to have the highest rate of sand flies and CL cases according to the data from the Vector Borne Diseases Prevention Center in Al Ahsa. Sand flies were collected from indoor and outdoor habitats using CDC miniature light trap (John W. Hock Company, USA) and sticky traps. After recording the sampling date, locations and weather parameters, collected female sand flies were sorted and gathered for further identification and analysis. DNA was extracted from all sand flies using commercial genomic DNA extraction tissue kits (QIAamp Fast DNA Tissue Kit, Qiagen, Germany) following the manufacturer`s instruction. Pools of 3-10 female sand flies were used for DNA extraction according to the number of sandflies collected from each region. All extracted DNA was amplified using a protocol targeting Leishmania genus and species-specific primers. Post PCR-Restriction Fragment Length Polymorphism (PCR-RFLP) technique was used for species identification. 113 pools of sandflies were included in the study. 10 were positive for Leishmania genus following our experimental protocol. Characterization of Leishmania species by PCR-RFLP established Leishmania major as the species found in the collected sand flies. In conclusion, to the best of our knowledge, this is the first study that provides a preliminary molecular characterization of leishmania species in the sand fly vector at Al Ahsa region. Leishmania major was the only species found in our study. Further comprehensive research about the vector and reservoirs is vital to establish Leishmania transmission dynamics in Al Ahsa.

7067

THE FIRST EPIDEMIOLOGICAL INVESTIGATION ON CONTACTS WITH MYCOBACTERIUM BOVIS FROM A ZOO IN THE REPUBLIC OF KOREA, JULY 2021-SEPTEMBER 2022

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Among 50 animals at the zoo's South American Pavilion in the Grand Seoul Park, 43 confirmed cases of bovine tuberculosis (TB) had been identified until 2 September 2022 after Mycobacterium bovis(M. bovis) had been first confirmed on 2 July 2021. This study aimed to assess the risk of getting infected with zoonotic TB after contact with animals infected with M. bovis. Through an epidemiological investigation, a total of 29 contacts who working in the zoo were found. A total of 27 IGRA tests among them were conducted, excluding two workers diagnosed with latent tuberculosis infection (LTBI) during the bovine TB outbreak in July 2021. Overall, 7 people (24.1%) were identified to with IGRA positive, which are composed of 3 veterinarians (42.9%), 2 staffs in maintenance (28.6%), 1 zookeeper (14.3%) and 1 laboratory technologist (14.3%). And there were five close contacts (71.4%) and two casual contacts (28.6%). As of January 2023, no cases have been developed with clinical zoonotic TB. However, long-term follow-ups will be necessary. This is the first study of screening for zoonotic TB among contacts exposed to bovine TB in the zoo, and also this is the first sharing incidence data from animal health authority of the Ministry of Environment. It is necessary to perform prevention measure such as contacts investigation through sharing surveillance data between human and animal health sectors. A one-health approach has been recommended to optimise zoonosis prevention and control programs.

7068

ASSESSMENT OF THE ZOONOTIC TRANSMISSION POTENTIAL OF ASCARIS IN HUMAN AND PIGS AND ITS IMPLICATIONS FOR ASCARIASIS CONTROL IN MAKENENE IN THE CENTER REGION OF CAMEROON

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Although Ascaris lumbricoides was acknowledged as human parasite and A. suum as swine parasite, changes in the epidemiological profile of ascariasis were reported with surprisingly high prevalence of Ascaris infections in human in areas under decades of mass administration of Mebendazole. In-depth understanding of this surprisingly high prevalence of Ascaris infections is fundamental for the designing of control measures that will lead to ascariasis elimination by 2030 as foreseen in the WHO road map. In such context, questions about the potential zoonotic transmission of Ascaris species were raised. Our hypotheses are that cross-transmissions of A. suum and A. lumbricoides exist between pigs and humans and such transmissions led to the surprisingly high prevalence of Ascaris in humans of some endemic areas. This study assessed the cross-transmission potential of Ascaris by detecting A. suum and A. lumbricoides in humans and pigs using molecular tools and genetically characterizing Ascaris species circulating in human and pigs from the same endemic areas. Stools were collected in pigs and humans from Makenene in center region of Cameroon. Parasitological examinations was used to search Ascaris eggs. Twenty milligrams of positive stools were spread on wathman paper. DNA extracts from spread stools enabled the identification of Ascaris species using allele specific PCR. The genetic characterization of Ascaris species were performed on three mitochondrial genes (NADH 1, COX 1 and 2 subunits). From 1775 collected stools, 94 (5.3%) had Ascaris infections. Allele specific PCR revealed that 20% of these infections were due to A. suum. Co-infections of A. suum and A. lumbricoides were detected in some children. The genetic characterization of Ascaris species confirmed their cross transmission between humans and pigs. This study highlighted A. lumbricoides and A. suum both in humans and pigs in the same area; thus providing evidences supporting the zoonotic transmission of A. suum to humans. Achieving acariasis elimination requires One Health concept in which strategies must be developed to both fight human and pig ascariais.

7069

DRIVING FORCE OF INDISCRIMINATE USAGE OF ANTIBIOTICS IN SMALL SCALE COMMERCIAL POULTRY FARMS IN BANGLADESH

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The ascent of antibiotic resistance is an emerging public health concern by, widespread use of antibiotics in livestock production. Reported overuse of antibiotics in poultry farming is potential for antibiotic resistance to emerge in humans. Hence, we conducted this study to explore driving forces of antibiotic usage in commercial poultry along with farmer's perception of antibiotics. We conducted a qualitative study in three districts of Bangladesh between September and December 2021. We collected data from 60 poultry farmers using in-depth interviews and participant observation to understand pattern of antibiotic use and perceptions of farmers on antibiotics and its effects. Recorded interviews were transcribed

and developed thematic codes from the transcribed data for analysis based on the grounded theory approach. The farmers use antibiotics for any kind of sickness of their birds without diagnosis of diseases. They believe that antibiotics do not have any side effects or transfer to humans. Farmers purchase chicks, poultry feeds, and antibiotics from poultry dealers on credit, they repay the debt by selling their poultry to these dealers. However, farmers are obligated to sell their poultry exclusively to these dealers. Dealers offer a reduced price and sometimes refuse to purchase their poultry. Dealers wield significant influence over farmers regarding antibiotic usage, as they decide which antibiotics to use and how frequently they should be administered. Occasionally, veterinary professionals of pharmaceutical companies provide treatment to poultry. Farmers reported that if they do not use antibiotics recommended by these veterinarians, who often represent a specific company, then the veterinarians do not provide further advice. Poultry farmers are often forced to use antibiotics by poultry dealers and veterinarian of pharmaceutical companies. Recommended interventions that offer economic benefits and increase farmers' awareness on antibiotics usage and impose stringent regulations on use of antibiotics in poultry farming to prevent emergence of antibiotic resistance.

7070

ASSESSING TRANSBOUNDARY ZOONOTIC DISEASE THREATS AT POINTS OF ENTRY BETWEEN IRAQ AND JORDAN: A ONE HEALTH APPROACH

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The One Health Systems Assessment for Priority Zoonoses (OHSAPZ) tool was created to facilitate a systematic assessment of One Health infrastructure and coordination mechanisms to prevent, detect, and respond to national priority zoonotic diseases. This framework identifies gaps and develops recommendations for action towards One Health systems strengthening. Our team adapted this tool to prioritize and assess systems for detection, reporting, coordination and response of transboundary zoonotic diseases (TZD) at Points of Entry (POE). The One Health Transboundary Assessment of Priority Zoonoses (OHTAPZ) tool was successfully piloted at the Libya-Tunisia border and the methodology was formalized. The OHTAPZ has now been applied to identify priority transboundary zoonoses, and assess One Health coordination mechanisms at POEs between Iraq and Jordan, countries which have previously conducted OHSAPZ assessments and continue to build national One Health capacities. Through a phased approach, our team set out to assess, evaluate and strengthen preparedness, detection and response plans as they relate to transboundary zoonotic threats between Iraq and Jordan using the OHTAPZ tool as the guiding framework. With the completion of Phase 1, we have updated analysis on Iraq and Jordan's national priority zoonotic diseases and mapped progress to date to measure and identify where gaps still exist or have been created over time. In addition, we have identified a joint priority TZD list and using the OHTAPZ tool assessed mechanisms in place at POEs to identify areas for capacity building.

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SNAKEBITE PREVALENCE AND RISK FACTORS IN A NOMADIC POPULATION IN KENYA: A COMMUNITY-BASED SURVEY

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Introduction: Snakebite is an important public health concern, especially in tropical areas, but the true burden remains unclear due to sub-optimal reporting and over-reliance on facility-based data. Methods: A community-based cross-sectional survey was conducted in Samburu County, Kenya from December 2019 to March 2020. Geospatial techniques were used to create a sampling frame of all households in Samburu County and a multi-stage cluster sampling strategy to select households and recruit study participants. This strategy was selected to address the epidemiological challenges posed by the predominantly nomadic populations of Samburu County. Results: We recruited 3610 individuals living in 875 households from 30 clusters. The 5-year prevalence of snakebite was 2.2% (95% CI 1.4% - 3.4%), and the 5-year mortality rate was 138 (95% CI 44 - 322) deaths per 100,000 inhabitants, resulting in an estimated 1,406 snakebites and 88 deaths from snakebites per year. Most snakebite incidents occurred at night (44%, n= 36), and the participants were mostly sleeping (32%, n = 27) or walking/playing outdoors (51%, n = 41) when they were bitten. Independent risk factors were household socioeconomic status and the number of people per house, after adjusting for clustering. Conclusion: Samburu County has a high snakebite burden and most victims get bitten while sleeping or walking outdoors at night. Snakebite prevention and health promotion programs in Samburu County, and other endemic regions, need to be contextualized and consider the geographic, seasonal, and temporal specificities found in our study. Our findings also have consequences for health care delivery, especially night-time staffing and antivenom availability. Health facilities may need to ensure 24-hour availability of antivenoms and of expertise in the management of snakebites, especially in endemic areas.

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USING A ONE HEALTH SYSTEMS ASSESSMENT TOOL TO STRENGTHEN TRANSBOUNDARY ZOONOTIC DISEASE DETECTION, SURVEILLANCE AND RESPONSE BETWEEN LIBYA AND TUNISIA

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Points of entry (PoE), such as land border crossings, are prime locations for detection and surveillance of zoonotic disease threats with the potential for transboundary spread. The border between Tunisia and Libya is challenged by illicit movement of materials, livestock and people increasing the risk of transboundary zoonotic diseases (TZD). This project aims to determine how current national frameworks for zoonoses in Libya and Tunisia can be strengthened to build sustainable One Health strategies for binational prevention, detection, surveillance and response of TZDs at PoEs. The established One Health Systems Assessment for Priority Zoonoses (OHSAPZ) methodology was first adapted for the cross-border setting. Following prioritization of five TZDs, we developed systems maps outlining the current operations and intersections of communication and coordination between public and veterinary health sectors within

and across the two countries. We assessed the current TZD detection, surveillance and response operations at the PoEs, identified strengths in capacity and limitations to timely information-sharing, and developed targeted recommendations for both national and joint action planning. After completing our transboundary assessment pilot and receiving feedback from in-country partners, we determined evident gaps in existing international guidance and assessment tools for PoEs, which provide limited instruction on and integration of One Health practices for cross-border coordination. Following an in-depth literature review, we developed the One Health Transboundary Assessment for Priority Zoonoses (OHTAPZ) tool which supports binational strengthening of transboundary zoonotic disease detection, surveillance and response systems.

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TAILORING A ONE HEALTH COURSE FOR AN ESTABLISHED NON-ONE HEALTH GRADUATE PROGRAM IN BRAZIL

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One Health (OH) approaches recognize the interconnectedness and interdependence of human, animal, and environmental health and aim at improving the health and well-being of living beings and the ecosystems in which they live. While OH initiatives initially focused on infectious and zoonotic diseases, the broader concepts extend beyond this, and cover a wide range of complex health issues at the interface of human, animal, and environmental health. Given the potential for OH to be tailored and applied to a broad range of fields and disciplines, it is critical to introduce the OH concept in diverse settings, so that various audiences can adapt and use OH to address the specific challenges they face. Teaching students about OH is crucial, as they are the future generation that will be developing, implementing, and likely modifying OH approaches. Integrating OH into the curriculum of academic programs has been identified as a fundamental strategy for promoting OH principles and enhancing human capacity building. However, integrating OH into established non-OH graduate programs can be challenging as the OH content may not initially align with the program's main research lines and goals. To address this challenge, we present a case study of tailoring an OH syllabus to the Graduate Program in Health, Environment, and Work at the Federal University of Bahia in Salvador, Brazil. The syllabus was developed from scratch by identifying relevant OH content from the literature and tailoring it to meet the specific needs and goals of the program while teaching critical OH elements. By doing so, the syllabus content became more naturally integrated into the program, rather than appearing as an isolated or unconnected topic. As a result, the course offered faculty members and students of the program an opportunity to learn and discuss OH concepts, which intersects with several ongoing projects and lines of research in the program. We believe our work contains significant information that may assist others in tailoring syllabuses to implement OH concepts in diverse educational settings.

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RIFT VALLEY FEVER VIRUS AND GENOME STABILITY IN RAW MILK

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Rift Valley fever virus (RVFV) is a zoonotic arbovirus which represents a threat to both humans and ruminants across Africa and the Middle East. In humans, RVFV causes a spectrum of mild to lethal disease including self-limiting febrile illness, retinitis, hepatitis, meningoencephalitis, and hemorrhagic fever. One significant gap in the understanding of RVFV epidemiology is the risk of handling and consumption of animal sourced foods, including milk, which have strong epidemiologic links to exposure, including in urban settings in the absence of direct animal contact. In various populations in Kenya, 5-36% of participants report consuming raw milk, and there are many actors in the informal milk value chains that handle milk daily, representing a public health risk. Recent studies detected RVFV by rt-PCR in cow milk in East Africa; however, the stability of infectious virus in milk has not been assessed. In this study, the stability of infectious RVFV and viral RNA was measured in fresh cow's milk across a range of temperatures to simulate field relative storage and ambient temperatures in Kenya. In milk, RVFV titers decreased 10-100-fold over 24 hours, but infectious virus was still detectable after 96 hours at 4C. Furthermore, at 25C virus was infectious up to 72 hours and up 24 hours when incubated at 30C. Viral RNA was detectable at 96 hours with minimal changes in CT values throughout all tested temperatures. Despite this stability, RVFV was inactivated by standard pasteurization techniques of heating milk to 60C for 30 minutes or 72C for 15 seconds as well as boiling. These findings support mounting epidemiologic data suggesting unpasteurized milk products containing RVFV may carry risk even after several days. More research on the infectious potential of milk is required, and public education highlighting pasteurization of milk, particularly during outbreaks, could reduce the risk of RVFV direct infection. Regardless of public health risk, testing milk from animals could potentially be leveraged as a non-invasive surveillance method to monitor RVFV transmission levels and should be further assessed.

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GENOMIC EPIDEMIOLOGY OF CAMPYLOBACTER JEJUNI AND C. COLI ISOLATED FROM INDUSTRIAL AND HOUSEHOLD POULTRY IN IQUITOS, PERU

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Campylobacter is the leading cause of bacterial gastroenteritis in children living in LMICs. C. jejuni and C. coli are adapted to the avian gut, and poultry meat and by-products are the main source of Campylobacter related outbreaks in high-income countries. In LMICs, industrial poultry

production is rapidly increasing, as well as the unrestricted use of antibiotic within the system. In rural settings, the markets are also serviced by informal poultry production and backyard production. These non-industry poultry production streams are highly relevant activities given that small-scale backyard production provides a source of income and protein for low-resource households. The multiplicity of production scenarios and lack of regulatory practices are expected to contribute to important differences in the ecology, diversity and MDR risk of poultry derived human campylobacteriosis. Fecal samples from industrially produced chickens were sampled monthly 18 months. Fecal samples from backyard raised poultry were sampled as part of an ongoing cohort during the same time frame. All Campylobacter isolates were sequenced using Illumina short-read technology. Colonization heterogeneity, phylogeny and genomic determinants of AMR were assessed and compared between both production systems. A total of 200 isolates from backyard poultry 800 isolates from industrial poultry were sequenced. Campylobacter sequence types from industrial poultry were distinct from those of backyard poultry, with only few shared STs (such as ST 6091). Newly assigned ST such as ST-11957 - ST-11967 have not been isolated in other parts of the world, suggesting a unique ecology of C. jejuni and C. coli in poultry of the Peruvian Amazon. AMR was higher in industrially raised poultry. Phylogenetic comparisons and prevalence of resistance genes and point mutations are presented. These distinct characteristics of Campylobacter epidemiology in backyard and industrially produced poultry will impact source attribution models that estimate the risk of human disease, and as a result, intervention strategies to reduce the overall burden of Campylobacter.

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FACTORS ASSOCIATED AND PREVALENCE OF ABNORMALITIES OF VENTILATORY FUNCTION IN ATTÉCOUBÉ, ABIDJAN, CÔTE D'IVOIRE, JANUARY-FEBRUARY 2022

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Ventilatory function abnormalities are one of the causes of public health problems worldwide. In Côte d'Ivoire, the prevalence of respiratory diseases differs in the professional sector, in particular bakers, sales assistants/ cashiers, cleaners and administrative staff, respectively from 9.7%, 2.3%, 0.6% and 1.2%. This study aim to determine the prevalence of respiratory symptoms & ventilatory function abnormalities in the population of the lagoon district of Attécoubé in Abidjan, Côte d'Ivoire. A cross-sectional study with an analytical aim was conducted among 170 people in the town of Attécoubé lagune. A questionnaire set up on the Kobo collect tool relating to socio-demographic, environmental characteristics & respiratory symptoms was inspired by that of the American Thoracic Society (ATS). Pulmonary function tests were performed in the subjects investigated by baseline spirometry and a beta 2 mimetic test. Data analysis was done with Epi-Info software version 7.2.1. The study population was composed of 103 women and 67 men with a sex ratio (Male/Female) of 0.65. The average age was 35.92 years ± ET15.28. The most common respiratory symptoms were chest tightness (29.41%), dyspnea (28.82%), sneezing (22.94%).) & cough (22.35%). The prevalence of ventilatory function abnormalities was 43.24% among residents of Attécoubé lagune. The most common ventilatory function abnormality was ventilatory restriction (35.2%). Obstruction (4.85%) was the second ventilatory anomaly. The factor associated with abnormalities in ventilatory function was heavy pollution [OR=2.581; CI: 1.051 - 6.342; P=0.039]. Residents of the lagoon district of Attecoubé presented many respiratory symptoms & had a high prevalence of ventilatory function abnormalities. The associated factor was heavy pollution. Improving air quality is urgently needed in this municipality.

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LAND USE CHANGE DRIVES BAT ROOSTING ECOLOGY AND HUMAN-BAT FOOD COMPETITION ON CULTIVATED FOOD RESOURCES PROMOTES NIPAH VIRUS SPILLOVER TO HUMANS IN BANGLADESH

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Understanding the bat roosting and feeding ecology in rapidly changing landscape like Bangladesh is critical to design effective interventions of Nipah virus (NiV) spillover to humans. Hence, this study aimed to determine how land use change drives bat roosting ecology and human-bat food competition on cultivated food resources promotes viral transmission to humans in Bangladesh. We performed an ecological and qualitative survey in eight NiV outbreaks and non-outbreak districts in Bangladesh between 2021 and 2022. We conducted an observational study on bat roost ecological characteristics, human-bat interactions and 65 ethnographic interviews with fruit orchard owners, raw date palm sap (RDPS) harvesters, consumers, and bat hunters. We identified 61 bat roosts, 85.2% of which are within 30 meters of human dwellings and 14.8% near croplands and marketplaces. Domestic animals graze underneath 85% of bat roosts. 40% of the roosts were disturbed by roost tree cutting and hunting. Hunters hunt bats for their own protein needs, for sale, and for traditional medicinal purposes. The participants reported rapid conversion of forest areas to agricultural land, human settlements, and urbanization. People have planted more timber trees than fruits trees. The wild fruits trees are scarce in their communities. Consequently, bats are heavily dependent on human cultivated fruit resources and RDPS drinking and roosting close to human residences. Participants reported declining local bat populations due to hunting and ecological changes. People reported eating unwashed dropped fruits and bat bitten fruits and occasionally feed to their household animals. Orchard owners use mist net to protect bat visiting in their garden and bat entangled on net and died. The findings of the study highlight the significance of human-bat feeding competition on cultivated fruit resources in modified landscapes, as well as shared RDPS by bats and people, as critical pathways of NiV spillover in Bangladesh. We recommend future study on ecological and behavioral interventions to prevent bat borne viral spillover from bats to humans and domestic animals in Bangladesh.

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TUBERCULOSIS MORTALITY: A SCOPING REVIEW

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Tuberculosis (TB) has killed more people than any other infection and reducing deaths caused by tuberculosis is a United Nations priority. The aim of this scoping review is to describe and critically appraise the published literature concerning TB mortality. The PRISMA-ScR checklist was used. We systematically searched the PubMed database with the following search terms: "tuberculosis" AND ("death" OR "fatality" OR "mortality"). Eligibility criteria and categorisation were applied by three investigators using the Rayyan tool. Of 1730 articles found, 841 fulfilled the eligibility criteria, including 18 trials. There were far fewer publications concerning TB mortality than other similarly frequent causes of death, and other aspects of TB such as diagnosis or therapy. TB mortality publications principally originated in high-income countries, relatively neglecting countries where tuberculosis causes most deaths. Also, children were under-represented as the focus of only 4.3% of TB-mortality publications, much less than the 14% of tuberculosis deaths that occur in children. TB mortality publications

focused principally on: 38% (323/841) risk factors and scores, 35% (296/841) epidemiology, 7.7% (65/841) prevention, 4.4% (37/841) reviews, 4.3% (36/841) modeling studies, 4.3% (36/841) mechanisms of death, 3.0% (25/841) long-term mortality, and 2.7% (23/841) ascertainment. TB mortality prevention studies (n=63) principally concerned improving disease diagnosis (25%), treatment (60%), and healthcare systems (6%), versus only 2 studies addressing the more holistic aspects of tuberculosis care. Thus, TB mortality research should be prioritized to become more proportionate to other similarly frequent causes of mortality. Research equity should be increased by more appropriately including high burden countries, children and people who are not receiving tuberculosis treatment. TB mortality prevention research should include more trials and should have a more holistic focus in addition to the current almost total emphasis on biomedical diagnosis and treatment of their disease.

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DISPROPORTIONATE COVID-19 DISEASE SEVERITY AND MORTALITY IN A DIVERSE POPULATION OF HOSPITALIZED PATIENTS

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Limited data exist on the relationship between presenting symptoms, comorbidities, and the development of severe COVID-19 across hospitalization in diverse patient cohorts, despite COVID-19 tracking information highlighting disparities according to race/ethnicity. This observational study included all adult symptomatic COVID-19 patients (n=1319) admitted to the University of New Mexico Hospital from 3/2020 to 7/2021. Self-reported race/ethnicity, presenting symptoms, comorbidities, and clinical events were obtained by manual chart review and aggregate data queries. Severe COVID-19 included ICU admission and/or death during hospitalization, while non-severe cases survived without requiring ICU support. The distribution for the three primary racial/ethnic groups was: 39.8% American Indian/Alaska Native (AI/AN), 44.0% Hispanic, and 16.2% non-Hispanic White (NHW). The average age was 57.7±16.1 years, with 45.9% being female. Presenting symptoms differed among the groups with Hispanic patients having the highest proportion of nausea (P=0.015), vomiting (P=0.013), and headache (P=0.001). Altered mental status was most prevalent in the NHW group (P<0.001), while shortness of breath was highest in AI/AN (P=0.017). At admission, NHW patients had significantly more comorbidities, including hypertension (P<0.001), stroke (P<0.001), chronic obstructive pulmonary disease (P<0.001), hyperlipidemia (P<0.001), and hypothyroidism (P<0.001). During hospitalization, 839 patients had non-severe COVID-19 and 480 patients developed severe disease. The AI/AN group experienced higher rates of secondary bacterial pneumonia (P<0.001), acute respiratory distress syndrome (P=0.022), cardiac failure (P<0.001), and myocardial infarction (P<0.001), consistent with longer hospitalization. Logistic regression modeling revealed that AI/AN ancestry is a strong predictor of severe COVID-19 (OR=1.93, CI=1.23-3.02, P=0.004) and is associated with higher mortality (OR=1.74, CI=1.06-2.86, P=0.028). Interventions aimed at reducing COVID-19 disparities are critical for improved health outcomes in diverse communities.

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PREDICTORS OF DISPOSITION STATUS IN HOSPITALIZED COVID-19 PATIENTS IN DIVERSE POPULATIONS: A CURRENT AND FUTURE MODEL

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Following COVID-19 hospitalization in diverse populations, information remains limited about patient discharge status [i.e., home, skilled nursing facility (SNF), or death]. Such information is important since higher rates of hospitalization have been reported in some ethnic/racial groups. To foster improved preemptive care for current and future pandemics, a retrospective observational study on COVID-19 patients (n=1309) admitted to the University of New Mexico Hospital from 3/2020 to 7/2021 is presented. Self-reported race/ethnicity, vital signs, and clinical laboratory measures were captured within 48 hours of admission. Disposition status was determined upon discharge and categorized as (a) returning home: defined as discharged home, COVID isolation shelters, correctional facilities without the need for nursing care, and nursing homes; (b) skilled-nursing facility (SNF): defined as discharge to any facility that provided additional care; or (c) death: defined as mortality during hospitalization. Of the 1,309 patients included in the analyses, 777 (59.4%) patients were discharged home, 304 (23.2%) transitioned to SNF, and 228 (17.4%) died during hospitalization. Multinomial logistic regression analyses were performed using disposition status as the dependent variable with race/ethnicity (reference: non-Hispanic White), age, sex at birth, vital signs, and clinical laboratory parameters as the predictor variables. Factors associated with adverse disposition (i.e., SNF or mortality) included increased age, admission to ICU, and American Indian/Alaska Native ancestry. Higher levels of mean arterial pressure, platelets, hemoglobin, Ca2+, Cl-, CO2, albumin, and HbA1C were associated with home disposition status. Conversely, predictors of adverse disposition status included dysregulated kidney and liver function tests. These results demonstrate that clinical laboratory variables, as well as race/ethnicity and age are important predictors of disposition destination. As such, these factors can be taken into consideration when developing patient care plans to achieve the most favorable patient outcomes.

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CROSS SECTIONAL OBSERVATIONAL STUDY ON PERINATAL OUTCOMES AFTER SARS-COVID-2 VACCINATION DURING PREGNANCY IN TERTIARY CARE SETTING IN URBAN PUNE , INDIA

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The aim of present study was to assess perinatal outcomes after SARS-COVID-2 vaccination during pregnancy. This was a cross-sectional observational study conducted in tertiary care government hospital, in Pune (India). Delivery records for women admitted in delivery ward of the hospital were used to compare perinatal outcomes between vaccinated and unvaccinated women. Out of 510 participants enrolled in the study during February 2022 and May 2022, 281 (55.09%) women were immunized with at least 1st dose of their SARS COVID-2 vaccine while 229 (44.9%) were unvaccinated during their antenatal period. Of these 281 vaccinated women 140 (49.8%) women had completed both of their doses before their delivery and 141 (50.2%) women had received only 1st dose of vaccine in their antenatal period and their 2nd dose was scheduled after their

delivery. There was no significant difference observed in all other antenatal or delivery complications including SARS-CoV-2 infection (<2% in each group). Neonatal parameter low birth weight (LBW) had significant values in neonates whose mother have administered SARS COVID-2 vaccine during their pregnancy (OR 0.52, 95% CI 0.35 to 0.78 p=0.001). The rate of perinatal outcome like Still Birth (0.8 %), IUD (1.2%) and foetal distress (6.3%) were not different than the national averages in India also, there was no significant differences for those outcomes between vaccinated and unvaccinated compared groups. There was no significant difference observed for all other neonatal outcomes between both the groups. From the present study it can be concluded that SARS-COVID-2 vaccination during pregnancy was not associated with adverse perinatal outcomes. These observations may assist health care provider and pregnant women to make informed decision regarding administration of vaccine.

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WEIGHTED FIDELITY OF DELIVERY OF AN INTERVENTION IN THE HEALTH FACILITY: A CASE OF TUBERCULOSIS SCREENING AMONG HIV CLIENTS IN SELECTED HOSPITALS IN GHANA

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Fidelity assessment is essential in health intervention implementation. Studies have assessed fidelity separately; either healthcare provider or facility levels with managers. However, there might be variations in facility resources and their utilization, skewing such comparisons. We assessed weighted fidelity of implementing the TB screening guidelines among PLHIV and examine its effect on TB screening coverage in HIV clinics in Ghana. We used cross-sectional study with 226 HIV care providers, 27 managers of district hospitals implementing the TB screening intervention, and extracted information from TB registers monthly for 2018. Weighted fidelity was measured based on the extent to which the intervention was implemented, considering both the facility and the provider level assessments. Response scores and extracted data on fidelity were analyzed and summarized using the median and inter-quartile range for non-normal data such as fidelity scores and coverage and frequencies and percentages for categorical data such as resources availability. Linear regressions models were fitted for TB screening coverage using the fidelities separately. The study revealed that the weighted fidelity median score was 67% (IQR: 59.9 - 74.9%), and the TB screening coverage was 71.3% (IQR: 56.9 - 96.7). Weighted fidelity of delivery was statistically associated with TB screening coverage ($p<0.01$). All the moderating factors investigated have no statistical association with weighted fidelity of delivery ($p>0.05$) except for IE&C. Facilities with TB IE&C materials available had a significantly ($p=0.025$) higher median fidelity score 75.4% (74.9 - 88.5) than their counterparts 65.7% (59.4 - 72.6). The combined provider-facility level assessment of fidelity demonstrated that weighted fidelity of delivery is positively associated with TB screening coverage and provided a better platform for assessing implementation fidelity. It also showed that the availability of IE&C materials significantly moderates the weighted fidelity of delivery. Weighted fidelity is an efficient way of holistically assessing fidelity within health facilities.

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SURVEILLANCE OF INFLUENZA-LIKE ILLNESS AT THE US. MILITARY CAMP LEMONNIER, DJIBOUTI

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Respiratory tract infections are the most common cause of infection in adults, and influenza-like illness (ILI) accounts for most of these infections. From May 2021 till end of 2022, ILI surveillance was conducted at the U.S. military base Camp Lemonnier, located in Djibouti (CLDJ). 1332 NP/OP samples from both deployed U.S. military and civilians were collected and tested. Eligible cases were those matching the WHO case definition of 2014. Samples were tested using the Biofire® Film Array® with the Respiratory Panel 2.1 (RP2.1) assay. From the 1332 tested samples an etiology was identified in 869 (65.2%) samples. Co-infection with 2 pathogens was identified in 13/869 positive cases. Data showed that 492/1332 (36.9%) were positive for SARS-CoV-2 with 8/492 (1.6%) were co-infection with other respiratory virus. For Influenza A, 25/1332 (1.9%) were positive for A(Pdm09), 3/1332 (0.2%) were positive for A(H1N1), 33/1332 (2.5%) were positive for A(H3N2), and 1/33 (3%) was reported with co-infection with Human Rhinovirus. Influenza B was detected in 6/1332 (0.5%) of the tested samples. Other respiratory pathogens were detected including Human Rhinovirus 193/1332 (14.5%) of samples tested. Additionally, 10/193 (5.3%) of the Rhinovirus cases reported co-infection with another respiratory virus. Human Respiratory Syncytial Virus was detected in 17/1332 (1.3%) of the samples. Seasonal corona viruses, human para influenza viruses, Adeno virus and HMPV were also detected. While quite challenging to undertake accurate near real-time respiratory surveillance in deployed austere military settings, the importance of establishing an early warning system that would help in identifying pathogens of pandemic potentials is critical. Furthermore, this type of surveillance provides the necessary data for enhanced risk mitigation and improved force health protection. It also has the potential to both decrease disease non-battle injury, and aid in maintaining medical readiness of the warfighter that help break the chain of disease transmission, by further reducing the risk to the deployed forces stationed in Djibouti and the Horn of Africa.

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SENSITIVITY PROFILE OF FUNGAL PATHOGENS RESPONSIBLE FOR LOWER RESPIRATORY TRACT INFECTIONS IN YAOUNDE

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Respiratory tract infections are usually further classified as an upper respiratory tract infection (URI or URTI) or a lower respiratory tract infection (LRI or LRTI). LRIs are the leading cause of death among all infectious diseases. The objective of our study was to bring out the sensitivity profile of fungal pathogens responsible for lower respiratory tract infections in Yaounde. We carried out a transverse and descriptive study during a 6 month period. (February to June 2021), at the Jamot hospital in Yaounde. Included in this study were patients suffering from a LRI from whom the medical practitioner had requested a sputum or broncho alveolar liquid analysis. A macroscopic, microscopic, fungal culture of the sample was carried out and a germ tube test, fungal sensitivity test as well as specie identification using the ID 32 C gallery was carried out on the positive cultures. Statistical analysis was carried out using the R version 3.6.1software. The mean was calculated with the aid of the Kruskal Wallis rank sum test. 300 patients participated in this study. They had mean age ± standard deviation of 41.59 ± 17.5 years and extremities of 1 and 91years. The male /female ratio was 2:1 Fungal infection was positive in 127 patients (42.33 %), 75(59%) Candida albicans, 25 (19.68%) Cryptococcus humicola, 10 (7.87%) Candida tropicalis, 6 (4.72%) Candida krusei, 4(3.14%) Candida famata, 4 (3.14%) Candida sake and 3 (2.36%) Cryptococcus curvatus. As far as antifungigram is concerned, the total drug susceptibility was ; Nystatine (98.47%), Amphotericine B (86.91%), Miconazole (55.42%), Econazole (52.61%), Ketoconazole (52.57%) and Fluconazole (14.42%).The prevalence of fungal pathogens was 42.33%. Of the 300 pateints, 71 had tuberculosis, 24 were HIV positive and 6 were diabetic. We had 5 patients with HIV, tuberculosis and fungal co-infection, 16 with HIV and fungal co-infection and 6 with HIV and tuberculosis co-infection. This study shows a relative high prevalence (42.33%) of the colonisation of the respiratory tract by the above listed fungal pathogens. The drug of choice is Nystatine and Fluconazole presents a very limited activity.

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TUBERCULOSIS IS A GOOD POINT OF ENTRY FOR THE SCREENING OF CARDIOVASCULAR EVENT RISK FACTORS IN A LOW-MIDDLE-INCOME COUNTRY: LESSON LEARNED FROM INTEGRATED HEALTHCARE IN GABON

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Many Low-middle income countries currently experience an epidemiological transition including a double burden of infectious and non-communicable diseases. Gabon is a high-burden tuberculosis country and 46% of tuberculosis patients carried cardiovascular disease comorbidities. This study aimed to assess the prevalence of high and intermediate risk of developing cardiovascular events (coronary heart disease, stroke, peripheral arterial disease, aortic disease) in ten years in patients consulting for tuberculosis symptoms. We performed a cross-sectional analysis among adult patients with tuberculosis symptoms, consulting in the two referral hospitals in Moyen Ogooué region in Gabon between 2020 and 2022. The American, ASCVD (atherosclerotic cardiovascular disease) score was used to identify patients at high risk of developing cardiovascular events(CVE) in the next ten years. A total of 405 patients have been included, with 151 (37%) having pulmonary tuberculosis. The majority of patients were men (216;53%). More than half (277,68%) of patients leave in an urban area. HIV infection accounted for 29% (119). A total of 31 (7.7%) and 51 (13%) have a medical history of diabetes, and high blood pressure respectively. Overall, 6% and 14% of study patients were at High-risk and Intermediate risk of cardiovascular events in the next 10 years. Men (aOR 4.5, 95% CI 2.6-6.5), a medical history of diabetes (aOR 7.5, 95% CI 5.5-10.5) and a medical history of Hypertension (aOR 6.5, 95% CI 3.5-10.5) were significantly associated with a considerable risk of having a CVE. Four out of five patients with considerable risk of developing a CVE were newly diagnosed with diabetes or hypertension. In conclusion, there is an epidemiological transmission in Gabon. Four out of five patients who are at risk to have a CVE in the next ten years would be saved if there is integrated care for communicable and non-communicable diseases. High-burden and endemic infectious diseases such as tuberculosis could be a good point of entry for earlier diagnosis of CVE in many African countries.

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EFFECT OF POST PCV13 ON VACCINE TYPE INVASSIVE PNEUMOCOCCAL DISEASE AMONG CHILDREN IN RURAL GAMBIA

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Introduction of pneumococcal conjugate vaccines (PCVs) has reduced the incidence of vaccine-type (VT) invasive pneumococcal disease (IPD) but non-vaccine type (NVT) serotype replacement disease remains a concern. PCV7 was introduced for routine use in Gambia in 2009 but was replaced with PCV13 in 2011. We conducted standardised, population-based surveillance for suspected pneumonia, septicaemia, and meningitis amongst children aged 1-59 months in the Basse Health & Demographic Surveillance System (BHDSS) between May 12, 2008, and Dec 31, 2022. We count annual IPD case counts of hospitalised children aged 1-59 months. Invasive samples were collected and microbiologic and latex serotyping. Surveillance in 2019, 2020 and 2022 showed extremely low rates of VT IPD and moderate serotype replacement disease. Annual IPD case counts increase in non-VT IPD cases in 2019-2021 but reduced in 2022 as shown in Table 1. In 2019-2021, 10/33 non-VT IPD cases were caused by serotypes included in Pfizer's candidate PCV20 product (type 8 [n=1], 11A [n=1], 12F [n=6], 15B [n=2]). Eight years after the introduction of PCV13 use in The Gambia, serotype replacement disease was not a significant issue in IPD. However, more recent surveillance suggests that replacement disease may be developing in the under-5 year age group. Higher valency PCVs should be prioritised.

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THE ADDED VALUE OF USING PULSE OXIMETER ROUTINELY INTO THE INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESS GUIDELINES TO BETTER IDENTIFY AND MANAGE SEVERE CASES AMONG CHILDREN UNDER-5 YEARS OLD IN WEST AFRICA, JUNE 2021 TO JUNE 2022

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The Integrated Management of Childhood Illness (IMCI) guidelines for children under 5 is a symptom-based algorithm guiding health care workers at the primary health center (PHC) level in resource-limited countries. Hypoxemia is a life-threatening event often underdiagnosed clinically. The AIRE project, UNITAID-funded, has implemented the routine Pulse Oximeter (PO) use into IMCI consultations at PHCs in Burkina Faso, Guinea, Mali & Niger. We measured the added value of PO use as part of IMCI compared to IMCI alone to improve the diagnosis & care-management of hypoxemia at PHC level. In 16 AIRE PHC research sites (4/country), all children aged 0-59 months attending IMCI consultations, except those aged 2-59 months classified as green case without cough or breathing difficulties were eligible for PO use, and enrolled in a cross-sectional study with parental consent. Severe cases were followed-up during 14 days. From June 2021 to June 2022, 39,360 children attended IMCI consultations at the research PHCs, of whom 31,600 (80.2%) was eligible for PO use. Overall, 9,8% were identified as severe cases using IMCI alone (3,103/31,600; 95%CI: 9.5-10.2); & 60 cases newly identified using IMCI+PO. Prevalence of severe case using IMCI+PO was at 10% (3,103+60)/31,600; 95%CI: 9.7-10.3). Overall +1.9% (60/3,103; 95%CI: 1.5-2.5) were detected using PO alone. This added value was heterogeneous between countries: +0.9% (95%CI: 0.1-3.4), +0.3% (95%CI: 0.09-0.9), +3.2% (95%CI: 2.3-4.2), +2.9% (95%CI: 1.4-5.2), in BF, Guinea, Mali, Niger, respectively. Among the 60 additional severe cases identified only with PO, 27 were included & followed, 20 (74%) were transferred to district hospital but only 14 (52%) received an oxygen therapy. In conclusion, the added value of IMCI+PO was estimated globally to +2% to better identify severe cases, with a similar effect except in Guinea and Burkina Faso. Their appropriate management remains challenging for West African governments

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FINE-SCALE SPATIOTEMPORAL DYNAMICS OF SARS-COV-2 INTRODUCTION AND SPREAD IN NAIROBI COUNTY, KENYA

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus of coronavirus disease 2019 (COVID-19), is a highly transmissible virus that was first reported in Wuhan in December 2019 threatening human populations, health systems and economies worldwide. As of March 2023, Africa has reported over 12 million confirmed cases

of COVID-19 and over 200,000 deaths although this is likely to be major underreporting of actual cases and deaths. Kenya reported the first case of SARS-CoV-2 on the 13th of March 2020 comprising one the first SARS-CoV-2 introductions in Kenya. Thereafter additional introductions and intense within country transmission contributed to increase in the number of infections (n= 341,235) over multiple successful waves and reported mortalities (n= 5,684). Nairobi, East-Africa's largest City (population =4,397,073) covering an estimated 692 square Kilometres (2019 Census) was a major epicentre of COVID-19 cases in the country. In this study, we sequenced and analyzed 168 Real Time- Polymerase Chain Reaction (RT-PCR) positive samples selected based on PCR cycle threshold score (&lt30). The samples were collected from seventeen sub-counties in Nairobi County between April 2020 and January 2022, yielding 141 sequences suitable for phylogenetic analysis to provide the region's fine-scale genomic epidemiology of SARS-CoV-2. Full genome sequencing was carried out using Oxford Nanopore Technologies (ONT) GridION machine. The sequence reads were assembled using the ARTIC bioinformatics pipeline. Sequence quality checks and mutation calling were performed using NextClade and then lineage analysis with Pangolin v4.0.6. The sequences were aligned using Nextalign version 1.4.1, and the phylogenetic and phylogeographic analyses performed. We describe the clustering patterns of the different SARS-CoV- 2 variants found in the different Nairobi sub-counties, the transmission patterns of the strains within the sub-counties and the impact of the containment measures on the spread on SARS-CoV-2 in Nairobi. The study is part of the strategy to develop a COVID-19 genomic surveillance system for the country.

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SCALING RISK FOR A GLOBAL TUBERCULOSIS PROGRAM IN AN OIL AND GAS COMPANY

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Workers in high-risk tuberculosis (TB) locations with incidence of more than 20 active cases per 100,000 per year may be at an increased risk for TB infection. This risk is greater in congregate settings (i.e., camps, offshore rigs, and vessels) with a mix of people from high and low endemic areas. To safeguard workers assigned to sites in high-risk settings, ExxonMobil requires enrollment of such workers in the company TB Control Program which consists of awareness, screening, and case/contact management. Screening includes annual questionnaire and testing with a skin test or preferably a blood test using Interferon Gamma Release Assays (T-SPOT or QuantiFERON). Chest X-rays are accepted as an indicator of no active pulmonary TB in specific situations. World Health Organization (WHO) estimated that a third of the world's population had latent tuberculosis infection (LTBI), with low rates in countries like the US at 4.7% but much higher in countries with higher TB incidence. These rates are reflective of what is seen in workplace screening and guidance is provided based on national program guidelines for LTBI. The critical objective of the workplace program is to have zero transmission at the workplace. During the past 12 years of implementation, over 100 active TB cases were diagnosed among our workers. They were all promptly identified and treated with no reported workplace TB transmission, following contact tracing. In 2021, WHO updated its guidance on systematic screening for tuberculosis. We used this to review our TB program including consultations with external experts and company executives. As a result, we adopted a more fit for risk TB screening approach by updating its periodicity from annual to every two years for offshore, mobile assets and onshore congregate settings in high-risk locations. Offshore fixed sites in areas with low risk discontinued the screening. The program guidance was updated, and communications with roll out completion are expected by end of 2023. In conclusion, using a risk-based approach for our TB program, we have an improved fit for risk screening guidance that amplifies efficiencies and maintains effectiveness.

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INVESTIGATION OF SUSPECTED PULMONARY TUBERCULOSIS CASES IN KATIALI IN THE DIANRA HEALTH DISTRICT, CÔTE D'IVOIRE, JUNE 2021

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On June 10, 2021, the health district of Dianra notified the epidemiological surveillance service of the National Institute of Public Hygiene four suspected cases of pulmonary tuberculosis residing in the village of Katiali located at 7 km from the district. We conducted an investigation to confirm the disease & to implement control and prevention measures. We conducted a descriptive cross-sectional study from June 23 to 26, 2021, in the village of Katiali with an estimated population of 719 in 2020. A suspected case was defined as any person in Katiali with a cough lasting more than 14 days, whether or not associated with any of the following signs: fever in the evening or afternoon; sweating at night; intense fatigue; lack of appetite; weight loss or weight loss; cessation of menstruation without pregnancy in women of childbearing age, between 18 March and 10 June 2021. A confirmed case was defined as any suspected case with a positive laboratory result for BAAR by microscopy or Xpert MTB/RIF test. Proportions and ratio were calculated by using Epiinfo 7. 12 suspected cases were recorded andone was confirmed with pulmonary tuberculosis for a positivity rate of 8.3%. The median age was 7 years (1-46). The sex ratio was 0.5 male for 1 female. The confirmed case was a 7-year-old girl, in a household of 3 members. 16 contacts of the confirmed case were identified & followed up, of which six (37.5%) tested negative by microscopy,eight contacts(50%) were not tested due to difficult of sampling collection and 2 were positive (12.5%). The confirmed case were isolated and treated with antituberculosis drugs & the close contacts under 5 years of age were put on isoniazid prophylaxis. A young girl was confirmed for pulmonary tuberculosis and two other additional contacts. The isolation of the confirmed case, its management, the prophylaxis of the contacts and their follow-up allowed limiting the spread of tuberculosis in Katiali. We recommend strengthening the technical platform of the general hospital of Dianra for early detection of tuberculosis; enhance testing capacities & sensitizing the community to massively adhere to the extended vaccination program.

7091

PRE-CLINICAL VALIDATION STUDIES OF NOVEL POINT-OF-CARE RNA TEST FOR COVID-19 DIAGNOSIS AND UTILITY FOR SARS-COV-2 GENOMIC SURVEILLANCE IN GHANA

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Rapid public health response to identify local and imported COVID-19 cases will need cost-effective RNA amplification tests with comparable sensitivity as PCR but without the requirements for expensive equipment. To fill this need, we developed ZIP-CoVx-P2 (zip-test), a CE-certified SARS-CoV-2 RNA test, integrated into a portable isothermal device, for COVID-19 diagnosis at the Point-of-Care, with a 30 mins sample-to-results capability. A pre-clinical trial (ACTRN12623000066684) was conducted to validate the zip-test performance in field settings, and to assess its integrability into SARS-CoV-2 genomic surveillance programs in Ghana. This report discusses the trial implementation, study demographics and preliminary test performance. From Oct-Dec 2022, we conducted a multi-site prospective cross-sectional survey to enrol, and collect two oropharyngeal/nasal swabs and clinical data from 1,000 consented participants residing in

12 communities in Greater Accra and Central regions of Ghana. Where permitted and within biosafety limits, zip-testing was performed on site, else the swabs were transported to COVID-19 testing laboratory for zip-testing followed by RT-PCR confirmation. Positive test samples were further processed for sequencing. Demographically, 92.8% of the participants were above 18 yrs and 60.5% were females. Additionally, 55.0% reportedly received ≥ 1 dose of a COVID-19 vaccine, and 73.5% reported having no COVID-19 symptoms. Among suspected cases (26.5%), fever, cough and head were the most reported symptoms (>54%), with 67.8% of these cases reportedly confirmed COVID-19-positive by RAT/PCR test. Using the zip-test, the overall positivity rate among 980 study samples was 15.5%, with 13.6% giving positive tests for the two SARS-CoV-2 targets - orf1ab and M genes. RT-PCR testing (ongoing) on the paired study samples will be used to determine sensitivity and specificity of the zip-test but the positivity rates in our study population are comparable to the mean 12% positivity rate reported by the Ghana Health Services in August 2022. The zip-test presents prospects for COVID-19 diagnosis at the Point-of-Care.

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A CASE OF TUBERCULOSIS PERICARDITIS

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Tuberculosis pericarditis is one of the most critical complications in 1-2% of patients with pulmonary tuberculosis infection. The pathophysiology of Tuberculosis pericarditis occurs by extension of infection from the lung or tracheobronchial tree adjacent to lymph nodes, spine, or miliary spread. Pericardiectomy and abscess drainage are effective surgical procedures for managing disseminated tuberculosis with complications such as pericarditis and abscess formation. A 7-year-old male child presents to Adama Hospital with a persistent dry cough for a week and fever. Later patient's condition worsened with dyspnea at rest and orthopnea. The patient was evaluated, and the initial vital signs were BP: 118/74 PR: 138 BPM, T: 38c Sap02: 96% RR: 40-45, weight: 24kg. Physical examination showed accessory muscles use, coarse crackles over the right lung, and hepatomegaly. Lab work showed a white blood count of 24x10^3/uL with 13% lymphocytes, hemoglobin count of 10.0g/dl, and no parasite on the blood film. Abdominal and chest ultrasound revealed complex pericardial collection, bilateral pleural effusion, and ascites. An echocardiogram showed an extensive exudative pericardial collection with internal pericardial thickening. Due to worsening respiratory distress, the patient was transferred to the ICU. Ceftriaxone, Vancomycin, Azithromycin, prednisolone, and anti-TB medications were initiated along with intranasal oxygen. The patient was suspected of having severe community-acquired pneumonia and cardiac tamponade secondary to disseminated TB. Pericardiocentesis and thoracentesis were noted with pus-containing fluid, but the culture was inconclusive. Despite pericardiocentesis, ultrasound still revealed pericardial fluid accumulation, necessitating pericardiostomy, and abscess drainage. The patient was hospitalized for 42 days and was discharged with outpatient anti-TB treatment; currently in stable condition. This care demonstrates the importance of prompt and accurate diagnosis and treatment of disseminated TB- related pericardial effusion in improving patient outcomes in developing countries.

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SCHISTOTRACK: A COMMUNITY-BASED, PROSPECTIVE COHORT IN RURAL UGANDA TO EXAMINE CAUSES OF PERIPORTAL FIBROSIS ASSOCIATED WITH INTESTINAL SCHISTOSOMIASIS

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Periportal fibrosis is a severe morbidity associated with intestinal schistosomiasis, including Schistosoma mansoni and S. japonicum. These parasitic blood flukes live in the mesenteric venules. The eggs produced by mature female flukes must traverse the intestinal mucosa to be excreted. Only ~50% of the eggs are successfully excreted with the remaining eggs being swept back into the liver and spleen. The inflammation, granulomas, and subsequent fibrosis in and around the portal veins contributes to vascular restructuring within the liver and distinct patterns of fibrosis associated with intestinal schistosomiasis. Understanding the risk factors and predictors of progression within and across individuals is challenging due to imperfect diagnostics, confounders of ongoing treatment, and interacting co-infections within the liver. SchistoTrack is a community-based, prospective cohort in three rural districts of Eastern and Western Uganda that aims to assess the within and across individual causes of periportal fibrosis. Nearly ~4000 individuals randomly sampled from 2080 households in 52 rural villages are being followed over five years with detailed clinical examinations and a further ~6000 individuals are assessed through medical histories. This talk will introduce the SchistoTrack Cohort and share findings on the risk factors for periportal fibrosis, focusing on the challenges of developing clinical phenotypes within the context of a cohort and on the contributions of coinfections with hepatitis B, malaria, and HIV for predicting the likelihood of periportal fibrosis.

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NAVIGATING BARRIERS TO CREATING AWARENESS OF FEMALE GENITAL SCHISTOSOMIASIS IN GHANA-CASE STUDY IN THE CENTRAL REGION OF GHANA

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The prevalence of Female Genital Schistosomiasis (FGS) in Sub-Saharan Africa is staggering, with an estimated 56 million women and girls affected by this condition.FGS occurs when the female genital tract is infected with a parasitic worm.The symptoms of FGS include bleeding and lower abdominal pain.The situation is particularly dire in Ntroanoa, a community in Cape Coast located in the central region of Ghana, where girls and women are living with FGS.This community has freshwater source and that puts members at risk of exposure to the snail vector.However, little is known about FGS in the community. Significant barriers to raising awareness about FGS include stigmatization,perception of members, and health-seeking behavior.Identifying community members who had seen their symptomatic relations becoming asymptomatic after adhering to treatment for FGS played a key role. Members started opening up for treatment.Targeted educational programs is so crucial due to the complex social dynamics at play in affected communities.This can be accomplished through increased investment in education and training programs for healthcare providers and targeted awareness campaigns.Ultimately, the key to ending the neglect of FGS lies in our collective commitment to raise awareness and support those who are affected by this devastating condition.

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THE MEASURING OF TREATMENT COVERAGE AS COMPARED TO ADMINISTRATIVE COVERAGE FOR SCHISTOSOMIASIS WITH PREVENTIVE CHEMOTHERAPY IN BONG, LOFA, AND NIMBA COUNTIES IN 2018 IN LIBERIA

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Schistosomiasis or Bilharzia is a parasitic disease caused by infection with the trematode blood-flukes schistosomes. There are two major forms of human schistosomiasis that occur in Sub-Saharan Africa, which include intestinal schistosomiasis caused by Schistosoma mansoni infection and urinary schistosomiasis due to Schistosoma haematobium infection. Schistosomiasis is among the neglected tropical diseases (NTDs), which remain one of the serious public health problems, posing unacceptable threats to human health where there is a high prevalence of the disease. The World Health Assembly Resolution 54.19 urges all member states to regularly treat at least 75% of all school-aged children who are at risk of morbidity. To determine if these global goals are being reached, each

national program routinely reports administrative drug coverage from the annual mass drug administration. In order to monitor and support the NTDs program performance, independent drug coverage surveys are recommended by the World Health Organization to compare the administrative coverage and an independent survey coverage to validate the reported coverage by the national program for control and elimination. The result of the survey assists in the identification of recommended actions to improve program delivery. The aim of the coverage survey was to evaluate the effectiveness of preventive chemotherapy in reaching the targeted population in endemic counties. The survey was based on the SCH data collected during the 2012 baseline survey in the 15 counties in Liberia. During the surveys, the total number of children interviewed was 651 while the number of adults was 1023. The survey contains 14 villages per county (42 in total) and 15 households per village. The PZQ coverage for SAC and adults was 75% while the administrative coverage was 76% which shows the validity of the data.

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MAPPING THE TRANSMISSION DYNAMICS OF SCHISTOSOMIASIS: INSIGHTS FOR CONTROL AND ELIMINATION STRATEGIES

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Schistosomiasis (SCH), is a parasitic infection caused by several species of flatworms or blood flukes of the genus Schistosoma. While several species of freshwater snails are the intermediate host, the infection are transmitted to humans. SCH is a neglected tropical disease prevalent in tropical countries and estimated to affect more than 200 million people worldwide. Nigeria accounts for over 25% of the global burden of schistosomiasis, with an estimated 29 million people infected. SCH is endemic in the 36 States and Federal Capital Territory (FCT) in Nigeria. The results of the epidemiological baseline survey conducted in FCT showed prevalence ranging from 7%-52%. Mass administration of medicine (MAM) using Praziquantel commenced in FCT in 2014.In 2020, an outbreak of SCH was reported in some communities in AMAC, Gwagwalada and Bwari area councils (ACs) thus, prompting a new round of survey to: validate the claim of the outbreak, determine the current prevalence and endemicity of SCH in the reported communities and provide data for informed decision making on the appropriate intervention strategy. A purposive sampling of 26 communities across AMAC, Gwagwalada and Bwari ACs were conducted. About fifty-five children and adults were systematically and conveniently sampled respectively in each community. Urine samples collected from selected school children were examined in the laboratory for Schistosome eggs using urine filtration technique; while stool samples were examined for parasite eggs using the Kato-Katz technique. A total of 2,364 participants were sampled. The mean prevalence were 27.7%, 8.9% and 26.4% in AMAC, Bwari and Gwagwalada ACs respectively. Community prevalence ranged from as high as 64% to as low as 2.1. While the result revealed marginal reduction of prevalence in Gwagwalada, more effort is required to reduce SCH prevalence in AMAC and Bwari ACs. This is a pointer that MAM alone cannot halt interruption of transmission. There is cogent need for prioritization and integration of Water Sanitation and Hygiene Services and investment in snail intermediate hosts control if we are to achieve the 2030 NTDs elimination goals.

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COMPARATIVE GENOMIC EVOLUTIONARY ANALYSIS OF BIOMPHALARIA SUDANICA, A NEGLECTED INTERMEDIATE HOST VECTOR OF SCHISTOSOMIASIS

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Biomphalaria sudanica is a major vector host of Schistosoma mansoni in the highly endemic African Great Lakes region, notably the largest transmission sites where current snail control methods are impractical to apply. New targets for vector control and reducing transmission of schistosomes to humans, perhaps through utilizing natural resistance mechanisms in snails, may provide approaches that are scalable to these vast transmission sites. Here, we report the first genomic and transcriptomic characterization of B. sudanica, providing a foundation for understanding the biology of this species and evolutionary history of this important group of vectors. Our PacBio genome assembly size of 946.6 Mb for B. sudanica, is larger than other Biomphalaria species and is comprised of 23,598 genes representing a close to complete genome annotation for Mollusca. Gene family expansion/contraction analysis (genetically orthologous relationships estimated in Phylogenetically Hierarchical Orthogroups) show a clear trend toward the simplification of the genome of several species of Biomphalaria, and phylogenetic analysis of specific genes of interest support the phylogenetic position of B. sudanica as diverging more recently relative to B. pfeifferi after colonization of Africa several million years ago. Intraspecies nucleotide diversity was calculated through the sequencing and alignment of four additional genomes of B. sudanica isolates. The resulting alignment was used to search for molecular signatures of balancing selection, that may be the result of host-pathogen coevolution and therefore present in immune genes. Our bioinformatic pipeline identified 1,047 of the top most diverse genes, ~25% of which were broadly immune related genes (AIG molecules, lectins, redox proteins, TLRs) and orthologs to gene families conferring resistance to S. mansoni in closely related B. glabrata (PTC1, PTC2, FREPs, SOD, Biomphalysin). These results illuminate the complexity and diversity of snail molecular biology which underlies their interaction with schistosomes and the transmission of these parasites.

7098

RE-ASSESSING THERMAL SENSITIVITY OF SCHISTOSOMIASIS TRANSMISSION RATES IN THE ERA OF CLIMATE CHANGE: EVIDENCE OF A HIGHER THERMAL OPTIMUM THAN PREVIOUSLY PREDICTED

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The geographical range and seasonal transmission risk for schistosomiasis is affected by the ecology of schistosome parasites and their obligate host snails, and their response to temperature. Previous thermal sensitive models predicted optimal transmission at 21.7 °C, which is at odds with field observations of disease prevalence in sub-Saharan Africa where schistosomiasis is endemic. We performed an extensive literature search and identified the most comprehensive set, up to date, of experimental studies reporting the effect of temperature on physiological and epidemiological parameters regulating the dynamics of the free-living stages of S. mansoni and S. haematobium and of their corresponding host snails, i.e., Biomphalaria and Bulinus spp, respectively. We used empirically derived nonlinear thermal responses fitted on these data to parameterize a mechanistic, process-based model of schistosomiasis dynamics, and re-casted the basic reproduction number, long-term mean parasite burden and prevalence of infection in the human population as a function of temperature. By resampling experimental data to account for uncertainty in model parameters' thermal response, we found that thermal optimum ranges between 23.1-27.3°C for S. mansoni and 23.6-27.9°C, in both cases at significantly higher temperature than previously determined. A large data set on schistosomiasis prevalence in Africa validates our model projections. Using these more accurate nonlinear thermal-response models will improve our understanding of the effects of current and future temperature regimes on schistosomiasis transmission risk under climate change scenarios.

7099

USING WHO SCHISTOSOMIASIS COMMUNITY DATA COLLECTION FORM TO IDENTIFY FACTORS CONTRIBUTING TO HIGH PREVALENCE IN MALI

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Baseline mapping conducted in 2004 showed that schistosomiasis (SCH) was endemic in all 75 health districts (HD) in Mali. Impact surveys conducted from 2014 - 2018 in 46 HDs showed that mass drug administration (MDA) with praziquantel was still needed according to World Health Organization (WHO) guidelines. To avoid over- or under-treatment in HDs, Mali was one of the first countries to implement MDA at the sub-district level in 2020, as recommended by WHO, to ensure the treatment strategy appropriately reflected the epidemiological situation. In 2021, the National Schistosomiasis and Helminthiasis Control Program (NSHCP) used the community-level schistosomiasis endemicity data collection form made available to the NSHCP from ESPEN/WHO to update SCH endemicity at the sub-district level, which are health areas (HAs) in Mali, and re-categorized them according to the WHO treatment decision tree: "0" non- (0% prevalence), "1" low- (<10% prevalence), "2" moderate- (10-49.9% prevalence), and "3" high-endemicity (≥50% prevalence). Health center directors completed the form at a SCH data review workshop with the NSHCP and national and international experts. Out of 1,510 HAs categorized, 20.6% (311/1,510) were classified as high prevalence. A logistic model was constructed to identify environmental and behavioral factors influencing high prevalence in HAs. Environmental and behavioral factors associated with high prevalence were the presence of irrigation canals [OR=3.88, 95% CI (2.88 - 5.22)], rice fields [OR=2.2, 95% CI (1. 65 - 2.93)], ponds as a water supply source [OR=1.84, 95% CI (1.42 - 2.36)], agriculture activities [OR=4.22, 95% CI (3 - 5.94)] and fishing activities [OR=1.61, 95% CI (1.25 - 2.07)]. These risk factors were identified as being statistically associated with high SCH prevalence. These results will allow the NSHCP to better direct community dialogue activities and messages to influence behavior change, which will complement other SCH control and elimination interventions in Mali.

7100

SCHISTOSOMA OCCUPATIONAL EXPOSURE RISK IN RICE FIELDS IN THE SENEGAL RIVER BASIN

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Schistosomiasis is a debilitating disease caused by parasitic waterborne trematodes and is the second most devastating parasitic disease worldwide. Schistosoma mansoni and Schistosoma haematobium, transmitted by freshwater molluscoid hosts, account for almost all human infections in West Africa. The distribution of exposure risk in the Senegal River Basin has predominately focused on river and lake water bodies where communities may come into contact with infectious forms of S. mansoni and S. haematobium. Rice-farmers face an additional occupation exposure to freshwater in irrigation canals and rice fields; however, less is known about the biology of host snails and exposure risks to humans in these systems. The first step in understanding the occupational risk was to establish the presence of host snails shedding Schistosoma cercariae (stage infectious to humans) in rice fields and irrigation canals. Rice fields and canals were tested using a combination of sweep net and baited snail traps. We tested fields and canals of four villages in the Saint-Louis and Richard Toll region of Senegal from May 2022-March 2023. Testing at the end of the rice field season before harvest, identified host snails in 90.9% (n=10/11) of paired fields and canals tested and schistosome-infected snails in 27.3% (n=3/11) of these sites. There was temporal variability in the risk of infection to humans, measured by the cercarial output of host snails. At the end of the rice field season, from the site with maximal host snail abundance across seasons, the 14 infected Bulinus snails (n=370 total snails) shed a total of 83 S. haematobium cercariae in 1 hour shedding trials. At the start of the growing season at the same site, the 13 infected Biomphalaria snails (n=74) and the 24 infected Bulinus snails (n=90) shed 216 S. mansoni cercariae and 178 S. haematobium cercariae, respectively. These results show Schistosoma occupational exposure risk to rice farmers across the rice seasons and will be used to inform future intervention work targeting snail populations.

7101

BARRIERS TO FEMALE GENITAL SCHISTOSOMIASIS CARE MANAGEMENT IN NIGERIA: COMMUNITY MEMBERS AND HEALTH WORKERS PERSPECTIVES

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Female Genital Schistosomiasis (FGS) poses a major threat to the schistosomiasis elimination agenda in developing countries including Nigeria. FGS is a complication of urogenital schistosomiasis in females caused by Schistosoma haematobium, FGS symptoms are often confused for sexually transmitted infections. It is estimated to affect more than 56 million women and girls in Africa. There is no specific guideline for FGS treatment and management in Nigeria's schistosomiasis control programme, due to dearth of evidence around the barriers to treatment for persons affected. Using a cross-sectional study design with a mixed method approach, investigation will examine the prevalence of FGS among girls and women (>15 years) in twenty endemic communities in two

Nigerian States. Urine samples will be collected from 500 participants and examined for S. haematobium by microscopy. All consenting adult women will receive gynaecological investigation by colposcopy, assessing for and classifying lesions according to the WHO (World Health Organization) FGS pocket atlas. Focus group discussions will be conducted with select females and health workers to assess the various barriers to FGS related care seeking. Quantitative and qualitative data will be analyzed using Stata 16 and Nvivo 12, respectively. Our findings will describe the experiences, barriers, and facilitators associated with accessing FGS care from affected females and health workers in the communities. Reports will also provide insights into the burden and spotlight challenges and experiences specific to females and health workers in FGS endemic communities of Nigeria. Findings will encapsulate participants' indigenous recommendation to guide future intervention design, progressing towards FGS management guidelines for Nigeria. The reported prevalence and narratives of experience by affected persons as well as the health workers will provide a trajectory for policy. Data will be finalized by mid-July and preliminary findings available for dissemination August 2023.

7102

A SURFING PARASITE: HOW SCHISTOSOME CERCARIAE COUPLE TO INTERFACIAL BOUNDARIES TO EXTEND DISPERSION AND DISEASE SPREAD

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Schistosomiasis remains a persistent public health concern despite mass drug administration efforts, highlighting the importance of understanding the biophysical mechanisms contributing to infection risk upon contact with contaminated water. Schistosome cercariae exhibit a unique swimming behavior, characterized by active upward swimming and passive vertical sinking. In this study, we report a previously unrecognized swimming mode, termed "surface swimming," wherein cercariae swim laterally directly beneath the air-water interface. To accurately characterize cercarial swimming motion, we developed portable microscopes using modified low-cost action cameras, enabling us to examine their behavior in both laboratory settings and natural environments in Senegal, encompassing 3D spaces with water flows, vegetation and wind. Furthermore, we modeled the swimming hydrodynamics of cercariae using a linkage model and derived the swimming efficiency as a function of ecological parameters such as viscosity and surface tension. We demonstrate that surface swimming enables efficient active lateral displacement of the parasite and facilitates long-distance passive travel through wind-driven water surface flows, both of which being important factors determining the local concentration of parasites near potential human hosts within a water body. Our findings emphasize the significance the cercarial swimming behavior in the context of schistosomiasis infection and provide crucial insights for assessing risks and devising effective environmental interventions.

7103

INVESTIGATING THE PRESENCE OF SALMONELLA SPP. IN LOCALLY MADE CHEESE IN MONTERÍA, CORDOBA, COLOMBIA IN 2021

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Fresh coastal cheese is a fundamental part of the diet of the population of Cordoba, Colombia. However, there is a concern about the presence of Salmonella spp. in artisanal cheese, which can pose a public health risk. This study aims to detect, isolate, and characterize Salmonella spp. in fresh artisanal cheese sold in Montería, the capital of Cordoba, using the method suggested by INVIMA (National Institute of Food and Drug Surveillance, 2021) and evaluate its resistance or susceptibility to specific antibiotics. This study is a descriptive exploratory cross-sectional study that took place in Montería, Cordoba, during the first quarter of 2021. A total of 25 retail outlets were selected from the list provided by the Health Department of Cordoba.The INVIMA method was used for the isolation and identification of Salmonella spp. The black colonies suspected of Salmonella spp. were identified using conventional biochemical tests. Serological identification was performed using the Kauffman-White scheme. The sensitivity or resistance to specific antibiotics was determined using the agar diffusion method, following the international standards set by the CLSI in 2008. Out of the 75 samples analyzed, 18 (24%) showed growth of black colonies, which were classified as suspected for Salmonella spp. The results of this study indicate the presence of Salmonella spp. in fresh artisanal cheese sold in Montería, Cordoba, Colombia. This study revealed the resistance of Salmonella spp. to specific antibiotics, namely amikacin (62.5%) and gentamicin (15%). In conclusion, the study highlights the need for measures to control the production and sale of fresh artisanal cheese to prevent the transmission of Salmonella spp. to humans. The findings of the study can provide valuable information to public health authorities and policymakers to design appropriate interventions to control the transmission of Salmonella spp. through fresh artisanal cheese.

7104

IMPACT OF THE WASH IN SCHOOLS FOR EVERYONE (WISE) PROGRAMME ON THE HEALTH AND SCHOOL ATTENDANCE OF KINDERGARTENERS IN ADDIS ABABA, ETHIOPIA: A CLUSTER-RANDOMISED CONTROLLED TRIAL

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Water, sanitation and hygiene (WASH) interventions in schools (WinS) have been proposed to reduce morbidity in schoolchildren, including gastrointestinal and respiratory infection, and improve school attendance. However, evidence of the impact of WinS interventions on pupil health and educational outcomes has been mixed. We evaluated the WASH in Schools for Everyone (WISE) programme implemented by US-based NGO Splash in partnership with the Government of Ethiopia, which aims to achieve universal WASH coverage in schools in Addis Ababa, Ethiopia over a five-year period. Within the context of a cluster-randomised trial assessing intervention impacts on primary school-aged children (WISE evaluation), we conducted a sub-study to specifically assess impacts on kindergarten (KG) pupils. We included schools enrolled in the main trial with KG classes and randomly selected and allocated additional schools with KG classes until 20 in total were each enrolled in the intervention and control arms. Schools were randomly assigned 1:1 to receive the intervention during the 2021/22 academic year or the following year (waitlist control). The intervention comprised WASH infrastructure improvements, including water storage and filtration, drinking water / handwashing stations and upgraded sanitation facilities, and behaviour change promotion. Within each participating school, we randomly selected 20 KG pupils (ages 3 - 6), and recorded caregiver-reported diarrhoea, respiratory illness and school absence over four consecutive weekly telephone interviews with caregivers of selected pupils between April and June 2022. We found consistent reductions in caregiver-reported diarrhoea, respiratory illness and absence, although only reduction in absence was significant at the 5% level (OR: 0.67, 95% CI: 0.46, 0.99). Dropout of three schools and the considerable challenges of telephone-based data collection resulted in large losses to follow-up, impacting statistical power. Further research should examine how the use of mobile health technology can be improved to obtain sufficient follow-up data for evaluating school-based interventions.

7105

ASSESSMENT OF KNOWLEDGE ATTITUDES AND PRACTICE KAP OF HAND WASHING HYGIENE AND THE ROLE OF PREVENTION PROJECT OF INFECTION CONTROL, GEZIRA STATE, SUDAN 2022

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Infection due to hand-transmitted microbes is considered as dangerous problem worldwide. Most infections today thought to be transmitted by hands particularly the school aged children in Gezira state. The application of hand hygiene in Gezira villages is too poor with prevalence of infectious diseases in Gezira .The aim of study is to assess knowledge, attitude and practice regarding hand hygiene practices among schools' children before and after extensive intervention program ,and to identify areas of gaps in their knowledge and attitude.This is KAP study ,a three months study period from August until December 2022 in alhafayer village . The study composed of three phases-initial assessment -The intervention-Post interventions assessment,The intervention program depend on the health education and practical skills teaching (hand washing techniques) to school children and to Their family's at school and home.Their level of knowledge was assessed based on the hand hygiene by self-designed knowledge questionnaire and then assessed by direct case presented to village health center .A total 239 respondents were studied about their knowledge and attitude towards hand hygiene practices. The KAP score change is generally optimistic. First,knowledge improved by about 80% to reach about 92%in study pupils, followed by an improvement in attitude of about 85% to reach 100% in study pupils, and finally, practice improved by about 74 percent to reach 98 percent in study pupils.Most of them practice and know the international hand washing technique with soap and water from(3%to74%). The majority of the respondents accept the training sessions regarding hand hygiene practices (81%). Decrease hospitalization, which is due to infectious disease (80%to 38%). The majority of the students learned the importance of infection control by hand washing (27%to95%). Present study highlights the need of extensive interventional programs regarding hand hygiene practices among the primary school students to provide the current knowledge in the area with behavioral change in attitudes and practices to reduction of infection and effective control.

7106

USE OF ENRICHMENT MNGS METHOD TO IDENTIFY RESPIRATORY PATHOGENS IN WASTEWATER FROM TREATMENT PLANT LOCATION IN SALVADOR, BAHIA, BRAZIL

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Wastewater-based epidemiology has emerged as a promising tool for pathogen monitoring, including the detection of endemic microbes and the identification of outbreaks earlier than clinical surveillance. This allows for timely interventions to prevent disease spread and reduce healthcare burdens. Additionally, frequent sampling can provide a comprehensive picture of disease spread, which can guide public health decision-making for intervention, control, and prevention of respiratory pathogen outbreaks. In this study, we aimed to evaluate the use of mNGS for wastewater-based surveillance to detect and monitor the circulation of pathogens in a population. Starting in March 2022, sewage samples were collected for six months from ten treatment plant locations in the city of Salvador, Bahia, Brazil, for respiratory pathogen surveillance. The genetic material of each sample was extracted followed by sequencing using the Respiratory Pathogen ID/AMR (RPIP) method (Illumina, Inc.). The generated data were analyzed using CZID platform to identify the circulating pathogens. The most frequent pathogenic bacterial identified at a genus level in all sewage locations and at most evaluated time points were: Acinetobacter, Citrobacter, Enterococcus, Escherichia, Enterobacterium, Klebsiella, Moraxella, Pseudomonas, Salmonella and Streptococcus. Vibrio cholerae was identified in two locations and at two time points calling attention to monitoring the possible emergence of this infection. The only pathogenic virus identified was HHV-4 in one location and time point. RPIP sequencing also revealed the prevalence of various types of antimicrobial resistance genes (AMR) demonstrating the antibiotic profile of the population. Our findings provide valuable insights into the potential of wastewater-based surveillance as a complementary tool for respiratory pathogen surveillance, which could help inform public health decision-making and support outbreak control efforts.

7107

CHOLERA OUTBREAK IN THE MIFI HEALTH DISTRICT OF CAMEROON, A CASE-CONTROL STUDY, JULY 2022

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Since 2018, Cameroon has experienced a resurgence of cholera epidemics. On May 18th, 2022, four cholera cases were confirmed in the Mifi Health District (MHD). By July 5th, there were 82 cases in 14 out of 20 health areas (HAs) of the district and the case fatality rate (CFR) was 3.7%. We conducted an investigation to identify cholera risk factors and evaluate the cholera surveillance system (SS) in the MHD. We conducted a 1:2 matched case-control study in the MHD in July 2022. Cases were patients with acute watery diarrhea having an epidemiological link with a confirmed case from May 5th to July 12th, 2022, or who were positive on culture. We identified cases by reviewing registers in health facilities and from the regional line list. We selected controls in cases' neighborhoods. We collected data using a semi-structured questionnaire and analyzed it using Epi info. We evaluated the SS using the CDC updated guidelines. We identified 172 cases in 15 HAs. Kouogouo (41/172, 24%), Famla (35/172, 20%), and Djeleng (26/172, 15%) were the most affected HAs. The median age of cases was 32 years (4 months – 85 years) and for controls was 31 years (4 months – 87 years). The attack rate was 0.39%, and CFR was 2.33% (4/172). Drinking untreated water (OR=13.1; 95% CI:2.3-75.1) and not washing hands with soap (OR=4.7; 95% CI:1.6-13.7) were identified as risk factors. Among staff, 83% (24/29) mastered cholera case definitions and found notification forms easy to fill. Notification forms were available in 28% (8/24) health facilities, and 89% (26/29) of staff considered cholera surveillance part of their routine activities. The cholera epidemic in the MHD affected 75% of HAs. Drinking untreated water and poor hand hygiene were associated with cholera. The SS was acceptable, simple, unstable, and not sensitive. Sensitizing the population on water purification and hand hygiene could limit the spread of cholera.

7108

CONTROLLED BEFORE-AND-AFTER STUDY OF A MULTI-MODAL HAND HYGIENE INTERVENTION IN HEALTHCARE FACILITIES IN CAMBODIA

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Hand hygiene (HH) is a critical component of infection prevention and control in healthcare facilities. However, intervention models to improve HH behavior in low resource settings are limited. Building on previous learnings from Cambodia, we adapted and tested a multimodal intervention

to improve HH among healthcare workers (HCW) during childbirth in referral hospitals in Kampong Cham Province, Cambodia. The intervention included a low-dose high-frequency participatory training, installation of HH facilities, visual cues and nudges, and a system of peer support among midwives. The intervention was tested in a controlled before-and-after study (3 intervention facilities, 3 control) and lasted approximately 4 months. Across the study period we observed 92 births for a total of 801 events requiring aseptic technique (hands washed with soap, clean gloves worn, and potential recontamination avoided). HH of HCWs was classified at each event into three categories: adequate HH (aseptic technique maintained), inadequate HH (clean gloves worn, but hands not washed with soap), or HH invalidated. In control facilities, at baseline, only 12% of all observed aseptic procedures were conducted with adequate HH, dropping to 8% at endline; 21% were performed with inadequate HH at baseline, increasing to 23% by endline. In intervention facilities, 5% of all observed aseptic procedures were conducted with adequate HH, increasing to 13% at endline; 32% were performed with inadequate HH at baseline, which dropped to 22% at endline. In a differences-in-differences logistic regression model, after controlling for repeated observations on the same mother and shift time of HCWs, the odds that a HCW would perform an aseptic procedure under adequate HH was 5.3 times higher in intervention facilities compared to control facilities [CI 1.20-23.62; p=0.028]. Although absolute improvement in adequate HH was low, the observed effect suggests the potential for a multimodal behavior change intervention to improve HH among HCWs. Forthcoming analyses will explore how sequencing of aseptic events and additional factors are associated with adequate HH in this context.

7109

FACTORS INFLUENCING HOUSEHOLD WASH PRACTICES

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Healthy WASH behaviors are key to reducing the burden of childhood diarrheal disease, which in Nigeria remains a leading cause of child mortality. Lack of WASH infrastructure is a serious hurdle; however, low utilization of improved water and sanitation sources poses a significant threat to improving child health outcomes through WASH interventions. In Nigeria, particularly in the northwest region, use of improved WASH is low among households, and there is conflicting evidence regarding the relative importance of different factors driving healthy WASH practices. Literature reviews have indicated that WASH behavior change models overemphasize psychosocial factors, neglecting environmental context and technological features of WASH infrastructure; other studies indicate that psychosocial factors indeed play a larger role in behavior change and contextual factors contribute very little. Undoubtedly, WASH behaviors are multidimensional and there is sparse information on potential behavioral determinants within the northwestern Nigerian context. Therefore, this study examines a spectrum of contextual, psychosocial, and technological factors quantifying their association with using improved water sources and sanitation facilities. Data were collected in September 2019 using an interviewer-administered, cross-sectional survey. A stratified, multi-stage sampling strategy targeted pregnant women and non-pregnant women with a child under two years. Respondents were asked about access to WASH resources and WASH practices, prevalent cases of under-two diarrhea, and diarrhea-associated ideations. Crude bivariate estimates are calculated for the water and sanitation outcomes over each contextual, psychosocial, and technological factor. Mixed-effects logistic regression models are used to identify potential determinants of health WASH practices. The results of this study could have important implications for the programmatic development of WASH interventions by informing behavior change strategies for the northwestern region of Nigeria, particularly among households with children under two years.

7110

BEHAVIORAL DETERMINANTS OF ARSENIC-SAFE WATER USE AMONG GREAT PLAINS INDIAN NATION PRIVATE WELL USERS: RESULTS FROM THE COMMUNITY-LED STRONG HEART WATER STUDY PROGRAM

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The objective of this study was to evaluate the behavioral determinants associated with exclusive use of arsenic-safe water in the Strong Heart Water Study (SHWS) program. The SHWS is a randomized controlled trial designed to reduce arsenic exposure among private well users in American Indian Great Plains communities. All households received point-of-use arsenic filters at baseline and were followed for 2 years. Behavioral determinants selected were those targeted during the development of the SHWS, and were assessed at baseline and follow-up. Exclusive use of arsenic-safe water for drinking and cooking at follow-up was associated with higher self-efficacy for accessing local resources to learn about arsenic (OR: 5.19, 95% CI: 1.48-18.2) and higher self-efficacy to resolve challenges related to water arsenic using local resources (OR: 3.11, 95% CI: 1.11-8.17). Higher commitment to use the arsenic filter faucet at baseline was a significant predictor of exclusive arsenic-safe water use for drinking (OR: 32.6, 95% CI: 1.42-746.7) and cooking (OR: 15.90, 95% CI: 1.33-189.5) at follow-up. Over the study period, the SHWS significantly increased perceived vulnerability to arsenic exposure, self-efficacy, descriptive norms, and injunctive norms. Changing one's arsenic filter cartridge after installation was associated with higher self-efficacy to obtain arsenic-safe water for drinking (OR: 6.22, 95% CI: 1.33-29.1) and cooking (OR: 10.65, 95% CI: 2.48-45.68) and higher perceived vulnerability of personal health effects (OR: 7.79, 95% CI: 1.17-52.0) from drinking arsenic-unsafe water. The SHWS conducted a theory-driven approach for intervention development and evaluation that allowed for behavioral determinants to be identified that were associated with the use of arsenic-safe water and changing one's arsenic filter cartridge. These results demonstrate that theory-driven, context-specific formative research can influence behavior change interventions to reduce water arsenic exposure. The SHWS can serve as a model for the design of theory-driven intervention approaches that engage communities to reduce arsenic exposure.

7111

MICROPLASTICS EXPOSURE AND THEIR ASSOCIATION WITH DIARRHOEA, GROWTH, AND DEVELOPMENT OF CHILDREN IN MALI

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Micro- and nanoplastics (MnP) are omnipresent in the natural and urban environment. Despite progress in identifying MnP pollution sources, as well as its presence in water, drinking water, food and soils, the accumulation and exposure by people, consequences for health effects have not been

explored epidemiologically or for childhood diseases. Prior literature indicates the ingestion of MnP by the adult body, and into the gut has a correlation to cause gut inflammation in relation to MnP concentration found in stool. Our study aims to explore this further, by assessing MnP in drinking water and from the stool of children aged 6-36 months in Mali. We are also examining the presence of any geographical gradient (regional, urban vs rural). Cross-sectional random samples from children's drinking water (n=110) and stools (n=100) were taken from children (6-36months) who were sampled in 60 urban and 60 rural communities during the baseline data collection of the MaaCiwara 120 cluster RCT. Fluorescence microscopy and Raman spectroscopy were conducted to identify and quantify MnP abundance, size and polymer type, respectively. Preliminary results show that MnP are detected in both water (>90%) and stool in Mali (>60%). Water samples indicate an increased level of MP in urban areas with a higher frequency of fibre-type MnP found. In stool both fibre and fragments are found, with abundant polymer types identified as: Polyvinyl Chloride (PVC), Polyethylene terephthalate (PET) and Polyamide (PA). Our results highlight that MnP pollution is prevalent in drinking water and stool. Further findings and implications to health are to be presented at the conference. Presence of MnP in young children's drinking water and stool is of concern, warranting further investigation at larger scale.

7112

BEHAVIORAL AND ENVIRONMENTAL FACTORS ASSOCIATED WITH SELF-REPORTED DIARRHEA AND ENTERIC PATHOGEN DETECTION IN INFANTS DISCOVERED BY COMPARING HOUSEHOLD CLUSTERS WITH DISTINCT LIVING CONDITIONS

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Designing effective strategies to prevent enteric infections in disease endemic populations is challenging due to the diverse viral, bacterial, and parasitic pathogen species transmitted by multiple host species through many interconnected transmission pathways. This study used data from the Safe Start cluster randomized controlled trial in Kisumu, Kenya to examine how household environmental and behavioral conditions influenced self-reported 7-day diarrhea and the detection of enteric pathogens in feces for enrolled infants. Correlation between exposure conditions and between pathogens in infant feces was common, so latent class analysis (LCA) was used to identify 5 distinct Clusters of participants who shared similar living conditions to each other. Correlation in pathogen detection, measured using a 19-pathogen molecular diagnostic tool, was examined as species diversity in feces at 6 and 9 month age timepoints. After adjusting for intervention effects, logistic regression analysis of 7-day diarrhea in infants between Cluster groups showed that diarrhea was significantly less likely at both 6 and 9 months of age for Clusters 1, 2, and 5 compared to Cluster 3, which had the lowest frequency of food-related handwashing. Regression comparisons of pathogen diversity in infants by Cluster identified Cluster 4 as having significantly higher rates of pathogen diversity compared to other Clusters at 6 months age, although these differences disappeared by 9 months age. Norovirus GII and typical Enteropathogenic E. coli contributed most to pathogen diversity at 6 months of age. Cluster 4 was unique from other Clusters in having the highest numbers of households using unimproved latrines, owning domestic animals, living on dirt floors, using water and pasteurized cow milk for infant feeding, and low rates of handwashing after defecation. Results suggest that in high transmission environments improving food-related handwashing behaviors may be effective for reducing diarrhea burden in infants but reducing infection rates may require comprehensive upgrades of multiple living conditions and hygiene behaviors in targeted households.

7113

EARLY LIFE DIETARY SUPPLEMENTATION OF PROBIOTICS AND SYNBIOTICS IMPROVES GUT HEALTH AND REDUCES SYSTEMIC INFLAMMATION AMONG INFANTS IN WESTERN KENYA: AN OPEN-LABEL RANDOMIZED CONTROLLED TRIAL

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Malnutrition remains persistent and common in resource-poor countries, particularly amongst under-fives. Modulating the developing gut microbiome by targeting environmental enteric dysfunction, may offer an additional intervention to improve gut health, nutrition and growth. We undertook a head-to-head comparison of 3 different multi-strain, high-dose preparations of live bifidobacteria and lactobacilli (pro/synbiotic), in an open-label, 4-arm, randomized controlled trial among infants in western Kenya, to test whether they would reduce systemic inflammation and improve gut health in infants exposed to poor sanitation and hygiene and at risk of growth faltering. We enrolled 600 newborns < 4 days old from Homa Bay County Teaching and Referral Hospital, between October 2020 and January 2022. They were randomly allocated, stratified by HIV exposure, in a 1:1:1:1 ratio to receive either Labinic synbiotic, Lab4b synbiotic, Lab4b probiotic given daily for ten days and then weekly until six months of age or no supplement. At 6 weeks, 3 and 6 months, we assessed biomarkers of systemic inflammation, gut health and growth in blood and stool. Plasma α1-acid glycoprotein, (AGP) [primary outcome], a marker of chronic systemic inflammation, increased progressively at 3 and 6 months among the controls. However, this was almost completely abrogated in each of the intervention arms ($p<0.001$). At 6 months, plasma AGP was raised (>1g/L) in 56/134 (41.8%) infants in the control arm but in <1.5% infants in each of the intervention arms ($P<0.001$). Similarly, other biomarkers of systemic and gut inflammation, intestinal permeability and mucosal damage were significantly increased at 3 and/or 6 months among the controls ($P<0.001$). Growth hormones (plasma insulin-like growth factor-1 and IGF binding protein 3) were significantly lower in the controls at 6 months ($P<0.05$). Raised systemic inflammation in the control babies was associated with more leaky guts, intestinal mucosal damage and gut inflammation. Pro/synbiotics offer a novel approach to improving gut health and reducing systemic inflammation in young infants in limited resource settings.

7114

TARGETING INFLAMMATION IN CHILDHOOD MALNUTRITION: A RANDOMIZED CONTROLLED CLINICAL TRIAL OF ADDITION OF FISH OIL TO THE STANDARD OF CARE NUTRITIONAL INTERVENTION

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Systemic inflammation and impaired intestinal barrier function contribute to the pathogenesis of malnutrition. Lipid (energy)-dense supplements are commonly used to treat malnutrition, but they are rich in pro-inflammatory omega-6 (n-6) fatty acids (FA). We hypothesized that adding anti-inflammatory n-3 FA (fish oil) to the standard nutritional intervention could reduce malnutrition-associated inflammation. We conducted a double-blind, randomized, controlled trial among children 9-24 months of age with moderate acute malnutrition (MAM), living in Kibera slums,

Nairobi. Children with MAM were randomized to receive a 12-week daily supplement of either Corn-Soy flour Blend (CSB) with soybean oil plus an additional 2 mL of fish oil (1136 mg total n-3) (n=40) or CSB with soybean oil (standard-of-care) plus an additional 2 mL of soybean oil (n=40; CSB-VO). A convenience sample of 20 healthy controls was also evaluated. The primary endpoint was a change in markers of inflammation and intestinal barrier function. Secondary endpoints included growth recovery and plasma n-3 FA concentrations. Growth recovery by 12 weeks was >92% in both study arms. Comparison of serum inflammatory markers at the end of the treatment to baseline (pre-intervention) showed that IL-1b, LPS binding protein, lipocalin, CXCL1, and CXCL2 were significantly reduced after the intervention. There was also post-intervention improvement in markers of intestinal barrier function, including soluble CD14 ($p<0.0001$), intestinal FA binding protein ($p<0.05$), and bacterial LPS ($p<0.0001$). Plasma FA analysis revealed that children with MAM had lower levels of plasma total n-3 FAs and a lower n-3/n-6 ratio compared to healthy controls ($p<0.001$). Children from both study arms fully and equally recovered from the n-3 deficiency after the nutritional intervention. Recovery from MAM led to less inflammation, improved intestinal barrier, and normalization of plasma n-3 levels. However, improvement was not enhanced by supplemental fish oil, suggesting that the soybean oil supplies adequate precursor FA substrates for endogenous synthesis of long-chain n-3 FAs.

7115

CHILD STUNTING FROM BIRTH TO AGE TWO: A LONGITUDINAL COHORT STUDY IN AMHARA, ETHIOPIA

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The Sustainable Development Goals set out an ambitious goal to end all forms of malnutrition by 2030. Although there has been a reduction in stunting (length-for-age Z score <-2SD), the prevalence of malnutrition in Ethiopia is still high. To improve nutritional outcomes, accurate data are needed to determine key time points for child growth, vulnerabilities and potential for recovery. The Birhan maternal and child health cohort in Amhara, Ethiopia, enrolled children between December 2018 and November 2020, and followed them through age 2. On scheduled visits at home and in health facilities, children's lengths were measured and recorded to the nearest 0.1 cm. We investigated the burden, incidence and reversal of stunting at birth, four weeks, six, 12 and 24 months. We enrolled 4,354 children under the age of two, among which 3,961 (91.0%) had their length measured at least once and were included in this study. Our findings indicate that median population-level length in this population is consistently below global standards from birth to age two. Growth velocity was slowest compared to global standards during the neonatal period and after children reached six months of age. The observed prevalence of stunting was 16.5% at birth and highest at age two (57.9%). Among all newborns who were not stunted at birth, 24% developed stunting within the first month of life. The incidence of stunting increased over time and was highest between the ages of 12 to 24 months (52.4%) followed by the 6 to 12 months period (32.6%). Rates of stunting reversal were highest between the ages of birth to six months. Among children who were already stunted at birth and thus had a chance to reverse stunting later in life, 65.4% were able to do so by 6 months of life and 58.3% reversed by the end of the first year of life. Overall, the evidence from this study highlights a dynamic process of incidence and reversal resulting in a chronically malnourished population with much of the burden driven by growth faltering during the neonatal periods as well as after 6 months of age. To end all forms of malnutrition, growth faltering in populations such as that in young children in Ethiopia needs to be addressed.

7116

MICRONUTRIENT STATUS DURING PREGNANCY IS ASSOCIATED WITH YOUNG CHILD TELOMERE LENGTH

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Antenatal nutrition, cortisol, inflammation, and estriol may impact child telomere length (TL) and health. In rural Bangladesh, we explored associations between these antenatal factors and child TL. In the WASH Benefits trial, maternal nutrition status (vitamin D, iron (ferritin and soluble transferrin receptor), and vitamin A (retinol-binding protein (RBP)); inflammation (C-reactive protein, alpha-1-acid glycoprotein, and 13 additional cytokines), and morning cortisol and estriol were analyzed during the first two trimesters. Children's whole blood relative TL was measured at Year 1 (age 14 months) and Year 2 (age 28 months) using qPCR. We estimated associations using generalized additive models, adjusting for potential confounders, reporting estimated mean differences between the 75th and 25th percentiles of each exposure distribution. Telomeres were analyzed from 466 children at Year 1, 515 children at Year 2, and 403 children between Years 1 and 2. Maternal vitamin A deficiency (RBP < 0.70 µmol/L) during pregnancy was not significantly associated with child TL at Year 1 (adjusted difference: -0.42 z-score of T/S ratio, 95% CI: -1.17, 0.33), significantly associated with child TL at Year 2 in the same direction (adjusted difference: -0.75, 95% CI: -1.42, -0.09), and not significantly associated with change in TL between Years 1 and 2 (adjusted difference: -0.54, 95% CI: -1.35, 0.27). Higher vitamin D levels (nmol/L) were associated with less TL lengthening from Years 1 to 2 (adjusted difference: -0.49, 95% CI: -0.96, -0.02). We found no associations between iron status, cortisol, estriol, CRP, AGP, or cytokines and TL nor change in TL. These results suggest a potential association between vitamin A and vitamin D status during pregnancy and subsequent child TL. Because of increased cell division during the postnatal period, maternal vitamin A and D levels could affect children's TL dynamics and long-term health.

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MICRONUTRIENT STATUS DURING PREGNANCY IS ASSOCIATED WITH CHILD IMMUNE STATUS IN RURAL BANGLADESH

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Poor immune function increases children's risk of infection and mortality. Several maternal factors during pregnancy may affect infant immune function during the postnatal period. We conducted observational analyses within the WASH Benefits Bangladesh randomized controlled trial. We measured biomarkers in 575 pregnant women and postnatally in their children. Maternal biomarkers measured during the first and second trimester of pregnancy included: nutrition status via vitamin D (25-hydroxy-D [25(OH)D]), ferritin, soluble transferrin receptor (sTfR), retinol binding protein (RBP); cortisol; estriol. Immune markers were assessed in pregnant women at enrollment and their children at ages 14 and 28 months, including: C-reactive protein (CRP), alpha-1-acid glycoprotein (AGP), and thirteen cytokines (including IFN-γ). We generated a standardized sum score of log-transformed cytokines. We analyzed IFN-γ individually because it is a critical immunoregulatory cytokine. All outcomes were pre-specified. We used generalized additive models and reported the mean difference and 95% confidence intervals at the 25th and 75th percentiles of exposure distribution. At child age 14 months, concentrations of maternal RBP were inversely associated with the cytokine sum score in children (-0.34 adjusted difference between the 25th and 75th percentile [95% confidence interval -0.61, -0.07]), and maternal vitamin A deficiency was positively associated with the cytokine sum score in children (1.02 [0.13, 1.92]). At child age 28 months, maternal RBP was positively associated with IFN-γ in children (0.07 [0.01, 0.14]) while maternal vitamin A deficiency was negatively associated with child AGP (-0.07 [-0.13, -0.02]). Maternal iron deficiency was associated with higher AGP levels in children at age 14 months (0.13 [0.04, 0.23]), and maternal sTfR concentrations were positively associated with child CRP levels at age 28 months (0.18 [0, 0.36]). Maternal deficiencies in vitamin A or iron during the first two trimesters of pregnancy may shape the trajectory of child immune status.

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SEROPREVALENCE FOR NOVEL ORAL POLIOVIRUS VACCINE TYPE 2 (NOPV2) FOLLOWING OUTBREAK RESPONSE IN LIBERIA: FINDINGS, IMPLICATIONS AND FUTURE DIRECTIONS

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Liberia recorded its first circulating vaccine-derived poliovirus type 2 (cVDPV2) isolates from environmental surveillance (ES) in December 2020. Two months later, the country declared Public Health Emergency (PHE). As a rapid response strategy, two nationwide supplementary immunization activities (SIA) rounds with Novel Oral Poliovirus Vaccine Type 2 (nOPV2) were conducted in March and May 2021. As such, there was a critical need to determine the effectiveness of nOPV2 delivered during the outbreak response campaigns to induce protection against poliovirus serotype 2. The primary objective of the study was to measure seroprevalence against type 2 poliovirus in children 0-59 months residing in areas targeted by two nOPV2 outbreak response campaigns in Liberia. We conducted a clustered cross-sectional seroprevalence study in 3 of 4 regions of the country since the 4th region was impassable. A child was enrolled per household and appropriate informed consents obtained. If there were more than 1 eligible children per household, simple random sampling was performed for enrollment. Trained health and non-health personnel were recruited and further trained to administer the survey and collect dry blood spots (DBS), respectively. Administrative and ethical approvals were obtained from the Ministry of Health (MoH) and appropriate ethical committees. We screened 511 eligible children, enrolled 500 to administer the survey, collect DBS and conduct the laboratory serology, with 436 samples included in the final analysis. After two rounds of nOPV2 campaigns in Liberia, the seroprevalence in children aged 0-59 months against serotype 2 poliovirus was about 38% and there was no significant differences between type 2 seroprevalence in children who reportedly received two doses of nOPV2 (43%), one dose of nOPV2 (36%), or no doses (38%). We report the first study to assess the seroprevalence of nOPV2 received through outbreak response campaigns in potentially naïve children in Africa. We recommend that future studies be conducted to further explore the determinants that affect antibody response to nOPV2 administered during outbreaks.

7120

GENOMIC SURVEILLANCE OF TRICLABENDAZOLE RESISTANCE IN FASCIOLA HEPATICA

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Triclabendazole (TCBZ) is the most effective medication to treat fascioliasis, a globally distributed foodborne parasitic zoonosis caused by Fasciola hepatica. The emergence of wide-spread resistance (TCBZ-R) in livestock and a rapid rise in resistant infections in humans threatens our ability to control the disease. Alterations in drug metabolism/efflux have been postulated as resistance mechanisms, however those studies did not consider the population genetic and phenotypic variations, resulting in partial/inconsistent results. To understand the genetic basis of TCBZ-R and to facilitate the development of approaches for molecular surveillance, we whole-genome sequenced (17 Gb per sample) and analyzed 99 TCBZ sensitive (TCBZ-S) and 210 TCBZ-R field isolates (Cusco, Peru), resulting in 42.5 million SNPs. There was little genetic structuring (FST < 0.001) between samples from different collection sites and between samples with divergent TCBZ sensitivity, suggesting panmixia. Positive Tajima's D values (~0.65) were observed, consistent with recent population contractions in the region. Autozygosity levels of Peruvian isolates were lower than those from UK and Uruguay, suggesting a higher outcrossing rate. Genomic regions of high differentiation (FST) were identified, representing the top 0.15% outlier by genome length (1.8 Mb). These candidate loci under TCBZ selection overlapped with 25 protein-coding genes, including EGFR-mTOR-S6K pathway genes (EGFR, REPS, SIK3, LAMTOR, and S6K) and genes involved in microtubule function, either as physical binding partners (CEP120 and DNAH) or as modification enzymes (KTNA1 and UCH). The S6K pathway contributes to cell survival under stressed condition and promotes tubulin acetylation that can protect microtubules from treatments with depolymerizing drugs. Differentiation of TCBZ-S and -R parasite was

achieved with >97% accuracy using ~100 SNPs. Our data suggest that TCBZ-R is a polygenic trait, and provide valuable resources for developing a genetics-based resistance surveillance for sustainable control.

7121

NATURAL VARIATION IN A PARASITIC FLATWORM ION CHANNEL UNDERPINS DIFFERENTIAL SENSITIVITY OF PARASITES TO PRAZIQUANTEL

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The drug praziquantel (PZQ) is the primary treatment for infections caused by parasitic flatworms. A target for PZQ was recently identified in schistosomes, a transient receptor potential ion channel in the melastatin subfamily (TRPMPZQ); however, little is known about the properties of TRPMPZQ in other flatworms. TRPMPZQ orthologs were scrutinized in all currently available parasitic flatworm genomes and functionally profiled. TRPMPZQ is present in all parasitic flatworms, and the consensus PZQ binding site is well conserved. Three loci of variation were identified across the parasitic flatworm TRPMPZQ pocketome, including an acidic residue in the TRP domain that acts as a gatekeeper residue impacting PZQ residency within the TRPMPZQ ligand binding pocket. Functional profiling of trematode, cestode, and free-living flatworm TRPMPZQ orthologs revealed differing sensitives to PZQ, matching the varied sensitivities of flatworms to PZQ documented clinically. In trematodes and cyclophyllidean cestodes, which display high sensitivity to PZQ, the gatekeeper TRP domain residue is an aspartic acid, allowing for nanomolar activation by PZQ. However, the presence of a glutamic acid residue, found in pseudophyllidean cestode TRPMPZQ, was associated with lower PZQ potency. Functional profiling of a pseudophyllidean channel revealed micromolar potency of PZQ at Spirometra erinaceieuropaei TRPMPZQ. The definition of these different binding pocket architectures explains why PZQ shows high therapeutic efficacy against specific fluke and tapeworm infections. Effort to identify new therapeutics that tolerate this TRP domain residue would be immensely valuable if analogous variation were to ever occur in natural trematode populations, and for the development of targeted therapies towards specific infections.

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CHARACTERIZATION OF AN ENDOGENOUS ION CHANNEL ACTIVATED BY PRAZIQUANTEL WITHIN A LIVE, ADULT SCHISTOSOME

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Praziquantel (PZQ) serves as the main clinical treatment for schistosomiasis, and other infections caused by parasitic flatworms. PZQ causes a rapid, spastic contraction of schistosomes ex vivo that results from PZQ action on a parasite transient receptor potential ion channel known as TRPMPZQ. While the properties of TRPMPZQ have been characterized following expression of this parasite ion channel in mammalian cells, whether a similar endogenous conductance is activated by PZQ in the intact worm is unresolved. No recordings of endogenous currents evoked by PZQ in schistosomes have been reported. Here, we identify and characterize endogenous single channel responses evoked by PZQ within a living schistosome worm. Electrophysiological recording from neuronal structures in immobilized male, adult worms revealed PZQ-evoked single channel fluctuations. No channel activity was observed in the absence of PZQ. PZQ-evoked single channel activity was also resolved on the background of endogenous current oscillations in worms that displayed rhythmic contractions. PZQ-evoked single channel activity was observed at both positive and negative voltages without rapid desensitization. The slope of the linear current-voltage relationship for the inward current was 135±10pS in worms bathed in Hanks' balanced salt solution containing 20mM HEPES and 10μM PZQ. The recording pipette solution contained cesium (140mM CsMeSO3, 10mM HEPES, 1mM EGTA, pH 7.4). This value is consistent with the conductance of Schistosoma mansoni TRPMPZQ (112±12pS) in the same buffer measured after heterologous expression of in mammalian cells. Substitution of recording solutions with different ionic buffers resulted in similar changes in the conductance of PZQ-evoked responses in intact worms as seen with heterologously expressed TRPMPZQ channels. Similar conductance shifts were also observed in situ and in vitro with different TRPMPZQ agonists. We therefore resolve for the first time the properties of an endogenous ion channel activated by PZQ within a live adult schistosome, and the properties of this ion channel are consistent the properties of TRPMPZQ in vitro.

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CHROMOSOME LEVEL ASSEMBLY OF BAYLISASCARIS PROCYONIS GENOME

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Baylisascaris procyonis, the racoon roundworm, is a zoonotic nematode causing a visceral larval migrans syndrome complicated by severe neurological manifestations that oftentimes are fatal. Despite the severity associated with human infection, little understanding of the molecular nature of this parasite is available nor has there been a full-length genome assembled. To this end, nanopore long-read sequencing was employed to generate a chromosome level genome assembly of B. procyonis. Roadside racoon carrion was dissected to obtain B. procyonis females. The uteri of these females were removed, and eggs allowed to embryonate in culture after which in vitro hatching led to the production of viable L3 larvae. High molecular weight (HMW) DNA was extracted from these L3 larvae, and 2 sequencing rounds were performed. The first used the MinION sequencer with an ultra-high molecular weight (UHMW) protocol; the second used the PromethION platform with a nanopore ligation sequencing kit. Basecalling was conducted with Guppy, and assemblies were created using Flye, SMARTdenovo, Shasta, and Canu. Assembly contiguity was improved with Purge Haplotigs and Quickmerge, and 3 rounds of Pilon polishing was performed. The final assembly comprised 51 contigs. The B. procyonis assembled genome has a total length of ~250MB organized. The assembly has an N50 of 7,029,608, and a GC content of 37%. Repetitive sequences, as identified by RepeatModeler and RepeatMasker, composed 6% of the total nucleotide content and 5' and 3' telomeric sequences could be identified. We identified ~19,000 genes with the Braker2 annotation pipeline that incorporated transcriptomic data obtained from RNAseq on the L3s and the adults. This resulting genome will support further investigation into host-pathogen interactions and expand the capacity of metagenomic diagnostics to detect B. procyonis in clinical cases.

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A UNIVERSAL METABARCODING PIPELINE AND HOST SIGNAL REDUCTION METHOD FOR CHARACTERIZATION OF VERTEBRATE SYMBIONT/PARASITE ASSEMBLAGES

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Our understanding of host-associated bacterial, archaeal, and fungal communities far exceeds our understanding of eukaryotic symbiont/parasite communities. Whereas metabarcoding of prokaryotes and fungi are commonplace, no single method for eukaryotic symbiont/

parasite metabarcoding has been adopted due to issues with primer complementarity and high off-target read abundance. We assessed published eukaryotic symbiont/parasite metabarcoding protocols and created new primers to recognize all symbionts/parasites of vertebrates. In silico PCR and single organism PCR of published primer sets (n = 22) alongside our new primers (n = 4) showed that only our new primers successfully amplified all clades of symbionts/parasites and had the highest overall taxonomic coverage. We then created a novel mock community standard of 16 cloned parasite DNAs and used it to show that one of our new primer sets more closely recovered the underlying community than any other. When applied to human (n = 12) and nonhuman primate (n = 40) clinical samples, our new protocol (Vertebrate Eukaryotic endoSymbiont and Parasite Analysis, or VESPA) outperformed the "gold standard" method of microscopy, with 51.3 % of identifications made by VESPA alone. VESPA identified taxa not found with microscopy, resolved a cryptic species complex not resolved by microscopy, and revealed greater prevalence and richness of parasitic organisms than microscopy. To reduce off-target PCR amplification, we designed a novel CRISPR-Cas9 based method that selectively digests host DNA. When applied to blood and tissue samples, our method resulted in a mean 92 % decrease in host read abundance compared to no treatment, a 61 % decrease compared to the most commonly published blocking method, and allowed for detection of hemoparasite infections that would otherwise have been missed.

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THE PROGNOSTIC POTENTIAL OF BIOMARKERS ASSOCIATED WITH FILARIAL LYMPHEDEMA DEVELOPMENT

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Lymphatic Filariasis causes chronic morbidity, which usually manifests as lymphedema (LE) or hydrocele. MDA to control LF infection primarily does not treat patients with chronic morbidities. Such people will continue to suffer from the disease even after a community is declared "LF-free". Thus, a hygiene-based LE Morbidity Management and Disability Prevention (MMDP) plan has been established by the WHO to reduce LE morbidity. Nonetheless, there are no established biomarkers for LE prognosis and thus predicting the outcome of LE after MMDP measures have been initiated has become difficult. Lymphangiogenic molecules such as VEGF-C, sVEGFR3, TIMP-1, etc. are reported to be involved in LE development. The study aimed at assessing the prognostic potential of biomarkers associated with LE development. A total of 175 LE-affected individuals from the Upper East Region of Ghana were enrolled, strictly trained, and resourced with hygiene-based LE morbidity management materials, and followed up for 24 months. The Friedman test with Dunn's posthoc comparison, receiver operating characteristic curve, and logistic analyses were performed to estimate the association between baseline and follow-up biomarker levels and LE outcomes. Overall, 26.8% saw LE improvement, whiles 96.6% lacked progression. The mean plasma levels of VEGF-C, sVEGFR-3, CEACAM-1, MMP-2, and IGF-1 in study participants who experienced LE progression rose, with a rise in one marker up-regulating the others. TIMP-1 up-regulation resulted in lower levels of VEGF-C, sVEGFR-3, CEACAM-1, MMP-2, and IGF-1 in participants who had LE improvement. Reduced TIMP-1 levels, on the other hand, resulted in up-regulation and over-expression of these biomarkers leading to lymphatic vessel dilation, extracellular matrix remodeling, and LE progression. To conclude, the study demonstrated that lymph/angiogenic biomarkers have a prognostic value in LE pathology and could be used for prognosis after MMDP measures have been initiated. In mitigating the best care for LE-affected individuals, efforts aimed at drug development can be focused on increasing TIMP-1 levels in blood plasma

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MULTIANTIGEN PRINT IMMUNOASSAY: TOWARDS A GLOBALLY ACCESSIBLE SEROLOGICAL DIAGNOSIS OF NEUROCYSTICERCOSIS

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Neurocysticercosis (NCC) is the most common helminthic infection of the human central nervous system. The antibody detection assay of choice is the enzyme-linked immunoelectrotransfer blot assay (EITB, Western blot) using lentil-lectin purified parasite antigens, an immunoassay with exceptional performance in clinical settings. However, its use is mainly restricted to a few research laboratories because the assay is labor-intensive and requires sophisticated equipment, expertise, and needs large amounts of parasitic material. We report a new multiantigen print immunoassay (MAPIA), which consists in directly spraying of antigen into a nitrocellulose membrane, that overcomes most of these barriers by using recombinant antigens that correspond to the three diagnostic protein families GP50, T24/42, and 8kDa. We initially compared the performance of five antigen combinations in a subset of defined samples in the MAPIA format. After selecting the best performing format, 148 archive serum samples were tested, including 40 from individuals with parenchymal NCC, 40 with subarachnoid NCC and 68 healthy controls with no evidence of neurologic disease. MAPIA using three antigens (rGP50 + rT24H + sTs14), was highly efficient for antibody detection in NCC, detecting 39/40 parenchymal NCC cases and 40/40 subarachnoid cases in relation to the EITB, with a specificity of 98.53% (67/68). Thus, MAPIA using three recombinant and synthetic antigens is a simple, reproducible, and economical tool with a performance equivalent to the LLGP-EITB assay; even more, the EITB protein family responses were concordant with its recombinant form responses. We propose the MAPIA test (rGP50, rT24H, and sTs14) as a new affordable, globally available diagnostic tool for detecting antibodies in serum, providing a suitable option to overcome the availability limitations of the current standard assay, and that could support the clinical diagnosis of NCC or contribute to epidemiological studies in endemic populations.

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EPIDEMIOLOGY OF THE HOOKWORM, NECATOR AMERICANUS, IN BEPOSO, GHANA: APPLICATION OF MOLECULAR AND SEROLOGIC METHODS TO DEFINE THE PREVALENCE OF INFECTION

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In 2022, a study was initiated to characterize the epidemiology of human hookworm infection in Beposo, Ghana (Bono East Region). After obtaining informed consent, 1,047 subjects (age 3-100 years; 48% female) were enrolled and completed a questionnaire to assess demographic, behavioral and socioeconomic characteristics. Baseline hookworm prevalence was 28.6% (285/996) as measured by Kato Katz (KK) fecal microscopy, with 92% (262/285) of infections defined as light intensity by WHO standards.

The highest prevalence of infection was noted in subjects aged 11-20 years (33.5%) and in those over 60 years old (36.4%). Individuals who reported having taken anti-parasitic medication fewer than 30 days before screening were more likely to be hookworm positive than those who did not (31.7% vs 25.9%; p=0.04). Subjects who reported regular use of water from boreholes were more likely to have hookworm than those using piped or well water (p<0.05), based on a $\chi 2$ unadjusted analysis. Analysis of 110 fecal samples using a probe-based TaqMan RT-qPCR assay detected Necator americanus genomic DNA in 39% (22/56) of KK-negative samples, while 98% (53/54) of KK-positive samples were confirmed by qPCR. An ELISA assay was developed to quantify serum antibody (IgG) responses to larval protein extracts (LEX) or adult worm excretory/secretory proteins (ES) isolated from a Beposo strain of N. americanus recently adapted to an animal model. Preliminary data (n=227) showed that antibody levels to LEX (p<0.03) and ES (p<0.0001) both correlated with KK infection status, with an AUC of 0.77 derived from Receiver Operator Curve analysis of anti-ES IgG levels (p<0.0001). These data confirm the poor sensitivity of KK microscopy for measuring the prevalence of hookworm in endemic communities, especially those characterized by low-intensity infections. The study also demonstrates the potential for serologic testing as an accurate, high throughput and potentially cost-effective tool for monitoring the impact of mass drug administration on hookworm prevalence in endemic communities.

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BIOMETRIC DATA CAPTURE DURING SOIL-TRANSMITTED HELMINTHS AND SCHISTOSOMIASIS MASS DRUG ADMINISTRATION IN A LARGE-SCALE GESHIYARO PROJECT

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Neglected tropical diseases are a diverse group of infectious diseases that affect one billion people globally. The Geshiyaro Project is a seven-year intervention-based research program that aims to identify the optimal design of soil-transmitted helminths (STH) and schistosomiasis (SCH) elimination programs. The project assesses different combinations of Water, Sanitation, and Hygiene interventions and community-wide mass drug administration (MDA) in the Wolaita Zone of Ethiopia. This project uses biometric fingerprint technology to evaluate the impact of different treatment strategies and WaSH interventions. Biometric fingerprint technology enables accurate identification and tracking of participants who will receive deworming tablets during the Geshiyaro Project. To interrupt the transmission of STH and SCH, community-wide MDA is targeted with reaching 90% of the population at each round. Since 2019, Albendazole and praziquantel were administered across the Wolayita zone. During each treatment round, Geshiyaro census records were used to identify participants through a tiered hierarchy of methods; biometric identification, subject ID card identification, or name search of the database. The realities of fieldwork have highlighted issues with implementing electronic data capture. Over time, participants often lose their ID cards and swap them with family members leading to unreliable identification. Name searching is hindered primarily by the translation from the local dialect to English spellings, similarly named individuals in a village. Biometric registration and identification of participants begin to alleviate these named issues, however, come with their own caveats. For example, manual laborers and young children are unable to provide a valid fingerprint, due to 'illegible' or inadequately sized prints. Ensuring community acceptance of the technology required additional sensitization methods, beyond the scope of traditional MDA protocols. The Geshiyaro project has had the unique opportunity to integrate this novel biometric capture as part of a large-scale control program.

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RAPID SPREAD OF TRICHURIS TRICHIURA INFECTION FOLLOWING TREATMENT AMONG POPULATION LIVING IN RURAL AREAS OF GABON, CENTRAL AFRICA

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Soil-transmitted helminths (STH) remain a public health issue in sub-Saharan countries. As their elimination is not yet possible in the region, the current WHO's recommendations are the control of the disease burden, through large-scale treatments of at-risk populations and implementation of measures to reduce transmission. However, the effectiveness of those programs seems to depend on STH species. The objective of the present analysis was to assess the occurrence of different STH species before and after anthelminthic treatment, using the incidence rate (IR). The study was longitudinal. Participants were followed-up (FU) in 2 consecutive phases of 6 and 9 months. Stool samples were collected at baseline, at 6 and 15 months of FU. STH diagnosis was by Kato-Katz and Coproculture techniques. At the 6-month FU, all participants infected with STH were treated with albendazole 400mg once a day for three consecutive days. The IR was calculated before treatment among participants negative at baseline, and after treatment among participants negative or treated at month 6. We included 262 participants with a mean (SD) age of 12.1 (4.8). Of them, 53% tested positive for STH infection over the study course. Before treatment, the IR was 41 (95%CI: 28 - 55) cases per 100 person-years for any STH and 14 (95%CI: 6 - 26), 15 (95%CI: 6 - 29), and 13 (95%CI: 5 - 25) cases per 100 person-years for A. lumbricoides, T. trichiura, and hookworm, respectively. After treatment, a statistically significant increase in the IR was observed for T. trichiura (36 cases per 100 person-years, 95%CI: 27 - 47, p-value<0.001). For A. lumbricoides and hookworm infection, the IR following treatment was 15 (95%CI: 9 - 24) and 12 (95%CI: 7 - 20) cases per 100 person-years, respectively. In conclusion, our results indicate a rapid spread of T. trichiura infection in our community after treatment, with a potential effect on the effectiveness of programs implemented for the control of STH. This calls for further investigation of the epidemiology and morbidity of T. trichiura infection and for the assessment of the efficiency of those programs on T. trichiura specifically.

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NATURAL AND VACCINE-MEDIATED IMMUNITY TO NIPPOSTRONGYLUS BRASILIENSIS

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Hookworm infects over 220 million people worldwide. As a leading cause of iron-deficiency anemia in children and pregnant women, hookworm infection reinforces the cycle of poverty through growth stunting, physical and cognitive delays, and a decline in work performance. Vaccines remain a promising preventative strategy, with ongoing clinical trials of vaccine candidates against hookworm. However, one candidate, recombinant protein (r)Na-ASP-2, failed in trials due to an unanticipated preformed IgE-mediated systemic urticarial response to immunization in a cohort endemic for Hookworm. Two subsequent vaccine candidates, rNa-APR-1 and rNa-GST-1, needed to be recently re-formulated with additional co-stimulatory TLR-4 and TLR-9 agonists, in hopes of inducing a more robust and durable immune response. Given the substantial cost to bring a vaccine candidate to clinical trials targeting low-resource populations, a poor understanding of vaccine immunity against helminths may be detrimental to finding a successful candidate. It remains unclear how protective immunity develops after natural infection to Hookworm in certain animal models or how prior

infection influences the immune response to vaccination. We have adapted a murine model for Nippostrongylus brasiliensis, the rat hookworm, and have found that recurrent challenge in wild-type C57Bl/6J mice induces near sterilizing immunity. RAG-1 deficient mice, which lack mature B or T cells, remain completely susceptible to repeated challenges. This will be a framework to compare the acquired immune pathway to natural infection as opposed to the human-relevant vaccine candidates rNa-GST-1 and rNa-ASP-2, which we have found induce at least partial protection, a 54% and 52% intestinal worm burden reduction, respectively when co-formulated with an Alum-based adjuvant. We have characterized the correlative roles of antigen-specific T cells (type 1, type 2, T follicular helper, germinal center, and T regulatory) and antigen-specific B cells (plasma cells, IgG1+, memory, and germinal center) in natural and vaccine-protected mice.

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WASTEWATER-BASED EPIDEMIOLOGY FOR SOIL-TRANSMITTED HELMINTH SURVEILLANCE IN BENIN AND INDIA

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Surveillance of soil-transmitted helminth (STH) infections is critical for targeting interventions like mass drug administration (MDA). While microscopy-based stool surveillance of STH in humans is resource-intensive and may miss most asymptomatic or mild-intensity STH infections or clusters that contribute to continued transmission, wastewater surveillance of STH environmental DNA (eDNA) may be a useful, low-cost approach for detecting ongoing STH transmission in communities, even in low prevalence, high aggregation scenarios. We leveraged the cluster-randomized DeWorm3 trial to pilot a wastewater-based molecular surveillance approach in Benin and India. We optimized methods to detect STH eDNA in wastewater samples (grab, sediment, and Moore swab) collected from non-networked open drains in Benin (N=68) and India (N=60) in June-July 2022. Using qPCR to detect STH targets from purified eDNA, we detected hookworm (Necator americanus) in 28% (17/60) of samples and roundworm (Ascaris lumbricoides) in 15% (9/60) of samples in India. In Benin, hookworm (N. americanus or Ancylostoma duodenale) was detected in 3% (2/68) and roundworm (A. lumbricoides) in 9% (6/68) of samples. Whipworm (Trichuris trichiura) was not detected in any samples. Across both study sites, STH eDNA was most frequently detected in wastewater sediment samples at 9.4% (12/128), followed by grab samples at 5.5% (7/128), then Moore swabs at 4.7% (6/128). Wastewater surveillance of STH eDNA could offer national control programs a simpler and more cost-effective way of targeting communities for MDA and monitoring for recrudescence over time compared with the standard stool-based Kato-Katz method.

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TWENTY-FOUR MONTH LONGITUDINAL STUDY OF HOOKWORM INFECTION IN GHANAIAN SCHOOL CHILDREN

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Worldwide, 576 million people and 156 million children are estimated to be infected with hookworm in tropical regions, causing an estimated 3.2 million disability-adjusted life-years annually. We randomly selected school-aged children (4-16 yrs) to participate in a two-year longitudinal study of hookworm infection in rural Ghana (n=274) to identify nutritional status and environmental exposures that impact hookworm infection and response to treatment. After the longitudinal study we conducted a cross-sectional survey in the study communities to assess spillover effects of the longitudinal study. Every six months (baseline Jan 2013) we collected anthropometric measurements, fecal samples and venous blood samples. Household surveys and multiple pass twenty-four-hour food intake recalls were collected at baseline and 18 months. The overall prevalence of hookworm infection among study subjects was reduced from 21% (58/274) at baseline to 10% (21/208) two years later. Sixty percent (60.6%; n=166) of participants were hookworm negative every time they were tested and 16.4% (n=45) were infected two or more times. Fecal egg reduction rate in the 27.7% (23/83) of children who were hookworm positive at least once after treatment ranged from 0-99%. Hookworm status and albendazole treatment outcome at baseline was the dominant influence on infections at six months. Albendazole treatment efficacy was greater in older children and those from food-insecure households, and these relationships were nonlinear. The subsequent cross-sectional community study recruited additional subjects from households with a child who participated in the longitudinal study (n=131) and households without a participating child (n=136). Prevalence of infection in non-participating children with a sibling who participated in the longitudinal study did not differ significantly from children without participating siblings. While rates of hookworm infection in Africa have declined, additional strategies are likely needed for sustainable control. Results from this innovative study add to our current knowledge of hookworm infection in school-aged children.

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STRONGYLOIDES STERCORALIS COINFECTION IS ASSOCIATED WITH ALTERED SYSTEMIC CYTOKINE PROFILES, GREATER DISEASE SEVERITY, HIGHER BACTERIAL BURDENS AND INCREASED FREQUENCIES OF UNFAVORABLE TREATMENT OUTCOMES IN PULMONARY TUBERCULOSIS

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Helminth infections and tuberculosis are both major public health problems which share considerable geographical overlap affecting mostly lower and some middle-income countries worldwide. Helminth infections are known to induce modulation of T cell mediated immune responses to tuberculosis disease. Hence, we explored the systemic levels of cytokines, chemokines and growth factors in individuals with pulmonary tuberculosis (PTB) (n=483) with (n=74) or without (n=409) coexistent Strongyloides stercoralis (Ss) infection. Type 1, Type 2, Type 17, pro-inflammatory cytokines and growth factors levels were determined by multiplex ELISA. Chest x-rays were used to determine cavitary disease and smear grade was used to determine bacterial burdens in PTB individuals. Treatment outcomes were classified as favorable (recurrence free cure) or unfavorable (treatment failure, death during treatment or TB recurrence) during 18 months of follow up. PTB

individuals with Ss infection showed higher bacterial burden and cavitary disease compared to PTB individuals without Ss infection. PTB individuals with Ss infection also exhibited a significantly increased frequency of unfavourable treatment outcomes compared to PTB individuals without Ss infection. We observed a significant increase in type 2 (IL-4, IL-5 and IL-13), pro-inflammatory cytokines (IFNα, IFNβ and IL-12) and growth factors (CCL2, CCL11, CCL19, CCL20, CXCL1, CXCL8, CXCL10 and CX3CL1) in PTB individuals with coexistent Ss infection and a significant decrease in type 1 cytokines (IFNγ and IL-2) in PTB individuals with coexistent Ss infection. Therefore, our data demonstrate that coexistent Ss infection is associated with modulation of systemic cytokine profiles, greater disease severity, higher bacterial burden and increased frequencies of unfavorable treatment outcomes in PTB.

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ACUTE ENCEPHALITIS SYNDROME IN ADULTS IN EASTERN INDIA: AN AETIOLOGICAL STUDY

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Seasonal outbreaks of Acute Encephalitis Syndrome (AES) with high case fatality have been reported most frequently in the state of Uttar Pradesh, India. The surveillance conducted by the National Vector Borne Disease Control Programme of India for AES focuses mainly on detecting Japanese encephalitis (JE) virus. Most published studies of AES have been done on children while it is a common health emergency even among adults. Thus, this study was done to identify the common causes of AES among adults in a tertiary care centre in eastern Uttar Pradesh.CSF and blood samples were collected from adults presenting with fever and altered sensorium of less than 15 days. ELISA was performed in serum samples for IgM antibody detection of Dengue Virus, Chikungunya virus, West Nile Virus, Scrub typhus, Leptospira. CSF samples were tested for IgM JE virus and tuberculosis by Gene Xpert. Malaria was detected by rapid kit. Among the 126 patients of AES, 54% were males, mean age was 32 years and duration of fever was 9.4 days. The common aetiology were Scrub Typhus (36.5%), Leptospira (36.5%), Chikungunya (25.4%), Dengue (25%), tuberculosis (14.38%) West Nile & JE virus was 6.3% each and only one had malaria. No aetiology could be identified in 20 patients and 42% had more than one infection. Mortality was 21/126 (16.66%).The most common cause of AES among adults in eastern Uttar Pradesh has shifted from JE to treatable causes like scrub typhus and leptospirosis. Vector borne viral diseases like dengue, chikungunya, west nile and JE has emerged as an important cause of AES. Tuberculosis should be ruled out in all cases of AES in adults in India.

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THE DIAGNOSIS OF SUBARACHNOID NEUROCYSTICERCOSIS IS OFTEN DELAYED AND OTHER FINDINGS OF A MULTICENTER RETROSPECTIVE IN THE USA

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Subarachnoid (racemose) neurocysticercosis (SANCC) is an uncommon but severe form of Taenia solium infection. There is limited evidence to guide clinical management of these patients. We performed a multicenter retrospective chart review of 15 U.S. sites. A total of 69 subjects with racemose disease was entered. The most common region of exposure was Mexico (67%) followed by Central America (24%). Median age was 43 years (range 15-76) and 71% were male. Common symptoms at the time of index admission were headache (80%), nausea/vomiting (46%), dizziness (44%), and blurry vision (33%). Cysts were intracranial in 64 (93%) subjects and exclusively intraspinal in 4. One patient had meningitis without visible cystic lesions. Incident admission magnetic resonance imaging (MRI) demonstrated ventriculomegaly in 41 (59%) and focal findings in 9 (13%) including ischemic infarct, subarachnoid hemorrhage, and/or arterial aneurysm. For 55 (80%), SANCC was first diagnosed during the index admission. Of these, 23 (42%) had prior medical visits and substantial delay in diagnosis (i.e. previously seen with hydrocephalus [27%], stroke [5.5%], and/or meningitis [11%], missed diagnostic radiologic features [4%], or inadequate imaging [5.5%]). Of the 69 subjects, 54% underwent a neurosurgical procedure during index admission (cyst removal n=16, EVD/shunt/ventriculostomy n=24). At the time of discharge, 6 (8.6%) patients were not given albendazole and/or praziquantel due to cost or availability. Six months following discharge, <10% of follow up MRIs demonstrated cyst resolution. Planned treatment course of <4 weeks at discharge compared to >4 weeks was associated with increased risk for new cyst development on follow up imaging at a median of 3.8 years following discharge (range 2.6 months-8 years). Those with a delayed diagnosis received a significantly longer total duration of corticosteroids than those without a delay. The diagnosis of SANCC is often missed, and most patients require neurosurgical intervention. Antiparasitic therapy is suboptimal, especially with regimens developed for parenchymal NCC.

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CO-INFECTION WITH STRONGYLOIDES STERCORALIS IN ADULTS WITH CRYPTOCOCCAL MENINGITIS IN AFRICA

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Cryptococcal meningitis is responsible for 15% of AIDS-deaths globally, with 75% of these occurring in Sub-Saharan Africa. The soil transmitted helminth Strongyloides stercoralis infects 30-100 million individuals globally and its distribution overlaps with that of cryptococcal meningitis. Host

immunity adapts to pathogens through differentiation of host CD4+ T cells into subpopulations. Co-infection with pathogens that each elicit different CD4+ T cell responses (Th1 vs. Th2) provides an immune conundrum; how should the host respond? In meningitis, helminth co-infection may modulate host immune responses. In a study of Vietnamese adults with tuberculous meningitis, S. stercoralis co-infection was associated with less severe inflammation and better outcomes, as immunomodulation towards Th2 appeared beneficial. However, in cryptococcal meningitis Th2 responses associate with impaired control of infection and poor outcomes. We hypothesize that S. stercoralis co-infection is associated with more severe disease and worse outcomes in cryptococcal meningitis. We will perform S. stercoralis serological testing on stored blood from 844 adults from AMBITION: a phase 3 clinical trial of cryptococcal meningitis therapy in five African countries. Stored serum will be defrosted and tested for S. stercoralis by enzyme immunoassay following manufacturer instructions. Testing will be performed at the London School of Hygiene and Tropical Medicine. Pre-treatment cryptococcal meningitis severity, routine cerebrospinal fluid (CSF) parameters, CSF cytokines, and mortality by 10 weeks, will be compared between S. stercoralis positive and negative groups. Additionally, clinical data will be analyzed stratified by optical density in S. stercoralis positive cases, to distinguish strongly positive cases from potential past infection. S. stercoralis serological testing and CSF testing will be performed in June 2023. If S. stercoralis seropositivity associates with worse outcomes, a future trial could evaluate ivermectin therapy for S. stercoralis eradication in cryptococcal meningitis - a low-cost high-impact intervention.

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SEROLOGIC RESPONSE USING ELISA ANTI-VI IGG ANTIBODIES AT SEVERAL TIME POINTS FOLLOWING IMMUNIZATION WITH THE TYPHOID CONJUGATE VACCINE, TYPBAR-TCV, AMONG HIV INFECTED CHILDREN IN KARACHI PAKISTAN

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Associated with outbreaks, complications and the evolution to novel strains that are extensively drug resistant, enteric fever remains a major public health concern in Pakistan. WHO recommends programmatic use of typhoid vaccines for the control of typhoid fever in typhoid endemic countries, however, individuals infected with HIV generally have a lower response to immunization as compared to the general population and there is no data to corroborate the post-vaccination serologic response of TCV in HIV-infected children. Therefore, this study was designed to assess the serological response of typhoid conjugate vaccine (TCV) in HIV-infected children in Ratodero, Larkana in Sindh. A prospective cohort study was conducted in HIV-positive children who received a single dose of the Typbar-TCV at Taluqa Hospital in Ratodero Larkana, Pakistan. A total of 336 HIV-positive children aged 6 months to 15 years were vaccinated and followed-up for 1 year, from December 2019 till January 2021. We measured the serological response using ELISA anti-Vi IgG antibodies at several time points following immunization with a single 0.5ml intramuscular injection of Typbar-TCV. Blood samples were collected at baseline, 6 weeks, 6 months and 12 months post-immunization with TCV and tested for anti-Vi IgG titers and the seroconversion rates were calculated. The mean age of the participants was 52.04 months, and the mean CD4 count was 841. The GMT titers were significantly lower in children aged 6 months to 5 years at 6 months and 1-year post vaccination. Besides age, high immunosuppression was significantly associated with lower seroconversion rates in children with high and low immunosuppression. HIV-infected children with high immunosuppression and younger age were associated with low seroconversion rates and failure to remain seroconverted at 6 months and 1-year post-immunization with TCV. Thus, it can be concluded that the overall seroconversion rates of TCV among HIV-positive children are lower as compared to healthy children. Therefore, the need for a booster dose of TCV should be assessed and administered accordingly amongst immunocompromised patients.

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TRIM-HIV: TARGETING THE RESTORATION OF INNATE IMMUNITY IN MEN WHO HAVE SEX WITH MEN WITH EARLY INITIATION OF ANTIRETROVIRAL THERAPY IN HIV-1 INFECTION FOR MANAGEMENT IN TROPICAL REGIONS

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Background: Natural killer (NK) cells play a crucial role in the immune response against viral infections, including HIV-1, and their impairment may contribute to disease progression. Early initiation of antiretroviral therapy (ART) is crucial for reducing morbidity and mortality associated with HIV-1 infection, particularly in tropical regions where the burden of HIV-1 is high. However, the effects of early ART on NK cell function and phenotype in early HIV-1 infection in men who have sex with men (MSM) in tropical regions are not fully understood.Methods: We longitudinally evaluated NK cell function and phenotype in five MSM in Nairobi, Kenya, who were initiated on ART immediately upon seroconversion. Blood samples were obtained fortnightly for three visits post-seroconversion. PBMCs were stimulated with K562 cell line and interleukins (IL)-2 and IL-15, stained with antibodies for NK cell phenotype, activation, and functionality and assessed by flow cytometry.Results: We observed a significant reduction in NK cell production of IFN-γ, expression of CD69, and NK cell inhibitory receptor Siglec7 in early HIV-1 infection. On the other hand, there were significant increases in NK cell degranulation and presentation of the cell exhaustion marker PD-1. Most of these changes seem to have been partially restored a few weeks after ART initiation.Conclusions: Our findings suggest that early ART initiation can partially restore some, but not all, perturbations of NK cell function and phenotype in early HIV-1 infected MSM in tropical regions. These findings have important implications for managing HIV-1 infection in resource-limited settings where early initiation of ART is not always possible and where the burden of HIV-1 is high. Further research is needed to fully understand how HIV-1 impairs NK cell effector functions and how ART can restore these functions in early HIV-1 infection in tropical regions. This knowledge can inform the development of effective HIV-1 vaccines and strategies to reduce the burden of HIV-1 in tropical regions.

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ASSOCIATION OF UROGENITAL SCHISTOSOMIASIS WITH HIV INFECTION IN A LARGE COMMUNITY-BASED COHORT IN ZAMBIA (THE ZIPIME WEKA SCHISTA STUDY)

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Co-infection of HIV-1 and Schistosoma haematobium (Sh) is highly prevalent in sub-Saharan Africa with evidence of an association between prevalent HIV-1 and schistosome infection. There is also suggestion of increased HIV-1 transmission in women with Female Genital Schistosomiasis (FGS), caused by Sh egg-deposition in the genital tract. The Zipime Weka Schista study is an ongoing longitudinal cohort aiming to integrate home-based genital self-sampling for Sh and High Risk Human Papillomavirus (HR-HPV) and self-testing for HIV and Trichomonas vaginalis(Tv) in two endemic areas in Zambia. Here we used baseline data to examine the association between Sh with HIV-1 prevalence. Sexually active women aged 15-50 years were randomly selected. Community health workers recruited women during a home visit and obtained two cervicovaginal self-swabs, a urine sample, self-test for HIV-1 and Tv and

completed a questionnaire . Women were referred to the clinic where a midwife collected genital samples and obtained images using hand-held colposcopy. A urine test was analysed via microscopy for Sh ova detection and self-swabs analysed for Sh and HR-HPV DNA. Overall, 2511 women were recruited (median age 28 [IQR: 22-36]); 17.5% (439/2510) were HIV-1 seropositive, of which 8.4% (37/439) previously undiagnosed. After adjusting for confounders (age, trichomonas result, marital status) there was no association between active egg-patent Sh status and HIV status (OR=0.97, 95% CI 0.54-1.76, p=0.93). There was a significant association between women with Tv and prevalent HIV-1 (OR=2.0, 95% CI 1.40-2.80, p<0.001). Our preliminary results differ from previous findings on the association between urinary Sh status and HIV status. Ongoing analysis of genital samples and images for FGS will help refine these associations.

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FALLING THROUGH THE CRACKS: APPLYING THE 95-95-95 METRIC TO PROVIDE INSIGHT INTO HIV PROGRAMME GAPS IN HIV-INFECTED INFANT DEATHS INVESTIGATED IN KENYA, SOUTH AFRICA AND MOZAMBIQUE

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National HIV programs aspire to achieve the 2025 UNAIDS 95-95-95 targets: 95% of people living with HIV know their status ('known status'); 95% of those are on antiretroviral therapy (ART), and 95% of those are virally suppressed (VLS). This cascade provides a snapshot of national HIV-programme progress towards epidemic control but has not been applied to research findings to understand how HIV service delivery gaps may contribute to HIV mortality. The multi-country Child Health and Mortality Prevention Surveillance (CHAMPS) investigates under-five (<5) mortality using clinical records, minimally invasive tissue sampling, extensive laboratory testing including a molecular HIV test, verbal autopsy, and a multidisciplinary panel to determine causes of death. We applied the 95-95-95 cascade to CHAMPS infant (<1 year) deaths due to HIV in 3 high-burden countries between 2017-2023, and compared them to available national data on live infant programme coverage in the public domain from within the same time frame, and restricted to ages <1 or closest age group available. HIV prevalence in CHAMPS decedents ranged from 4.0% in South Africa to 8.5% in Kenya. Among the HIV deaths, nearly 3/4 had wasting, 88.3% (30/34) of which was extreme wasting. In South Africa, 70% of CHAMPS <1 HIV deaths had known status compared to 75% nationally; 35% were on ART compared to 68%, and just over one-quarter in both CHAMPS and national cascades had VLS (i.e., 70-35-26 vs 75-68-27). CHAMPS-Kenya's cascade was 8%-0%-0% vs 79%-74%-49% in the national program, and CHAMPS-Mozambique was 54%-31%-0% compared to 72%-57%-35% nationally. Globally, pediatric HIV treatment lags behind adult coverage in all countries. We found that HIV program gaps measured in CHAMPS decedents with HIV were even larger than those reported in national infants from national HIV programs, and the pattern of gaps observed in CHAMPS cases differed between countries. Findings indicate that programme gaps contributing to HIV-related infant mortality are not uniform across countries, and that countries could learn from each other's best practices to further reduce pediatric HIV mortality.

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CULEX PIPIENS AND CX. MODESTUS ARE VECTORS FOR WEST NILE VIRUS AND USUTU VIRUS, RESPECTIVELY, IN BELGIUM

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West Nile virus (WNV) and Usutu virus (USUV) are emerging arboviruses in Europe. While Culex (Cx.) pipiens is widely acknowledged as their primary vector, studies have suggested a role for the less commonly known Cx. modestus. Recently, our lab showed for the first time that Cx. modestus is established in Belgium, but the vector competence for Belgian mosquitoes has not been studied. Therefore, our aim was to explore the vector competence of field-caught Belgian Cx. mosquitoes to WNV and USUV. Mosquitoes were captured in Leuven, Belgium using BG-Sentinel traps. Females were fed chicken blood containing WNV lineage 2 (a Netherlands chiffchaff isolate) or USUV European (USUV/EU) or African (USUV/AF) lineage 3 (Belgian blackbird isolates). After 14 days at 25°C, mosquito bodies and heads were dissected and saliva harvested to determine infection, dissemination, and transmission rates, respectively. Infectious virus was measured by plaque assay and virus titers quantified by qPCR. Cx. pipiens (biotypes pipiens/molestus/hybrid) were identified by qPCR and other species by Sanger sequencing. Finally, the presence of the Wolbachia wsp gene was detected by PCR. We captured a total of 1,137 Cx. females. Those that blood-fed were mostly Cx. pipiens (n=140) followed by Cx. modestus (n=8), Cx. molestus (n=1), and a Cx. pipiens-molestus hybrid (n=1). In Cx. pipiens, infection rates were 11% for WNV (n=5), 13% (n=7) for USUV/EU, and 16% (n=6) for USUV/AF. Cx. pipiens dissemination was 40% (n=2) for WNV and 17% (n=1) for USUV/AF, but there was no USUV/EU dissemination. Surprisingly, Cx. modestus showed a 75% infection rate for USUV/AF (n=3) with 100% dissemination (n=3). The sample size of Cx. modestus was too low to measure vector competence for WNV or USUV/EU. Finally, there was no significant difference in USUV/AF titers in Cx. pipiens and modestus. The measure of transmission in saliva and detection of Wolbachia is currently ongoing. We hypothesize that Cx. modestus may be a more potent vector for USUV than Cx. pipiens in Belgium. We are planning targeted collections of Cx. modestus in 2023 for additional data supporting their vector competence to WNV and USUV.

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INVESTIGATION OF VIRUS-HOST INTERACTIONS IN SEVERE FEVER WITH THROMBOCYTOPENIA SYNDROME VIRUS INFECTION USING A LIPIDOMICS APPROACH

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Severe fever with thrombocytopenia syndrome virus (SFTSV) is an emerging tick-borne bunyavirus endemic in parts of Asia that causes severe disease in human. SFTS is characterized by an acute febrile illness associated with high fever, thrombocytopenia, and hemorrhage. The pathogenesis of SFTS remains poorly understood. Viruses often reprogram the host lipid metabolism machinery to facilitate their own replication, and host-targeting lipid modulators have been reported to be potential broad-spectrum antivirals. To provide insights into virus-host interactions in SFTSV infection, we investigated the lipidomics profile of SFTSV-infected Huh-7 cells. Our lipidomics analysis identified >120 significantly changed lipids. These lipids belonged to 18 lipid classes, including cardiolipin (CL), ceramide (Cer), diacylglycerol (DG), ether-linked phosphatidylcholine (etherPC), ether-linked phosphatidylethanolamine (etherPE), lysocardiolipin (MLCL), n-acyl-lysophosphatidyl-ethanolamine (LNAPE), lysophosphatidylcholine, ganglioside GM3 (GM3), hexosylceramide (HexCer), oxidized phosphatidylcholine, phosphatidic acid (PA), phosphatidylcholine (PC), phosphatidylethanolamines (PE), phosphatidylglycerol, phosphatidylinositols (PI), phosphatidylserine (PS), and triacylglycerol (TG). Among them, TG,

PC, and Cer were the three most perturbed lipid classes. Around 20% of the perturbed lipids, including one CL, one MLCL, most of PA, PI, and PS were downregulated. Around 80% of the perturbed lipids, including all GM3, HexCer, LNAPE, etherPC, etherPE, DG, PE, most of TGs, PCs, Cer, and a few of PA, PI, and PG were significantly upregulated. Pathway analysis revealed glycerophospholipid metabolism, sphingolipid metabolism, glycerolipid metabolism, and phenylalanine, tyrosine and tryptophan biosynthesis as the four dominantly perturbed pathways. In summary, our study characterized the SFTSV-induced host lipidomics perturbations and may facilitate the identification of lipid metabolism modulators as potential antivirals for SFTSV infection.

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APOLIPOPROTEIN-A1 MIMETIC PEPTIDE 4F BLOCKS FLAVIVIRUS NS1-INDUCED ENDOTHELIAL BARRIER DYSFUNCTION

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Flavivirus infections result in a variety of outcomes, from clinically inapparent infections to severe, sometimes fatal, disease characterized by hemorrhagic manifestations and vascular leakage leading to organ failure. Although there are approved vaccines against several flaviviruses, potentially enhancing cross-reactive immune responses have complicated development and implementation of vaccines to dengue and Zika, and no therapeutics currently exist. The flavivirus non-structural protein 1 (NS1) stands out as a promising antiviral target because it is a well-conserved multifunctional virulence factor that in addition to its role in viral replication, also contributes to severe disease manifestations via induction of proinflammatory cytokine secretion and vascular leak. We previously showed that the ApoA protein and ApoA1 mimetic peptide 4F inhibit DENV infection and binding of DENV NS1 to murine macrophages. In this context, ApoA1 and 4F could potentially prevent NS1 binding to the cell surface by blocking the interaction of NS1 hydrophobic residues with the plasma membrane. Here, we evaluated the therapeutic potential of the 4F peptide against flavivirus NS1-induced endothelial dysfunction. In an in vitro model of endothelial permeability using human pulmonary microvascular endothelial cells (HPMECs), 4F inhibited NS1-induced hyperpermeability, as measured by a Trans-Endothelial Electrical Resistance assay, and blocked NS1-triggered disruption of the endothelial glycocalyx layer. We also demonstrate that treatment with 4F inhibited NS1 binding and internalization into HPMECs. Further, we found using an electrophoretic mobility shift assay and other approaches that 4F binds to NS1 and affects its oligomeric state. Together, our data demonstrate the potential of the 4F peptide as a novel therapeutic strategy to inhibit flavivirus NS1-mediated pathology.

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DEVELOPING A MODEL OF PERSISTENT POWASSAN DISEASE IN C57BL/6 MICE

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Powassan infection is caused by two closely related, tick-transmitted viruses of the genus Flavivirus (family Flaviviridae): Powassan virus lineages I (POWV) and II (known as deer tick virus (DTV)). Infection is typically asymptomatic or mild, but can progress to neuroinvasive disease. Approximately 10% of neuroinvasive cases are fatal and half of the survivors will experience long-term neurological sequelae. Understanding how these viruses cause long-term symptoms as well as the possible role of viral persistence is important for developing therapies. Animal models of acute Powassan infection have been developed, but models to study persistent infection are nonexistent. We hypothesized that a portion of DTV-infected C57BL/6 mice that survive the acute infection will become persistently infected. We intraperitoneal inoculated six-week-old C57BL/6 mice (50% female) with 103 FFU DTV and assayed for infectious virus, viral RNA, and inflammation during acute infection, and 21, 56, and 84 days post-infection (dpi). Although most mice (86%) were viremic 3 dpi, only 21% of the mice were symptomatic and 83% recovered. Infectious virus was only detected in the brains of mice sampled during the acute infection. Infectious virus was not detected in any other tissue. Viral RNA was detected in the brain until 84dpi, but the magnitude decreased by time. Meningitis and encephalitis were visible in acute mice and from mice sampled at 21 dpi. Inflammation was observed until 56 dpi in the brain and 84 dpi in the spinal cord, albeit at low levels. These results suggest that the long-term neurological symptoms associated with Powassan disease are likely caused by lingering viral RNA and chronic inflammation in the central nervous system rather than by a persistent, active viral infection. The C57BL/6 model of persistent Powassan mimics illness in humans and can be used to study the mechanisms of chronic disease. This work was funded by the Intramural Research Program of the National Institutes of Allergy and Infectious Diseases of the National Institutes of Health.

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FACTORS ASSOCIATED WITH LASSA FEVER FATALITY IN LIBERIA, 2016 - 2021: A SECONDARY DATA ANALYSIS

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Lassa fever (LF) is endemic in Liberia and is immediately reportable. Suspected cases are confirmed at the National Public Health Reference Laboratory. We described the epidemiological characteristics of LF cases and determined factors associated with mortality in Liberia from 2016 to 2021. We reviewed 867 case-based LF surveillance data from 2016 - 2021 obtained from the National Public Health Institute of Liberia (NPHIL). The cases that met the suspected LF case definition were tested with RT-PCR and only the confirmed cases were included in the analysis in Epi Info version 7.2.5. We calculated the LF positivity rate, case fatality rate, and factors associated with LF mortality using chi-square statistics and logistics regression at a 5% level of significance. Eighty-five per cent (737/867) of the suspected cases were tested and 26.0% (192/737) were confirmed LF positive. The median age of confirmed LF cases was 21(IQR:12-34) years. Age 10-19 years accounted for 24.5% (47/192) and females 54.2% (104/192). Bong 33.9% (65/192), Grand Bassa 31.8% (61/192), and Nimba counties, 21.9% (42/192) accounted for most of the cases. The median duration from symptom onset to hospital admission was 6 (IQR:3-9) days. A majority, 66% (126/192) of the cases were reported during the dry season (October-March) and annual incidence was highest at 12 cases per 1,000,000 population in 2019 and 2020. The overall case fatality rate was 44.8%. Non-endemic counties, Margibi, 77.8% and Montserrado, 66.7% accounted for the highest CFR, while 2018, 66.7% and 2021, 60.0% recorded the highest CFR during the period. Age ≥30 years (aOR=2.1,95%CI:1.08-4.11, p=0.027) and residing in Grand Bassa County (aOR=0.3, 95%CI:0.13-0.73, p=0.007) was associated with LF mortality. LF was endemic in three of the fifteen counties of Liberia, and the CFR remained generally high. The high fatality is currently being further investigated. There is a need to continuously train healthcare workers, especially in non-endemic counties to improve the LF treatment outcome. Lassa fever, endemic, Liberia, confirmed case, case fatality rate.

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EEG PATHOLOGIES IN LASSA FEVER INDICATING CEREBRAL INVOLVEMENT: RESULTS FROM 53 PROSPECTIVELY FOLLOWED PATIENTS

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Patients severely affected by Lassa fever (LF) often exhibit neurological symptoms, like seizures or meningitis. These neurological complications are strongly correlated with fatal outcome. Though Lassa virus (LV) has been isolated from cerebrospinal fluid in two case reports, it remains unclear whether LV is truly causing meningoencephalitis. Proofing a possible neurotropism of LV is highly relevant to develop appropriate medical countermeasures. The aim of the study was to implement electroencephalography (EEG) on the LF isolation ward at Irrua Specialist Teaching Hospital, Nigeria, to assess the cerebral involvement of LF correlating EEG findings with laboratory and clinical parameters. From August 2021 to February 2022 we enrolled 53 consenting patients with RT-PCR confirmed LV infection in our prospective, observational cohort study. Study visits consisted of EEGs, clinical exams and laboratory analysis. One patient had to be excluded due to insufficient EEG recording quality. Of the 52 remaining participants 34 % were female and the mean age was 29 years (range 9 - 67 years). Two experienced, blinded neurologists used the American Neurophysiology Society's Standardized Critical Care EEG terminology for EEG analysis. Thirty-six patients (69%) showed any neurological symptoms: meningitis occurred in 13 (25%), headache in 5 (10%) and seizure in 2 patients (4%). Metabolic derangement, most notably acute kidney injury did not occur in any of the enrolled patients. The most frequently observed EEG abnormality was a slowing of the EEG background activity in 8 patients (15%), closely followed by General Rhythmic Delta Activity (GRDA) and a focal slowing of the EEG activity seen in both 7 patients (14%). EEG abnormalities coincided with clinical neurological signs in a majority of cases pinpointing towards a possible neurotropism of LV. While slowing of the EEG background activity presents an unspecific EEG change indicating a generally "reduced" cerebral function, GRDA is a more specific pathology occurring in viral encephalitis. In summary our results pinpoint to a central nervous effect of LV in affected patients in our cohort.

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POTENTIAL FOR PREEXISTING IMMUNITY TO SARS-COV2 IN EASTERN SIERRA LEONE

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Since its emergence in December 2019, SARS-CoV2 has swept the globe, infecting over 700 million and resulting in over 6 million deaths. While countries in the global north have been hard hit by the disease, Sub-Saharan Africa has been widely spared. There are multiple theories as to why Sub-Saharan African has not seen a large burden of SARS-CoV2 infection and disease including: younger age, fewer comorbidities, and pre-existing immunity to the disease. Our group has shown that approximately 30% of samples collected prior to the pandemic (n=120) as part of an ongoing cohort study in Sierra Leone tested positive for anti-SARS-CoV2 nucleoprotein (N) antibodies. In the current study, further this investigation in a cohort of 322 subjects with two pre-pandemic samples (collected at a median of July 2017 and March 2019) and one intra-pandemic sample collected in March 2022. We used the human-CoV V-plex panel 3 from Mesoscale Discovery to assess antibody reactivity to the spike protein from seasonal coronaviruses (229E, OC43, NL63, and HKU1), emerging coronaviruses (SARS-CoV1 and MERS), and to spike (S), nucleoprotein (N), and receptor binding domain (RBD) from SARS-CoV2. Our preliminary analyses show that similarly to previous studies (including our own) approximately 30% of study participants had reactivity to SARS-CoV2 N protein which is highly conserved in beta coronaviruses. We saw low, but notable, seropositivity to SARS-CoV2 (S) and (RBD). Surprisingly, despite the lack of recognized cases in Sierra Leone, we saw a large jump in sero-positivity to all SARS-CoV2 proteins measured (80.1% N, 92.5% S, and 91.3% RBD) in by March 2022. Interestingly we saw no neutralization in pre-pandemic samples tested but saw high levels of neutralization in the intra-pandemic samples confirming widespread SARS-CoV2 transmission despite the lack of recognized clinical disease. Next we will investigate the impact of pre-existing antibodies to seasonal and emerging coronaviruses on neutralizing titer and presumed protection from disease.

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FIRST STAGE GENOME-WIDE ASSOCIATION STUDY OF LYMPHATIC FILARIASIS PATHOLOGY IN AN AFRICAN POPULATION

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Human genetic factors that confer susceptibility or resistance to neglected infectious diseases remain unclear. One of such diseases is lymphatic filariasis (LF). LF results from infection with either of the three filarial nematode species:Wuchereria bancrofti, Brugia timori or B. malayi. An estimated 40 million individuals infected with the filarial nematodes present with the symptomatic LF manifestations of lymphedema (LE) and hydrocele. These symptoms develop in only a subgroup of infected people, and host genetics have been attributed to the disease heterogeneity. Studies that have sought associations between LF and host genetics have focused mainly on candidate genes. This study presents the first genome-wide association study (GWAS) to identify genetic markers involved in LF disease conducted in an African (Ghanaian) population. Single nucleotide polymorphism (SNP) data from 3189 participants comprising 1508 LF cases and 1681 asymptomatic controls were analysed in the study. Cases were selected based on the presence of either LE and/or hydrocele while controls consisted of participants who had lived in the endemic community for at least 10 years prior to enrolment and had no LE and/or hydrocele. These unrelated participants were genotyped using the Infinium Global screening array with multi-disease drop by Illumina®. Independent signals, rs2245413, rs2245710 and rs7742085 were observed on two loci at genome-wide significance ($p<5x10-8$) to be associated with LF. Additionally, three HLA haplotypes (HLA- DQB1*04:02, -DRB1*03:02, and -C*17:01) were found to be associated with LF. Other studies have associated these

SNPs with renal abnormalities, LE and hydrocele, respectively. The identified SNPs were mostly non-coding and located in the intergenic regions; and do not directly cause the symptomatic disease, but are rather proxy markers for nearby genes. This first stage GWAS in a Ghanaian population identified novel SNPs associated with LF risk and underscores the potential of GWAS to provide gene candidates for functional analyses as therapeutic targets towards the 2030 elimination by the World Health Organization.

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GYPB GENE DELETIONS AFFECTS PLASMODIUM FALCIPARUM INVASION OF ERYTHROCYTES AND GROWTH OF SIALIC ACID DEPENDENT PARASITES

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In malaria, invasion of erythrocyte by Plasmodium falciparum, mediated by the active interaction of parasite ligands and host receptors involves sialic acid (SA) dependent or SA independent invasion pathways. GYPA, GYPB and GYPC genes encode glycophorins which serve as host receptors for the invasion of erythrocytes by the parasites. We determined effect of GYPB gene deletion on the invasion and growth of both SA dependent (Dd2) and independent (3D7) parasite strains of P. falciparum in vitro; and changes in the expression of other host erythrocyte surface proteins implicated in malaria pathogenesis. Growth and multi-preference invasion assays were performed using erythrocytes genotyped by PCR-RFLP as wild type (GYPB non-DEL), heterozygous or homozygous for GYPB gene deletion. Flow cytometry analysis was used to determine relative expression of host erythrocyte surface proteins involved in malaria infection comparing erythrocytes with GYPB deletion and wild type. Erythrocytes heterozygous for GYPB deletion were preferentially invaded followed by the wildtype; homozygous were the least invaded. Dd2 strain had significantly ($p<0.05$) poor growth in erythrocytes homozygous for GYPB deletion compared to the wildtype. There was no significant ($p>0.05$) difference in growth of SA independent strain (3D7) in the different erythrocytes. Furthermore, expression of Band 3, transferrin, GYPA and GYPC significantly ($p<0.05$) increased in erythrocytes homozygous for GYPB gene deletion. Integrin was significantly increased in erythrocytes heterozygous GYPB gene deletion whereas there was significant ($p<0.05$) increases in expression of Complement Receptor 1 in erythrocytes homozygous and heterozygous for GYPB deletion. Basigin expression was relatively same in the three groups of erythrocytes. In conclusion, GYPB gene deletions affect parasite invasion and also protein expression on erythrocytes surfaces. Together, these finding suggests a mild protective nature of the GYPB gene deletion in malaria infection and may contribute to explanation for differences in malaria infectious outcomes in different individuals and populations.

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OXIDATIVE STRESS AND ANTIMALARIAL RESPONSES OF BLOOD-STAGE PLASMODIUM FALCIPARUM

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Malaria caused by Plasmodium falciparum is one of the deadliest infectious diseases worldwide, responsible for more than 600,000 deaths in 2020. Rapidly evolving, drug-resistant parasites make the effort for finding new drug targets and understanding the cause of resistance a priority. Drugs treatment and fever condition, as well as infected sickle cells trigger oxidative stress in the asexual stages. Here, we hypothesize that oxidative stress is central to malaria parasite survival in blood stages. To test this, we performed large-scale forward genetic Plasmodium falciparum piggyBac-transposon mutant screens to identify genes with altered sensitivity to oxidative stress. We observed that these genes are linked to lipid metabolism, exportome components, endocytosis, unfolded protein response and splicing machinery. Then, we compared the oxidative stress screen with two previous piggyBac genetic screens: dihydroartemisinin (DHA) and heat-shock screens. Mutants of interest growing in pre-induced oxidative stress were further exposed to selected MMV compounds as well as known antimalarials, such as DHA, Qinghaosu (QHS, artemisinin) and lumefantrine, to determinate if the mutant's sensitivity to the drugs changes in the presence of elevated oxidative stress. Our data shows that exposure to environmental stress factors can alter the response of specific mutants to the inhibitory activity of some compounds. This shift seems to be due to overlap between the mechanism of action of the drug and the altered metabolic activity in the parasite due to the disrupted gene coupled to the commensurate metabolic changes induced by the parasite's stress response. These results suggest that the disruption of artemisinin and oxidative stress sensitive genes likely enhanced the parasite's capacity to mount a response to antimalarials, when the redox homeostasis is destabilized by the oxidative stress environment.

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IDENTIFYING THE DEVELOPMENTAL REGULATORS OF PLASMODIUM FALCIPARUM IN THE MALARIA MOSQUITO ANOPHELES GAMBIAE

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Plasmodium parasites have a complex developmental cycle in the Anopheles mosquito vector that is required for transmission to the next human host. After ingestions with a blood meal and fertilization, parasites form ookinetes that traverse the midgut and differentiate into oocysts, and then the oocysts grow over days and differentiate into thousands of daughter cells called sporozoites, which are the form that infects humans. The survival and growth of parasites is linked to the mosquito reproductive cycle, which is regulated by the steroid hormone 20-hydroxyecdysone (20E). Disrupting 20E signaling by knocking down its nuclear receptor (EcR) reduces the number of ookinetes that transform into oocysts, but the surviving oocysts grow faster and reach infectivity earlier. The multiple effects of 20E on parasites prompted us to determine the genetic mechanisms governing parasite survival and growth, especially during those stages that are essential for transmission. We used single cell RNA-sequencing on parasites isolated from control and EcR knockdown mosquitoes at time points critical for parasite survival and growth. We identified 10 clusters of parasites, including ookinetes, ookinete-oocyst transition stages, and subpopulations of growing oocysts. Our data show that ookinete-oocyst transition is accompanied by downregulation of invasion-related genes and upregulation of ribosomal genes. The growth of oocysts appears instead to be mediated by genes related to the TCA cycle and the mitochondrial electron transport chain. Moreover, genes encoding rhoptry proteins are upregulated in Day 7 oocysts from EcR knockdown mosquitoes relative to the controls, revealing the early processes related to rhoptry biogenesis in the mosquito stage. Overall, this study greatly advances our knowledge of parasite biology within mosquitoes, may facilitate the discovery of novel classes of targets for mosquito-targeted transmission-blocking interventions.

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GENETICS OF THE INTERACTION BETWEEN PLASMODIUM FALCIPARUM AND ANOPHELES ALBIMANUS

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Plasmodium falciparum isolates vary in their infectivity towards different species of Anopheles mosquitoes. This research aims to identify the genetic differences between P. falciparum parasite genotypes that might explain the variation in infectivity to the Central and South American mosquito vector, An. albimanus, and the African vector An. gambiae s.s. These two mosquito species varied in their refractoriness to two clones of P. falciparum (3D7 & HB3), which have been genetically crossed and many recombinant progeny produced. A linkage analysis approach (Quantitative Locus Analysis; QTL) was used to identify the parasite loci involved in the infection prevalence and oocyst intensity of P. falciparum in An. albimanus. Gametocytes of 3D7, HB3 and 17 recombinant progeny clones were grown in vitro, and were fed to mosquitoes using the membrane feeding method. The infected mosquitoes were dissected 10-11 days post-feeding and the midgut was examined for the presence of oocysts. QTL analysis identified three novel loci of which two loci are linked to the infection prevalence, named PfAlbip 1 and PfAlbip 2, spanning 79 kb & 183 kb, and containing 17 & 52 genes respectively. One locus was linked to oocysts intensity, named PfAlboi 1, spanning 46.5 kb, and containing 18 genes. These are the first loci linked to infection prevalence and oocysts intensity of Plasmodium falciparum in An. albimanus.

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FIRST EVIDENCE OF EXPERIMENTAL GENETIC HYBRIDIZATION BETWEEN CUTANEOUS AND VISCERAL STRAINS OF LEISHMANIA DONOVANI WITHIN ITS NATURAL VECTOR PHLEBOTOMUS ARGENTIPES

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Leishmaniasis is a neglected tropical disease caused by the protozoan parasites of the genus Leishmania. More than 20 species of this genus are known to cause disease in humans and other animals. L. donovani species complex is known to have a vast diversity of clinical manifestations in humans but underlying mechanisms for such diversity are yet unknown. Even though these parasites are shown to have a strict asexual life cycle; inter and intra-species genetic exchange of Leishmania spp. through a meiosis-like process in their invertebrate stages of the life cycle have been shown. We investigated the ability of two distinct variants of L. donovani which are responsible to cause visceral and cutaneous forms of the disease, to undergo genetic exchange, inside its natural vector Phlebotomus argentipes sandfly species. Clinical isolates of L. donovani from a Sri Lankan patient with cutaneous leishmaniasis and an Indian patient with visceral leishmaniasis were used as parental strains. Parasites were genetically modified to have single drug-resistant markers along with a fluorescent tag and they were re-suspended in mice blood and fed to sandflies. After the 8th day of post-infection, sandflies were dissected and midgut products were placed in double drug media to selectively grow hybrids. Results revealed two hybrid progenies out of 72 independent mating events that occurred in individual sandflies with a nearly 3% efficiency of hybridization. The intra-species genetic hybridization of L. donovani may explain the extensive phenotypic variations seen in patients in the Indian subcontinent. This provides the first evidence of the hybridization of L. donovani within its natural host Ph. argentipes and also confirms the existence of a sexual life cycle during its extracellular promastigote stages.

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REDUCING MORTALITY DUE TO MALARIA THROUGH IMPROVED HEALTH WORKER PRACTICE, LESSONS FROM A DATA DRIVEN MENTORSHIP PROGRAM IN BUSOGA REGION IN EASTERN UGANDA

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Maintaining adequate malaria surveillance systems is critical for any country to reduce malaria related deaths. According to the World Malaria Report 2022, Uganda contributed 5.1% to the global malaria cases and 3.2% to malaria-related deaths. Busoga Region, with a malaria prevalence of 21% in the Malaria Indicator Survey 2019, reported 390 malaria deaths in 2022 compared with the national average of 4,643 deaths. Malaria death audits, led by the Ministry of Health and health workers at facilities where the death occurred, aim to improve patient care, and avert future deaths. They are often not conducted. The PMI Uganda Malaria Reduction Activity, implemented by JSI, works with the MOH to strengthen malaria prevention and response efforts at all levels in the five highest burden regions of Uganda. In Busoga, a data driven mentorship approach was used to implement death reviews in 84%, 436 out of 517 health facilities. Between June and December 2022, patient records were reviewed to assess patient history, diagnosis, and treatment including complications, care and causes of death. Immediate feedback was provided and action plans developed to address gaps. Weekly malaria data bulletins were assembled, drawing from national HMIS surveillance data, and shared to monitor progress. Between April to December 2022, weekly surveillance data reporting by health facilities improved from 67% to 84% and the number of reported malaria deaths reduced from 103 to 56 deaths. Malaria in pregnancy deaths reduced from 38 to 6. Prompt identification of malaria deaths drove the formal introduction of malaria death audits and reviews in mentored hospitals and other high level health facilities. Better surveillance in Busoga Region through targeted interventions with MOH may have led to improved reporting, early detection of epidemics and contributed to reduced malaria deaths. Improved surveillance coupled with targeted clinical interventions at health facilities can improve reporting, data for decision making, and management of severe malaria cases, leading to a reduction in malaria deaths reported at health facilities.

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MAPPING THE EPIDEMIOLOGY OF DRUG-RESISTANT PLASMODIUM FALCIPARUM STRAINS IN THE GREATER MEKONG SUBREGION THROUGH CROSS-BORDER GENETIC SURVEILLANCE

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The spread of antimalarial-resistant Plasmodium falciparum is a threat to malaria elimination. Transnational data sharing collaboration is crucial,

since policy changes can affect the selection of resistant strains across borders. GenRe-Mekong is project conducting genomic surveillance in partnership with National Malaria Control Programs in the Greater Mekong Subregion (GMS). Here, we present an analysis of epidemiological changes, based on 6,910 P. falciparum dried blood spot samples routinely collected from symptomatic patients in Lao PDR (2017 - 2021), Vietnam (2017 - 2021) and Cambodia (2017, 2020 - 2021). Samples were processed using the SpotMalaria amplicon sequencing platform, which produces genotypes for markers of resistance to several antimalarials, and 101-SNP genetic barcodes. To facilitate translation of these data into actionable information for public health, we developed the grcMalaria R package, which produces intuitive geographical maps of prevalence, diversity and relatedness. This software library is also capable of identifying circulating strains, characterizing their drug resistance profile, and mapping their spread. Since 2020, a decline in case numbers was observed, coinciding with the decline of the dihydroartemisinin-piperaquine (DHA-PPQ)-resistant KEL1/PLA1 lineages which dominated the GMS for years. Piperaquine resistance reduced from 60% in 2017-2020 to 4% in 2021, after Cambodia, Thailand, and Vietnam switched from DHA-PPQ to other artemisinin-based combination therapies. Interestingly, this decline also occurred in Laos, where DHA-PPQ was not in use. Artemisinin resistance levels remained high, with an overall prevalence of 71%. Cluster analyses revealed that former KEL1/PLA1 lineages highly prevalent in Vietnam lost their pfplasmepsin2/3 amplification in the absence of piperaquine pressure. In Cambodia, where artesunate-mefloquine has been selected as frontline treatment, there is currently no indication of emerging resistance to mefloquine. Our results indicate that cross-border genetic surveillance is a strategic knowledge tool to inform elimination interventions.

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LOSING SLEEP OVER DENOMINATORS: A NOVEL METHODOLOGY FOR MALARIA EPIDEMIOLOGICAL SURVEILLANCE USING FACILITY BASED DATA FROM SOUTHERN SENEGAL

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Estimates of the heavy malaria burden in Senegal have varied. In 2013, the routine surveillance system calculated annual incidence by dividing the number of rapid diagnostic test (RDT) positives reported by all health posts and community health workers (CHWs) within a catchment area by the official National Health Information Service population of that catchment area. However, using the population of the entire zone in the denominator may artificially deflate the estimate as many inhabitants face considerable barriers to accessing RDTs. The Médina Yoro Foulah Health District had an officially reported annual incidence rate of 145 cases per 1000 persons in 2013, but 74% and 24% of its population lived more than 5k and 10k from a health post respectively. To better quantify malaria incidence, a review of patient consultation records from all health posts and CHWs for the April 2013-March 2014 transmission season was conducted. Five district-level annual incidence estimates were compared: (1) the officially reported incidence rate (ORIR) calculated as the number of RDT positives officially reported by all zones divided by the official district population; (2) the study derived catchment area incidence rate (SCIR) calculated as the number of RDT positives collected by this study from all zones divided by the official district population; (3) the adjusted SCIR which adjusted the number of RDT positives for periods of RDT stock-outs; (4) the study derived sample incidence rate (SSIR) calculated as the number of RDT positives of residents in towns with health posts divided by the population of these towns; (5) the adjusted SSIR which again accounted for RDT stock-outs. The ORIR for these nine catchment areas was 161 per 1000 persons (19,673 cases for the population of 121,928), SCIR was 217, adjusted SCIR was 233, SSIR was 323, and adjusted SSIR was 342. Spatiotemporal data across the sites will be described. Differences among the estimates highlight how aggregated facility-based data can severely underestimate incidence in rural catchment areas where the population has limited access to care.

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UPDATING THE MALARIA RISK STRATIFICATION IN LAO PDR TO INFORM INTERVENTION TARGETING AND RESOURCE ALLOCATION

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Lao PDR aims to eliminate P. falciparum malaria by the end of 2023 and all malaria species by 2030 through strategically targeted intervention packages that are tailored according to malaria burden. From 2019 to 2022, malaria cases have declined by 65% and as of 2022, 10 districts across 4 southern provinces accounting for 86% of all cases that year. The distribution of malaria burden is increasingly heterogenous and focalized, highlighting the importance of appropriately adapted interventions. To target remaining hotspots and efficiently use limited resources, the Lao Centre of Malariology, Parasitology and Entomology (CMPE), in partnership with WHO and CHAI, updated the country's malaria risk stratification in 2022. Health facilities were categorized into one of four strata, from malaria-free to high-risk, with each strata designated to receive a specific set of interventions. The update was based on case data from January 2019 through December 2021 and supplemented with a modeled risk map developed by the Malaria Atlas Project (MAP) based on combined epidemiological data and 16 ecological factors. In the 2022 stratification, 88 health facilities (7.2%) were classified as high risk, 97 (7.9%) as moderate risk, and 193 (15.7%) as low risk. Attapu and Salavan provinces had the most health facilities categorized as high risk, where 54% and 27% of all provincial health facilities are high risk, respectively. Compared to the previous stratification exercise in 2019, there was a 53% decrease in the number of health facilities classified as high risk, evidence of the substantial progress made towards reducing malaria burden in the highest-burden places. There was no change in the proportion of health facilities classified as low or moderate risk. Access to quality testing, treatment, education activities are universal. The highest-burden villages within the moderate-risk strata and all villages within the high-risk strata will be allocated village malaria workers and receive long-lasting insecticide-treated nets. CMPE will routinely update the stratification and adapt intervention packages as the country progresses closer to elimination.

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QUANTIFYING THE VALUE OF ENTOMOLOGICAL SURVEILLANCE FOR PROGRAMMATIC DECISION-MAKING ON MALARIA CONTROL IN SUB-SAHARAN AFRICA

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The availability of many different tools for malaria control leads to complex decisions on the most cost-effective intervention package based on local characteristics in a setting. We aimed to quantify the monetary value of information provided by entomological surveillance for programmatic decision-making. We used a mathematical model of Plasmodium falciparum to simulate the 3-year impact and cost of various intervention packages in a range of transmission settings in sub-Saharan Africa. Interventions consisted of combinations of increasing insecticide-treated net (ITN) usage, switching from pyrethroid-only to next-generation PBO or pyrrole ITNs,

and alternatives to vector control (increased treatment, seasonal malaria chemoprevention and/or the RTS,S vaccine). We compared their net monetary benefit at a threshold of US$250 per day averted and calculated the value of resolving uncertainty about the level of pyrethroid insecticide resistance, the associated effectiveness of ITNs, and biting behaviour in the local mosquito population. Across transmission settings, the most cost-effective intervention package on average was switching to pyrrole ITNs, increasing ITN usage and increasing vector control alternatives, but there was uncertainty in the optimal intervention in each setting. The median expected value of perfect information on the entomological indicators was US$0.09 (range 0.01-0.72) per person at risk, corresponding to 0.17 (range 0.03-1.02) times the annual cost of distributing pyrethroid ITNs at baseline. This was highest in high-prevalence highly seasonal settings and lowest in low-prevalence perennial and seasonal settings. Resistance levels and ITN effectiveness influenced intervention choice most, but the value of data collection on a single indicator was 0 in 89% of settings. These results suggest that further investments in entomological surveillance are needed to facilitate decision-making on malaria interventions. Integrated programmes for data collection on a range of entomological factors are preferable, while prioritisation of areas based on seasonality and prevalence could be considered.

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MALARIA ATLAS PROJECT (MAP) HIGH BURDEN HIGH IMPACT (HBHI) GEOSPATIAL FRAMEWORK; LESSONS LEARNT FROM SUPPORTING THE GLOBAL FUND APPLICATIONS

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Since inception of High Burden High Impact (HBHI) Initiative in 2018, Malaria Atlas Project (MAP) have provided estimates of burden metrics - particularly prevalence to support namely the HBHI countries. Between the cycles, the MAP team have worked to build a novel modelling framework. Such framework leverages strengths from local surveillance data coming from multiple streams, for example, routine case incidence routinely collected from health systems (DHIS2) and nationally representation cross-sectional surveys collecting information on malaria prevalence, fevers, treatment seeking and treatment (MIS/DHS). In turn, we are able to produce robust and accurate sub-national predictions of malaria prevalence and incidence at the finest temporal cadence available from the data (e.g. monthly), with intention that these maps would support evidence based decision making. This framework encapsulates many of the same conceptual thinking of malaria transmission from fever in the community, care seeking behavior, response to effective treatment, parasite clearance and testing rates. The framework builds on guidelines outlined by WHO when adjusting routine incidence data from health systems and takes advantage of several modelling frameworks at each stage to provide an accurate risk map. It further builds in a flexible and locally driven relationship learnt in space-time between prevalence and incidence. Here we present the outputs created for an HBHI country and review both metrics of incidence and prevalence against the previous iterations used in sub-national tailoring and discuss how use of different metrics can affect choices in the sub-national tailoring exercise. We explore how different analytical ways to categorize burden metrics can change perception of high, medium, and low risk in areas and provide recommendations to curb known biases.

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PROGRESS TOWARDS INTERRUPTING TRANSMISSION OF ONCHOCERCIASIS IN ETHIOPIA

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Ethiopia aims to eliminate transmission of onchocerciasis by 2030. The implementation unit for treatment decisions in Ethiopia is the district, which usually has a population of <200,000. Districts qualify for impact assessments after at least 10 rounds of semi-annual ivermectin mass drug administration (MDA) with at least 80% coverage of the eligible population. If Ov16 antibody prevalence in samples in 300-500 children 5-9 years of age is <1%, the district may proceed to stop MDA serological and entomological surveys. For stop MDA surveys, 2-3 districts were clustered together into operational transmission zones (OTZ) according to geographical proximity, common river basins, and similar epidemiology. A combination of multi-stage random and purposive cluster sampling was used to select the study sites and population. From each OTZ, more than 3,000 dried blood spots (DBS) from children aged 5-10 years and at least 6000 Simulium vectors were collected in accordance with WHO guidelines. Of the 96 districts undergoing impact assessment from 2016 to 2022, 73 (75%) had ≤ 1.0% Ov16 prevalence and became eligible for stop MDA evaluations. More than 58,500 DBS were then collected for these studies from Oromia, Southwest Ethiopia, and Amhara regions between 2017 and 2022. DBS were analyzed for Ov16 antibody prevalence by ELISA, while more than 40,000 black flies were collected and analyzed by O-150 PCR. Significant reductions in onchocerciasis prevalence were observed in many districts, with 28 (38%) satisfying WHO's stop MDA criteria of Ov16 antibody prevalence below 0.1% and black fly infectivity significantly less than 1/2000. An additional 25 (34%) districts passed the serological criterion but need entomological evaluation. In contrast, 19 (26%) districts failed their stop MDA evaluation and need to continue MDA with improved drug distribution and supportive supervision. Treatment compliance issues, migration, and vector dynamics could be driving continued transmission. Nonetheless, 3.2 million people in 28 districts no longer require MDA for onchocerciasis. Ethiopia is advancing towards onchocerciasis elimination.

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RESULTS FROM AN ENHANCED TRACHOMA IMPACT SURVEY IN FOUR LOW PREVALENCE DISTRICTS OF MOZAMBIQUE, 2022

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In Mozambique 47 out of 66 endemic districts have attained elimination of trachomatous inflammation-follicular (TF, prevalence <5%). However, persistent and recrudescent trachoma is a growing problem with districts reporting TF prevalences of 5-9.9%. It is not clear if this level of TF prevalence (5-9.9%) is due to ocular chlamydial infection or statistical sampling errors. We added testing of ocular Chlamydia trachomatis (Ct) infection and serology into routine trachoma impact surveys (TIS) to investigate: 1) if TF indicates conjunctival Ct infection in low prevalence settings; 2) population-level measures of trachoma transmission based on

antibody response; and 3) correlations of TF, Ct infection and serology. An enhanced TIS was done in four districts where 24 clusters were sampled in each district, and 35 households surveyed per cluster with the aim of including 1,164 children aged 1 to 9 years. The survey combined eye examination for trachoma with sampling of ocular swabs and dried blood spots (DBS). Ocular swabs were tested for Ct infection using iAMP CT detection Kit while DBS were tested for chlamydial pgp3 using lateral flow assay. We calculated yearly seroconversion rates using age-standardized district-level seroprevalence and examined correlation between cluster prevalences of each diagnostic result. TF prevalence ranged from 1.1% (95% confidence interview [CI]=0.3-2.2%) in Ilha Mozambique to 6.0% (95% CI=2.8-8.6%) in Inhassunge. Ct infection prevalence ranged from 1.1% (95%% CI=0-2.5% in Ilha de Moçambique to 4.8% (95% CI=2.2-7.4%) in Mossuril. Pgp3 prevalence ranged from 8.4% (95%CI=5.1-14.3%) in Ilha Mozambique to 25.1% (95% CI=(22.5-27.9%) in Inhassunge. Yearly seroconversion rates ranged from 2.1 (95%CI=1.7-2.5) in Ilha de Moçambique to 6.6 (95%CI=5.8-7.4) in Inhassunge. Correlations of TF, Ct infection and pgp3 varied across the four districts. Ct infection and pgp3 serology suggest ongoing transmission of ocular chlamydia in three out of four districts. Thus, despite having attained TF prevalence of <5%, further interventions or monitoring should be considered in Mossuril and Nacala-A-Velha districts.

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SOIL TRANSMITTED HELMINTH INFECTIONS FOLLOWING FOURTEEN YEARS OF MASS DRUG ADMINISTRATION IN SIERRA LEONE

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Baseline mapping surveys conducted in 2008/09 in Sierra Leone found soil-transmitted helminth (STH) infections in all 16 districts, with moderate prevalence (≥20% to <50%) in eight districts and high prevalence (≥50%) in eight districts. Since 2008, STH mass drug administration (MDA) has been integrated with lymphatic filariasis (LF) MDA for all persons five years and above in all districts. In 2016, an impact assessment was conducted to assess the impact of five years of MDA. The results of this survey found three districts with low prevalence (≥1% and <10%), five districts with prevalence ≥10% and <20%, and eight districts with moderate prevalence (≥20% and <50%). Current STH MDA is integrated with LF (1 district) or with onchocerciasis (targeting SAC only). A school-based impact assessment was conducted in October 2022, nine months after the last MDA, to determine the current prevalence and intensity of STH infections in children aged 5-14 years. The survey was carried out in 128 chiefdoms across nine districts (all identified as endemic for schistosomiasis in the 2016 assessment). A total of 201 communities were selected using probability proportional to population size of the chiefdoms, with specific sampling in large towns and small chiefdoms. Fresh stool samples were examined by Kato Katz (two slides per sample) from children aged 5-14 years. A total of 4,736 (male: 51%, female: 49%) children were examined for STH infections. Overall prevalence of all species and any STH was low - Ascaris lumbricoides: 2.2% (95% CI: 1.8-2.7), Trichuris trichiura: 0.3% (95% CI: 0.2-0.5), hookworm: 4.4% (95% CI: 3.8-5.0) and any STH: 5.4% (95% CI: 4.8-6.0). All districts had a prevalence of hookworm and any STH below 10% except for Kenema (12.1% and 14.5% for hookworm and any STH, respectively). The arithmetic mean intensity in all children examined for hookworm was 4.4 epg (95% CI: 3.3-5.4 epg) compared to 45.5 epg (95% CI: 36.0-55.1 epg) in 2016. STH infections in SAC have reduced significantly; however, the impact of MDA should be assessed in the remaining seven districts to ascertain the level of STH in Sierra Leone.

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PROGRESS IN THE ELIMINATION OF THE TRANSMISSION OF SOIL-TRANSMITTED HELMINTHS IN THE WOLAITA ZONE IN SOUTHERN ETHIOPIA. THE GESHIYARO PROJECT MID-TERM PROGRESS EVALUATION

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Repeated MDA is required to control SCH and STH due to the failure of the human host to build up acquired immunity to reinfection. This study's objective is to evaluate the effectiveness of community-based interventions delivered via the Ministry of Health's continuing neglected tropical disease (NTD) control programmes. The Geshiyaro is a large-scale project in Ethiopia funded by the Children Investment Fund Foundation (CIFF) that aims to interrupt transmission of SCH parasites. There are three intervention arms. These are community-wide MDA (cMDA) + expanded WASH (enhanced over the existing government run one-WaSH programme) in Arm 1, cMDA + one-WaSH in Arm 2, and school-based MDA (sMDA) with the one-WaSH program in Arm 3. Progress is evaluated with periodic parasitological surveys conducted before MDA rounds in longitudinal sentinel sites. Compared to the baseline survey, the prevalence of STH infection decreased significantly from 34.5% in 2018/2019 to 10% ($p<0.010$) in 2021/2022 in Arm 1 (Bolosso Sore part of Arm 1), from 27.4% in 2019/2020 to 10.2% in 2021/2022 ($p<0.001$) in Arm 1 (remaining districts in Arm 1), from 23% in 2019/2020 to 5% in 2021/2022 ($p<0.001$) in Arm 2, from 49.6% in 2019/2020 to 43.4% in 2021/2022 ($p<0.001$) in Arm 3. The decrease in prevalence in Arm 3 was low compared to the other arms. The mean intensity of infection (based on Kato Katz egg count measures) for all parasite species decreased significantly in Arms 1 and 2, but not in Arm 3. The reduction in prevalence and intensity in Arms 1 and 2 revealed steady progress towards transmission interruption. More progress is required, through increasing MDA compliance (swallowing of treatment) in all villages. In the long term, continued improvements in WaSH are required to sustain the benefits achieved by cMDA.

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METHODS FOR TRACHOMA SURVEYS AMONG MOBILE AND MIGRANT POPULATIONS OF KWEEN AND BULAMBULI DISTRICTS, EASTERN UGANDA

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Uganda has made progress towards elimination of trachoma with 56 out of 61 endemic evaluation units having attained trachomatous inflammation-follicular (TF) prevalence of <5%. However, trachoma has remained persistent or recrudescent in Karamoja Region (Eastern Uganda) where mobile and migrant populations (MMP) comprising of nomadic pastoralists seasonally migrate across the porous Uganda/Kenya border. Kween and Bulambuli districts, both neighboring Karamoja region, were not suspected to be trachoma endemic. The two districts, seasonally, host MMP from neighboring Karamoja districts and West Pokot in Kenya where trachoma is still endemic. Given the high risk of trachoma where the nomadic pastoralists come from, there is need to determine the prevalence of trachoma among the pastoralists and to investigate the prevalence of trachoma among the host communities in Kween and Bulambuli districts. This trachoma baseline survey aimed to estimate prevalence of (TF) in children aged 1-9 years and trachomatous trichiasis (TT) in adults aged 15 years and above in Kween and Bulambuli districts and the MMP. Three evaluation units (EUs) were defined, and sampling frames developed comprising: 1) permanent settlements in Kween; 1) permanent settlements in Bulambuli; and 3) temporary MMP cattle camps across both Kween

and Bulambuli. A two-stage cluster random sample design was used to select villages (clusters) at stage one and households at stage two. Based on sample size estimates, 20 clusters were sampled in MMP EU and 24 clusters sampled in the other 2 EUs; and 30 Households surveyed in each cluster. Examination for trachoma was done using the WHO grading system and data was collected using the Tropical Data system. Results showed that TF prevalence was <5% and TT prevalence was<0.2%. Findings from the MMP EU suggest that the cattle camp population comprised mainly on young boys and adult men who are primarily tasked with livestock grazing roles. Pre-school children, who typically have the highest prevalence of TF were absent from the MMP EU. Therefore, access to SAFE interventions is still needed among the MMP when they return to the home districts.

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USE OF INVERSE DISTANCE WEIGHTING INTERPOLATION MODELLING AND GIS-BASED SPATIAL MAPPING TO ESTIMATE THE RISKS OF HOOKWORM AND INTESTINAL SCHISTOSOMIASIS INFECTIONS IN GHANA

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The global health community has established 2030 as the target year for the elimination of Neglected Tropical Diseases (NTDs), including hookworm and intestinal schistosomiasis. The current strategy to achieve this objective includes integrated implementation of mass drug administration of deworming drugs, along with WASH and health education interventions. Questions have been raised about the feasibility of achieving the goal, especially with the challenges of implementation in low-resourced settings and hard-to-reach areas. To enable a focused targeting of resources to reduce transmission and achieve elimination in endemic communities, we aimed to identify the high-risk areas for hookworm infection and intestinal schistosomiasis in Ghana using Geographic Information Systems (GIS)-based spatial analysis with inverse distance weighting (IDW) interpolation. Residents from 52 communities in 17 districts from 11 regions across Ghana were enrolled in a baseline survey. 4,753 individuals were surveyed, and stool samples were collected for the detection of intestinal parasites using the Kato-Katz method. The community-wide prevalences of hookworm infection (range: 1-37%) and intestinal schistosomiasis (range: 1-49%) were plotted and georeferenced on the spatial polygon of Ghana. The IDW mathematical interpolation model was used to estimate unknown values by specifying search distance, barriers, and closest points to produce country-wide risk maps. The predictive model revealed a 21% risk of hookworm in the middle belt of Ghana, and a 33% risk of intestinal schistosomiasis in northern and south-eastern Ghana, mostly in areas along the Volta Lake and irrigation schemes respectively. Our findings provide information that will assist Ghana's national NTD Elimination Programme, allowing it to utilize its limited resources efficiently and in a timely manner by reinforcing preventive measures in the areas of highest risk.

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IMPROVED QUALITY OF NEGLECTED TROPICAL DISEASES MICRO PLANNING IN ROUTINE DEWORMING CAMPAIGNS THROUGH INNOVATIVE SOLUTIONS AND TOOLS IN KENYA

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Akros, the End Fund, and Kenya's Ministry of Health (MOH) aimed to improve the quality of neglected tropical diseases (NTD) microplanning in routine deworming programs. Collaborators adapted and piloted geo-enabled microplanning tools for the 2021 schistosomiasis (SCH) and soil-transmitted helminths (STH) campaigns in Kenya. All tools were adapted in line with the six steps of the WHO microplanning process. A qualitative approach was applied to gather and analyze user feedback to inform new iterations of the tools and processes. In 2022, the DVB-NTD Unit scaled the subnational microplanning tools to 142 wards across four counties. The digital Reveal platform was used during the MDA campaign implementation in Vihiga County to improve data collection and data use for decision making. In 2022/23, a qualitative assessment was used to evaluate the approach. Findings showed that microplanning tools improved coverage and reach of MDAs through better understanding of size and distribution of the target population. 92% of respondents felt that developing a microplan increased their geographic coverage; 84% felt that it increased their population reach. Microplanning improved allocation of resources for the MDA, through more efficient drug and HR allocation and improved social mobilization. 97% felt the microplanning process and tools led to more efficient allocation of drugs resources. 100% felt that data collection using the Reveal tool added value to efficient drug allocation; the dashboards provided real-time data on drug stock levels used to make mid-campaign re-allocation decisions. Finally, microplanning resulted in better assessment of program performance, through improved supervision and accountability and faster and more accurate reporting. A total of 97% of respondents felt that developing a microplan increased their data use when planning the 2022 MDA campaign. 90% felt that Reveal resulted in more timely and accurate reporting. Discussions are underway about integrating the Reveal microplanning features into the improved eCHIS for scale in Kenya.

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NON-HUMAN PRIMATE AOTUS NANCYMAAE MODEL FOR THE EVALUATION OF PLASMODIUM VIVAX BLOOD STAGE VACCINES

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Few well-established in vivo models reflect the biological complexity of human malaria immunity and infection, and even fewer have been predictive in testing potential malaria vaccines or prophylactic therapies. Previously, we performed a stringent pre-clinical Aotus nancymaae non-human primate model to evaluate active blood stage vaccination and passively administrated monoclonal antibodies against Plasmodium falciparum blood infection. Here, to develop a consistent and reliable P. vivax blood stage model, we identified a virulent monkey-adapted P. vivax strain capable of producing a robust blood stage infection in A. nancymaae monkeys, the Vietnam-IV strain. A second experiment was performed to determine the effective parasite infection dose of the Vietnam-IV strain. Spleen-intact monkeys were infected with doses of 0.3 x 10^6 infected Red Blood Cells (iRBC) (n=3), 1.0 x 10^6 iRBC (n=6), and 2.5 x 10^6 iRBC (n=3). Our data showed positive parasitemia by microscopy at day 11 ± 1, 6 ± 1, and 5 ± 1; day of peak parasitemia at 14 ± 3, 14 ± 3, and 13 ± 2; and maximum parasitemia of 2517 ± 1130, 41747± 68672, 16400 ± 3735 parasites/µL for the 0.3, 1.0 and 2.5 x10^6 dose, respectively. In addition, we measured hematocrit % (HCT) and platelets (PLTs) as markers of disease in monkeys infected with the lowest two doses. We observed a significant decrease in HCT from a baseline of 53 ± 2 to 39 ± 2 that correlated with cumulative parasitemia. In addition, we observed a significant decrease in PLTs from a baseline of 295 ± 102 vs 43 ± 25, which occurred prior to peak parasitemia and required treatment. The whole genome of Vietnam-IV was sequenced, and data for protein vaccine targets such as CSP, CelTOS, DBP, and MSP-1 are publicly available. Early analysis suggests the presence of a single gene copy for the leading P. vivax blood stage vaccine target, DBP-II, with only previously identified single nucleotide polymorphisms that do not correspond to antibody binding sites. In summary, we showed a

consistent and reliable P. vivax blood stage A. nancymaae model with well-characterized genomic data. This forms the foundation for the evaluation of emerging blood stage vaccines.

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A HUMAN ANTIBODY EPITOPE MAP OF PFS230D1 DERIVED FROM ANALYSIS OF INDIVIDUALS VACCINATED WITH A MALARIA TRANSMISSION-BLOCKING VACCINE

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Pfs230 domain 1 (Pfs230D1) is an advanced malaria transmission-blocking vaccine antigen demonstrating high functional activity in clinical trials. However, the structural and functional correlates of transmission-blocking activity are not defined. Here, we isolated sixty-three human monoclonal antibodies (hmAbs) with diverse transmission-reducing activity from vaccinees immunized with Pfs230D1. Epitope binning data from seventeen hmAbs showed they interact with distinct regions of Pfs230D1. We biophysically characterized the interaction of Pfs230D1 with nine individual hmAbs and showed they all have nanomolar affinities. Furthermore, we obtained atomic resolution structural definition of the binding epitopes of these complexes by X-ray crystallography. We compiled epitope-binning data and crystal structures of nine hmAbs complexes to construct a high-resolution epitope map and revealed the potent transmission-reducing hmAbs bound to one face of Pfs230D1 while the non-potent hmAbs bound to the opposing side. An additional structure of Pfs230D1D2 revealed that the non-potent transmission-reducing epitopes are occluded by the second domain. We further examined synergistic antibody combinations that may facilitate passive transfer of human antibodies as transmission blocking interventions. The hmAb epitope map identified binary hmAb combinations that synergized for extremely high-potency transmission-reducing activity. This work provides a high-resolution guide for structure-based design of enhanced immunogens, develops potent antibody combinations to combat transmission, and informs diagnostics that measure the transmission-reducing response.

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TWO NOVEL PFS230 DOMAINS DISCOVERED AS TARGETS FOR MALARIA TRANSMISSION-BLOCKING ANTIBODIES

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Malaria transmission-blocking vaccines (TBVs) aim to induce antibodies that block Plasmodium parasite development in the mosquito midgut, thus preventing formation of infectious mosquitoes. The clinically most advanced TBV candidate is Pfs230-D1M, which contains part of the Pro-domain (Pro) and first of fourteen 6-Cys domains (D1) of the gamete surface protein Pfs230. Whether other domains of Pfs230 contain epitopes that are targets for transmission-blocking antibodies is unknown. We identified a murine monoclonal antibody (mAb), 18F25.1, that targets an epitope outside Pfs230-ProD1. Using a panel of recombinant Pfs230 fragments produced in wheat germ cell-free system, we demonstrate that mAb 18F25.1 targets Pfs230-Domain 7 (D7). All functional Pfs230 mAbs described to date are complement-dependent, whereas 18F25.1 is a non-complement-fixing subclass mAb. We therefore generated a subclass-switched antibody, mAb 18F25.2a, using a CRISPR/Cas9-based hybridoma engineering method. mAb 18F25.2a potently lysed female gametes in vitro whereas the parental mAb 18F25.1 did not. Importantly, mAb 18F25.2a strongly, in a complement-dependent manner, reduced P. falciparum infection of Anopheles mosquitoes in standard membrane feeding assays (SMFAs). Inspired by this finding, we attempted expression of all fourteen individual Pfs230 domains in insect cells. Eight fragments were obtained in sufficient quantity for mouse immunizations. Sera raised against one of the non-ProD1 and non-D7 domains almost completely blocked parasite transmission in SMFA, with similar potency as sera raised against ProD1. The induced transmission-blocking antibodies were fully dependent on complement. We have raised a panel of 15 mAbs against this domain and are currently assessing epitope specificity and potency in SMFA. Results from these analyses will also be shared during the meeting. After 30 years of research on this leading TBV candidate, we provide the first conclusive evidence that Pfs230 domains D2-14 contain functional targets. Our study provides a strong incentive to further evaluate these identified Pfs230 domains as TBV candidates.

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NOVEL BLOOD-STAGE VACCINE CANDIDATE RH5.1/AS01B ELICITS A MIX OF NEUTRALIZING AND NON-NEUTRALIZING PLASMA IGG LINEAGES IN MALARIA-NAÏVE UNITED KINGDOM ADULTS

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Malaria Plasmodium falciparum blood-stage infection, initiated by merozoites, is susceptible to vaccine-induced antibodies. Reticulocyte Binding Protein Homologue 5 (RH5) is a merozoite surface antigen that has low polymorphism frequencies and uses a non-redundant red blood cell (RBC) invasion pathway, overcoming bottlenecks of previous blood-stage vaccine antigen candidates. The Draper Lab (Oxford University) clinically tested RH5.1, an engineered variant of RH5, in AS01B adjuvant (GSK) designed to boost long-lasting, protective antibody titers. United Kingdom malaria-naïve adult volunteers were vaccinated with RH5.1/AS01B and challenged with controlled human malaria infections. RH5-specific B cells were isolated from volunteers and their B cell receptors (BCRs) were sequenced, from which potent, neutralizing monoclonal antibodies (mAbs) were discovered able to inhibit merozoite invasion and growth in vitro. In contrast, the polyclonal plasma IgG of volunteers exhibited an average neutralizing potency over 10-fold greater than the average potency of individual mAbs cloned from B cells. This observation raised a question: what is the disconnect between the BCR and circulating IgG repertoires? To address this knowledge gap, we completed BCR sequencing coupled with plasma IgG proteomics to characterize in depth the polyclonal plasma antibody repertoires of individual volunteers. Plasma mAbs were identified that bind to previously described merozoite inhibitory epitopes, including those that block binding between RH5 and its RBC coreceptor, CD147 (Basigin), alongside a unique population of mAbs that synergize with neutralizing mAbs for increased potency. Notably, in the plasma repertoire of some donors, non-neutralizing mAbs targeting cryptic epitopes on the N- and C-terminus were found at much higher relative abundance than neutralizing mAbs; these mAbs are not well understood and suggest unknown functions. This dynamic between neutralizing and non-neutralizing plasma mAbs needs to be further explored in the context of blood-stage protection and future RH5 vaccine engineering efforts.

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PROTECTIVE IMMUNE MECHANISMS INDUCED BY THE RTS,S MALARIA VACCINE IN A PEDIATRIC PHASE IIB CLINICAL TRIAL

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Plasmodium falciparum malaria is a major cause of global morbidity and mortality, especially in children. RTS,S is the only available malaria vaccine, recommended for young children in regions with moderate to high malaria transmission. RTS,S is a virus-like particle expressing the major P. falciparum sporozoite surface antigen, circumsporozoite protein (CSP), but only has modest efficacy in malaria endemic populations. Protection is primarily mediated by anti-CSP antibodies, but the immunological mechanisms involved are unclear, which hinders efforts to improve RTS,S and develop next-generation vaccines. We recently discovered that anti-CSP antibodies can interact with serum complement proteins leading to parasite lysis and interact with Fcγ-receptors (FcγRs) to promote opsonic phagocytosis and NK cell activation. Here, we evaluated multiple functional antibodies that interact with complement and FcγRs in a phase IIb pediatric trial of the RTS,S vaccine in Mozambique (n=737) and machine learning methods to identify responses most strongly predictive of protection. RTS,S broadly induced antibodies (IgG, IgM, and IgA isotypes) that interact with complement and FcγRs (FcγRI, FcγRIIa, FcγRIII). Functional antibodies recognized the immunodominant central-repeat and C-terminal regions of CSP, which were correlated with the induction of IgG1 and IgG3 subclasses. Responses were variable and negatively correlated with age and magnitude of exposure to malaria. We identified antibody Fc-dependent functional activities targeting specific CSP domains that were associated with protection against malaria over 1.5 years of follow-up and found differences in protective associations in boys and girls. Our findings suggest that antibody Fc-dependent functional activities are important in vaccine-induced immunity, and the variable induction of responses may explain why efficacy is modest overall. Knowledge of the functional activities and targets of protective antibodies, sex-based differences, and the impact of malaria exposure on vaccine responses, provides a basis for designing novel vaccines to achieve higher efficacy.

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THE FINAL RESULTS OF A FIVE-YEAR, DOUBLE-BLIND, RANDOMISED CONTROLLED PHASE 3 TRIAL OF SEASONAL VACCINATION WITH RTS,S/AS01E VACCINE WITH OR WITHOUT SEASONAL MALARIA CHEMOPREVENTION IN YOUNG CHILDREN IN BURKINA FASO AND MALI

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Seasonal vaccination with the RTS,S/AS01E malaria vaccine combined with Seasonal Malaria Chemoprevention (SMC) prevented malaria in young children more effectively than either intervention given alone over a period of three years. The study objective was to determine whether this protection could be sustained when further doses of seasonal vaccination with RTS,S/AS01E were given until children reach the age of five years. Children 5-17 months of age were initially randomised to one of the three treatments groups, SMC plus control vaccines, RTS,S/A01E plus placebo SMC, or SMC plus RTS,S/A01E, and continued to receive the same interventions for two additional years. Over five year period of the trial, the incidence rate of clinical malaria per 1000 person-years at risk was 313 in the SMC alone group, 320 in the RTS,S/AS01E alone group, and 133 in the combined group. The combination of RTS,S/AS01E and SMC had a superior protective efficacy (PE) compared to both SMC (PE 57.7%, 95% CI 53.3, 61.7) and RTS,S/AS01E (PE 59.0%, 95% CI 54.7, 62.8) when given alone. RTS,S/AS01E remained non-inferior to SMC in preventing clinical malaria (hazard ratio 1.03 [95% CI 0.95, 1.12]). Over the five-year period, hospital admissions for WHO-defined severe malaria, malarial anaemia, blood transfusion, all-cause deaths, deaths excluding external causes/surgery, and deaths from malaria were reduced by 66.8% (95% CI 40.3, 81.5), 65.9% (95% CI: 34.1, 82.4), 68.1% (95% CI: 32.6, 84.9), 44.5% (95% CI: 2.77, 68.3), 41.1% (95% CI: -9.24, 68.3), and 66.8% (95% CI: -2.68, 89.3), respectively, in the combined intervention group compared to the SMC alone group. This study has shown the persistent high risk of malaria in children in Burkina Faso and Mali until they reach the age of five years and the need to provide these children with effective malaria control measures until they reach this age and perhaps beyond.

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RESULTS FROM A PHASE III TRIAL EVALUATING THE R21/MATRIX-M MALARIA VACCINE

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There is currently only one licensed malaria vaccine. Deployment is expected over 2023 but limited supply (6 million doses on average a

year for 3 years from 2023) may hinder efforts to substantially reduce the global malaria burden. Furthermore, its efficacy is below what is needed. Development of other malaria vaccines is required to achieve the WHO malaria goals by 2030. In 2021, 4800 participants, aged 5-36 months, were enrolled into a phase III double-blind, randomised controlled trial assessing the R21/Matrix-M™ adjuvant (R21/MM) malaria vaccine, at five African sites in Burkina Faso, Kenya, Mali, and Tanzania, with a range of transmission patterns (seasonal and perennial) and intensity. All participants were randomised 2:1, R21/MM: control rabies vaccine. They received 3 doses, 4 weeks apart, followed by a booster dose a year later. At 12 months following the primary series of vaccinations, evaluation of time to first clinical malaria episode demonstrated vaccine efficacy (VE) of 75% [71-79] at the seasonal sites and 68% [60-74] at the perennial sites. When combining all sites, VE was 73% [69-76]. VE was significantly higher when comparing the 5-17-month age group (VE 78% [73-82]) with the 18-36-month age group (VE 69% [64-74]. At six months following a booster vaccination (one year after the primary series), VE was 75% [71-78] at the seasonal sites. VE did not change significantly when assessing single or multiple episodes of malaria. Six SAEs, all febrile convulsions, were assessed as definitely, probably or possibly related to study vaccination following approximately 19,000 doses of the malaria or rabies vaccine. Further safety and efficacy data from the second year of follow-up will also be presented. WHO prequalification and regulatory licensure applications are underway and initial deployment of R21/MM is expected in the coming months. The Serum Institute of India Pvt. Ltd have committed to large-scale manufacturing and supply. High-level efficacy of this vaccine, combined with the commitment to large-scale supply, at low cost, should have a significant impact now, and in the long term, on the lives of those in malaria endemic areas.

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EXAMINING THE EFFECT OF NEIGHBORHOOD LATRINE COVERAGE ON CHILDHOOD DIARRHEAL RISK IN RURAL BANGLADESH

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Sanitation in low-income settings may have surprisingly minimal direct health effect on children living in households with toilets; but evidence suggests that neighborhood latrine coverage may impact herd protection against diarrhea. The mechanisms of this herd protection, though crucial to the design of effective interventions, remain unknown. The WASH Benefits (WASH-B) Bangladesh trial, coupled with a nested environmental impact study among a subset of participants, provide a unique opportunity to leverage trial data to address this important question. Diarrheal prevalence was estimated among children enrolled in the sanitation and control arms of the parent trial. The nested study collected compound-level information on each neighboring compound (n=8,317) within 100 m of each study compound (n=720), including GPS coordinates, number of people in the compound, and number and quality of latrines. Using neighborhood data from the nested study, we developed a function to estimate total neighborhood fecal exposure within 100 m for each study compound, accounting for population density, reduction of fecal exposure from both hygienic and unhygienic latrines, and spatial distance between compounds. We then modeled the relationship between total neighborhood fecal exposure and diarrheal disease using logistic regression. We found the odds of diarrhea increased by 27% (OR = 1.27; 95% CI 0.97, 1.67; p = 0.08) for each tertile increase in total neighborhood fecal exposure, adjusting for child's age and WASH-B treatment arm. Additional sensitivity analysis will be used to explore the impact of sample size and parameter choice (e.g., risk ratio of hygienic versus unhygienic latrines and baseline risk) in the neighborhood fecal exposure function on the relative risk. This exposure function can be used in transmission models to investigate the indirect effect of community latrine coverage on diarrheal disease risk and can subsequently be used to inform site-specific coverage needs to achieve efficacious sanitation interventions.

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FIRST-EVER ENVIRONMENTAL SURVEILLANCE AT HUMANITARIAN SETTINGS IN COX'S BAZAR, BANGLADESH: DETECTION OF SARS-COV2 AND ENTERIC PATHOGENS

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Nearly one million forcibly displaced Rohingya refugees have been living in crowded camps of Cox's Bazar, Bangladesh. The environment of camps is favorable for the spread of waterborne and respiratory diseases. Cox's Bazar municipality has no centralized sewerage system, where household toilets are directly connected to community drains. We conducted environmental surveillance from October 2022 to February 2023 on three refugee camps (4 Ext, 9, 13) and Cox's Bazar municipality to explore the spatial and temporal trend of four vaccine-preventable diseases causing pathogen-SARS-CoV-2, Group A Rotavirus, Salmonella typhi, and Vibrio cholerae. 192 wastewater samples (153 from refugee camps and 39 from the municipality) were collected from the end of the drain point and genetic markers were analyzed through multiplex qPCR. Rotavirus was positive in over 97% of the sample from both camps and the municipality. The positivity rate of S. typhi was much lower in both camps (5%) and municipality (18%). Positivity rates of SARS-CoV-2 were higher in the camps (68%) than in the municipality (31%), whereas positivity rates of V. cholerae were higher in the municipality (51%) than in the camps (29%). The highest log10 concentration of SARS-CoV-2 gene copies/Liter (gc/L) was detected in Camp 4 Extension [median=5.3 gc/L (range=4.2-6.9)], Rotavirus was in camp 9 [median=9.3 gc/L (range=6.9-10.8)], V. cholerae was in camp 15 [median=6.3 gc/L (range=5.4-6.9)] and S. typhi was in camp 15 [median=5.7 gc/L (range=4.9-6.4)]. Both in camps and municipality, positive detection of SARS-CoV-2 and V. cholerae declined from October 2022 to January 2023, but no temporal trends were observed for the other two pathogens. Environmental surveillance is a valuable tool for monitoring temporal and spatial trends of existing and emerging infectious diseases and provides guidance for public health measures especially in humanitarian settings.

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ENTERIC PATHOGEN FLOWS AT CITYWIDE SCALES

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Understanding the performance of extant sanitation infrastructure is a challenge for governments and development agencies in low-resource settings. A variety of tools have been developed to simplify the decision-making process. One tool that is being deployed widely is the “shit-flow diagram” (SFD), which pictorializes how safe and unsafe fecal flows occur throughout a city. However, the public health hazards of fecal wastes streams are often not equal. Fecal wastes may vary substantially based on the localized disease burden and by the persistence of different pathogens. Our research aim was to overlay pathogen data onto the SFD to advance our understanding of how pathogens flow at citywide scales. First, we identified sampling locations across Maputo, Mozambique corresponding to the nodes on the city’s SFD using satellite imagery and input from local government officials. Next, we collected 85 soil samples and 110 high-volume water samples. Sample collection locations included wastewater treatment plant influent and effluent, wastewater outfalls, surface waters, open drains, fecal sludges, and soils at solid waste disposal sites. We cultured samples for fecal indicator bacteria, concentrated water samples, extracted nucleic acids, and quantified genes corresponding to >25 enteric pathogens using multi-parallel real-time PCR. We observed substantial variation in the pathogen profiles and concentrations between sampling locations. For example, median Giardia concentrations (gene copies per liter) were highest in fecal sludges (108.1), followed by wastewater influent (106.7), wastewater effluent (105.8), wastewater outfalls (105.5), flood waters (101.8), open drains (101.7), and surface water (101.3). We combined these quantitative data with the data from Maputo’s SFD to generate novel pathogen flow tables, which visualize how pathogens move through the city. This approach may help prioritize investments in sanitation infrastructure to interrupt enteric pathogen transmission at citywide scales.

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INEQUALITIES IN CHILD DIARRHEA AND EFFECT MODIFICATION OF WATER, SANITATION AND HANDWASHING INTERVENTIONS BY SOCIOECONOMIC POSITION AND MONSOON SEASON IN RURAL BANGLADESH: A SUBGROUP ANALYSIS OF A CLUSTER RANDOMIZED TRIAL

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The benefits of water, sanitation and handwashing (WASH) interventions on child diarrhea could vary by household wealth and monsoon season. Identifying subgroups most likely to benefit can help inform equitable distribution of WASH programs. We conducted a secondary analysis of the WASH Benefits Bangladesh cluster randomized trial (8440 measurements, 360 clusters). We calculated Relative Index of Inequality (RII) and Slope Index of Inequality (SII) to measure relative and absolute inequalities in child diarrhea using an asset-based wealth index. We estimated effects of combined WASH by tertile of wealth index, and jointly by wealth tertile and monsoon season. We combined intervention trial effects estimated by wealth index with national surfaces of wealth and population to project diarrhea cases prevented by a combined WASH intervention throughout rural Bangladesh. Among the controls, we observed relative and absolute inequalities in child diarrhea disfavoring poorer households (RII>1 and SII>0, respectively) and that the WASH intervention reduced these inequalities. Reductions in diarrhea were largest in the poorest wealth tertile (interaction p-value=0.07) - with diarrhea prevalence of 8.1% in control versus 4.5% in WASH [difference=3.6% (95% Confidence Interval 1.4%, 5.7%)] and were larger during the monsoon season (interaction p-value < 0.001). There was no joint interaction between wealth and season, but reductions in diarrhea due to WASH were largest among the poorest tertile during rainy season (diarrhea prevalence of 10.3% in control versus 4.6% in WASH [difference=5.7% (2.7%, 8.6%)]). The projected diarrhea cases prevented by combined WASH across rural Bangladesh was 298 cases per 1000 children < 3 years per month, with marked heterogeneity by district. Our results show that the WASH Benefits intervention reduced the wealth disparity in diarrhea, with largest reductions in diarrhea amongst the poorest children during rainy season. The study provides a generalizable example of assessing equity of intervention effects and transporting effects from trials to help target programs to populations who would benefit most.

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INTER-RATER AGREEMENT OF FACIAL CLEANLINESS ASSESSMENTS IN RURAL COMMUNITIES OF THE PERUVIAN AMAZON BASIN

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Evidence suggests that an unclean face and poor personal hygiene are associated with trachoma. Despite the worldwide focus on face washing there is minimal data on facial cleanliness in the Amazon basin, where trachoma is a documented public health problem. Current methods for observing facial cleanliness are subjective and according to the reference’s study in Ethiopia, the measures of direct observation were (intraclass correlation coefficient [ICC] 0.76, range from 0.56 to 0.86, and 0.66 for ocular discharge, nasal discharge, and dirt, respectively). Therefore, we assessed the reliability of a novel quantitative facial hygiene measuring system in these rural communities of the Peruvian Amazon Basin. Four trained fieldworkers assessed facial cleanliness by two methods: first, by direct observation of the presence of ocular discharge, nasal discharge, dirt on the face, and flies on the face (i.e., traditionally used method), and second, by using sterile gauze pads to wipe the face (i.e., the novel method). The wipes were subsequently graded by up to 4 independent graders in a masked fashion on an 11-point brown scale with each point representing a 10% increase in color saturation (10 for unused gauze pad to 0 for the darkest decile). A convenience sample of 210 children was enrolled from 7 villages in the Peruvian Amazon. The prevalence of ocular discharge, nasal discharge, dirt on face, and flies on face was 12%, 24%, 15%, and 0%, respectively. A total of 1616 face wipe grades (mean 3.9 per child) were performed, with a mean score of 7.9 (SD 0.9). Inter-rater reliability was similar for the measures of direct observation (ICC 0.47, 0.71, and 0.77 for ocular discharge, nasal discharge, and dirt, respectively) and for wipe grades (ICC 0.66). Thus, a novel quantitative method for assessing facial cleanliness had similar inter-rater reliability to currently used methods, but with the added benefit of a quantitative scale that may be more sensitive for detecting differences in facial cleanliness between groups of children.

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INFLUENCE OF TEMPERATURE AND PRECIPITATION ON THE EFFECTIVENESS OF WATER, SANITATION, AND HANDWASHING INTERVENTIONS ON CHILDHOOD DIARRHEAL DISEASE AND ENTERIC INFECTIONS IN BANGLADESH

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Diarrhea is a leading cause of child morbidity and mortality in Bangladesh. Water, sanitation, and hygiene (WASH) interventions aim to reduce exposure to enteric pathogens, and weather and environment may impact effectiveness. Here, we investigated whether temperature and precipitation modified the effect of low-cost, household level WASH interventions on diarrheal disease, Giardia infection, and soil-transmitted helminths (STH) infection. We merged remote sensing data on temperature and precipitation to households from a cluster-randomized trial in rural Bangladesh that measured the diarrhea, Giardia, and STH prevalence in children 0-2 years from 2012-2016. To measure differences in WASH effectiveness, we estimated prevalence ratios (PR) for WASH interventions vs. control under different weather conditions using generative additive models and targeted maximum likelihood estimation. We found that WASH interventions more effectively prevented diarrhea when there was heavy rain in the previous week (heavy rainfall PR = 0.38, 95% CI 0.23-0.62 vs. no heavy rainfall PR = 0.77, 95% CI 0.60-0.98) and during the rainy season, when effectiveness peaked at a PR of 0.35 (95% CI 0.19-0.65). WASH interventions were also more effective against STH infections under heavy rain (PR 0.36, 95% CI 0.19-0.68 vs 0.92, 95% CI 0.77-1.10), with the strongest effect modification for hookworm infections (PR 0.32, 95% CI 0.17, 0.64 vs 0.82, 95% CI 0.64-1.05). There was moderate effect modification by weekly minimum temperature for Giardia infection, where the PR was 1.11 (95% CI 0.91-1.30) at 12.3°C and 0.81 (95% CI 0.64-0.99) at 21.0°C. Overall, WASH interventions were most effective against childhood diarrhea and STH infections under high precipitation and against Giardia infections under high temperatures. Our findings suggest that in settings similar to Bangladesh, WASH interventions should be prioritized during the rainy season and in areas that are prone to extreme precipitation.

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HUMAN FECAL CONTAMINATION OF HOUSEHOLD WATER AND SOIL AND ENTERIC PATHOGENS IN CHILD STOOL

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Recent household water, sanitation, and hygiene (WaSH) interventions have shown inconsistent effects on child health and modest impacts on fecal contamination, suggesting the household WaSH interventions did not prevent environmental exposure to enteric pathogens. Environmental exposure is often assessed using indicator organisms but relationships between fecal indicators and exposure to specific pathogens remain poorly characterized. We investigated whether E. coli and two human fecal markers (HF183 and Mnif) measured by quantitative polymerase chain reaction (qPCR) in urban Mozambican household soil and drinking water were associated with detection in child stool of eight bacteria, three viruses, and three protozoa measured by multiplex reverse-transcription PCR and soil transmitted helminths (STH) assessed by microscopy. For each sample matrix and indicator, we used Bayesian multilevel logistic regression with pathogen-varying intercepts and slopes to obtain a pooled estimate of the overall indicator-pathogen relationship while simultaneously estimating pathogen-specific associations with adaptive shrinkage. At least one pathogen was detected in 86% (173/201) of child stools, most frequently Shigella (51%), Giardia (50%), and Trichuris (43%); norovirus GI/GII was the most common virus (14%). Increasing E. coli concentrations in drinking water were associated with elevated stool pathogen prevalence (pooled OR: 1.32, 95% CI: 0.99, 1.73), though significant only for Ascaris (OR: 1.7; 95% CI: 1.1, 3.1). The odds of detecting Shigella (OR: 0.46; 95% CI: 0.16, 0.91) or Giardia (OR: 0.53; 95% CI: 0.21, 0.99) in stool were lower when human marker HF183 was detected in drinking water. No fecal indicator in soil was clearly associated with any pathogen. We did not find evidence to support human markers as reliable indicators of enteric pathogen carriage in a high-prevalence domestic setting. Future efforts to characterize environmental exposure pathways should prioritize direct pathogen assessment, which may offer richer, more relevant insights and be more responsive to WaSH conditions.

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TOWARDS ARTIFICIAL INSEMINATION AND IN VITRO FERTILIZATION OF THE MALARIA ANOPHELES GAMBIAE

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Malaria remains a leading cause of morbidity and mortality globally, hence there is a need for new control tools. The availability of the full genome of mosquito species that vector malaria and new molecular tools such as gene drive which target vector control through either population replacement or suppression. Consequently, numerous transgenic strains with potential for mosquito control have been generated by several research laboratories. However, continuous rearing of these transgenic lines can lead to the loss of unique genetic markers, genes and/or phenotypes due to genetic contamination and changes in genotype during passage of generations. Consequently, cryopreservation as a method that reduces the number of passages and therefore reduces genetic contamination has been proposed. Methods for mosquito embryos, larvae, and sperm cryopreservation are currently under investigation. Our collaborating partners at USDA in Fargo, North Dakota, have developed a procedure to cryopreserve Anopheles gambiae sperm and have achieved 70-95% sperm viability from cryopreserved testes. Nonetheless, a method for inseminating the A. gambiae females is needed. By combining a series of biochemical cell viability and sperm motility assays, we have formulated a medium for A. gambiae sperm harvesting and ex vivo capacitation. Molecular analysis of sperm incubated in this medium revealed an upregulation of three genes associated with flagella motility (AgSFP), cation influx channel (AgCatSper), and acrosomal reaction (AgSAP) during A. gambiae sperm capacitation. In addition, we employed immunodetection to map Protein Kinase A (PKA) and protein tyrosine phosphorylation patterns during sperm capacitation. Our findings highlight the biochemical signaling pathway during A. gambiae sperm capacitation and present a significant step towards achieving artificial insemination and in vitro fertilization of the malaria vector. We will also discuss our ongoing research on artificial insemination and in vitro fertilization of the malaria vector A. gambiae.

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AEDES AEGYPTI ARGONAUTE 2 CONTROLS ARBOVIRUS-INDUCED MOSQUITO DEATH

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The yellow fever mosquito, Aedes aegypti, is the principal vector of numerous medically important human viral pathogens, including dengue virus (DENV), Zika virus (ZIKV), chikungunya virus (CHIKV), and Mayaro

virus (MAYV). These pathogens are transmitted between humans and mosquitoes and are a major public health and socioeconomic burden globally. To defend against virus infection, mosquitoes use their innate immune system, which includes the small interfering RNA (siRNA) pathway, Toll pathway, JAK/STAT pathway, and the arthropod-borne (arbo) viruses usually do not cause fitness cost to mosquitoes in nature. It has been demonstrated that the small RNA interfering (siRNA) pathway is the major antiviral defense system against arbovirus infections in Ae. aegypti and plays an important role in maintaining the mosquito-arbovirus balance. The siRNA pathway degrades exogenous viral RNA genome into virus-specific 21-nt vsiRNAs through an RNA-induced-silencing-complex (RISC), which consists of three core components: the RNase III enzyme Dicer 2 (Dcr2), a dsRNA-binding protein (dsRBP) called R2D2, and the endoribonuclease Argonaute 2 (Ago2). In addition to the essential role of Ago2 in the siRNA pathway in the cytoplasm, this enzyme has been shown to regulate gene expression in the nucleus. Here, we generated Ago2-defective mosquitoes through CRISPR/Cas9 genome editing and reported a fundamental role for Ago2 in controlling arbovirus infection, as well as in protecting the mosquitoes from arbovirus-induced mortality by modulating DNA repair, apoptosis, and autophagy. Our study provides insights into the molecular interactions between mosquitoes and arboviruses that may facilitate the development of novel disease control strategies.

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INFLUENCE OF MOSQUITO IMMUNE CELLS IN ARBOVIRUS DISSEMINATION IN AEDES AEGYPTI

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Mosquito-borne viruses are a rapidly increasing threat to public health, causing more than 400 million infections annually and placing over half of the world's population at risk. Following the uptake of virus in an infectious blood meal, virus must traverse multiple physical barriers and evade immune defenses within the mosquito until it ultimately reaches the salivary glands where virus can then be transmitted to a new host upon blood-feeding. The mechanisms by which arboviruses elude these defenses and disseminate in the mosquito vector are a critical component of vector competence, yet these mechanisms are not well understood. In this study, we provide evidence for the importance of mosquito immune cells, known as hemocytes, in the dissemination of dengue virus (DENV) and Zika virus (ZIKV) in the mosquito Aedes aegypti. When phagocytic hemocytes are depleted prior to DENV or ZIKV infection, there is little effect on midgut infection, yet we demonstrate that the depletion of phagocytic hemocytes results in attenuated virus dissemination to the ovaries and salivary glands of mosquitoes, two tissues that are integral to virus transmission. Additional immunofluorescence experiments of virus-infected hemocytes demonstrate that phagocytic hemocytes (granulocytes) are a focal point for virus infection in the hemolymph and are capable of attaching to ovary and salivary gland tissues, establishing their role as a vehicle for virus dissemination in the mosquito host. To further dissect this mechanism, hemocytes from virus-infected mosquitoes were able to transfer infection to non-infected mosquitoes, demonstrating that hemocytes are an essential tropism for virus replication and dissemination. Taken together, the results of this study support a model for virus dissemination whereby hemocytes acquire a viral infection and transport that infection through the hemolymph to uninfected tissues. This study significantly advances our understanding of the dynamics of virus infection in mosquitoes and the role of hemocytes in mosquito vector competence for DENV and ZIKV.

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CHARACTERIZATION OF SENSORY NEURONS IN ANOPHELES MOSQUITO APPENDAGES

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As vectors of Plasmodium parasites, Anopheles mosquitoes are a threat to global human health. To locate hosts for blood-feeding, female mosquitoes follow different long- and short-range cues in the environment. To detect those cues and find us, they use sensory receptor neurons of their chemosensory appendages. However, a comprehensive characterization of the neurons innervating appendages of Anopheles mosquitoes has been lacking. To gain genetic access to all Anopheles coluzzii mosquito neurons, we created a knock-in of the pan-neuronal gene bruchpilot (brp) using the Homology Assisted CRISPR Knock-in (HACK) approach. We validated this line by co-staining brains and nerve cords of adult mosquitoes for a knock-in reporter and the Brp protein. Using this new genetic reagent, we visualized and quantified all neurons in female sensory appendages of the head (antennae, maxillary palps, and labella) and body (tarsi and ovipositor). For consistent and efficient 3-dimentional neuron counting, we developed and optimized a semi-automatic image processing pipeline. We found that Anopheles sensory head appendages contain ~3400 neurons. These include 1311 neurons on each antenna, 243 in each palp, and 153 in each labellar lobe, respectively. The terminal segment of each mosquito leg contains 42 neurons and there are 71 neurons in each ovipositor lobe. We compared these neuron numbers in our pan-neuronal mosquito line to those in a mosquito line with only odorant receptor neurons labeled, which contained 841, 151, 41 and 0 neurons in each antenna, palp, labellar lobe, and leg tips respectively. We found that 36%, 38%, 73%, and 100% of neurons in antennae, palps, labella, and legs, respectively, did not express any odorant receptors, suggesting that those additional neurons likely express ionotropic or gustatory gene families. Our pan-neuronal line allows genetic access and identification of new chemosensory gene targets for mutational and functional analyses of mosquito responses to important odors involved in host-seeking and blood-feeding, including attractants and repellents.

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MOSQUITO RESISTANCE TO DENGUE VIRUS REVEALED BY SINGLE-CELL GENE EXPRESSION AND METABOLOMIC PROFILING OF MIDGUT AND FAT BODY

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Viral pathogens transmitted by mosquitoes represent a growing threat to human health, due to global warming and globalization. For example, Aedes aegypti mosquitoes are the main vectors of dengue viruses (DENV) that infect 400 million people annually. Previous studies showed that ability of a given mosquito population to acquire and transmit a given virus is highly variable. The mechanisms underlying natural variation in susceptibility to viral infection between different mosquito populations remain mostly unknown. To explore this, we combined single-cell transcriptomics and metabolomics on Ae. aegypti populations showing contrasted infection phenotypes after DENV exposure. We identified Ae. aegypti mosquito populations, recently collected in the field, that are either resistant (<40% infected mosquitoes) or susceptible (>70%) to infection with DENV. When a mosquito bites a virus-infected human, the bloodmeal containing viral particles enters the mosquito's digestive tract and is digested in the midgut, which is the entry gate for viruses into the mosquito's body. Subsequently, the virus infects the fat body, the main immune and metabolic organ. We analyzed infection dynamics in those two mosquito organs and subjected them to single-cell RNA sequencing and tissue metabolomics analysis, in both resistant and susceptible Ae. aegypti populations. We described the metabolic functions of different cell subpopulations of the mosquito midgut

and fat body upon DENV infection. We revealed metabolic pathways and gene expression patterns associated with susceptibility to virus infection at the organ and cellular levels. The functional role of candidate genes and metabolites in DENV susceptibility is currently being investigated in vivo by gene silencing and enzymatic inhibition assays. Results obtained from this study identify mosquito factors underlying natural variation to DENV infection and could lead to innovative tools for preventing arbovirus transmission.

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PLASMODIUM PARASITOPHOROUS VACUOLE MEMBRANE PROTEIN PFS16 PROMOTES MALARIA TRANSMISSION BY SILENCING MOSQUITO IMMUNITY

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With rising cases for the first time in years, malaria remains to be a significant public health burden. The sexual stage of the malaria parasite infects mosquitoes to transmit malaria from host to host. Hence, an infected mosquito plays an essential role in malaria transmission and disease prevalence. Plasmodium falciparum is the most dominant and dangerous malaria pathogen. Previous studies identified a sexual stage-specific protein 16 (Pfs16) localized to the parasitophorous vacuole membrane (PVM). Here we elucidate the function of Pfs16 during malaria transmission. Our structural analysis identified Pfs16 as an alpha-helical integral membrane protein with one transmembrane domain connecting to two regions across PVM. ELISA assays showed that insect cell-expressed recombinant Pfs16 (rPfs16) interacted with An. gambiae midguts. Transmission-blocking assays demonstrated that specific polyclonal antibodies against Pfs16 significantly reduced the number of oocysts in mosquito midguts. However, on the contrary, feeding rPfs16 significantly increased the number of oocysts. Further analysis revealed that Pfs16 reduced the activity of mosquito midgut caspase 3/7, a key enzyme in the mosquito Jun-N-terminal kinase (JNK) immune pathway. We conclude that Pfs16 facilitates parasites to invade mosquito epithelial cells by actively silencing the mosquito's innate immunity through its interaction with the midgut.

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TEMEPHOS RESISTANCE IS ASSOCIATED WITH REDUCED VECTOR COMPETENCE FOR ZIKA VIRUS IN AEDES AEGYPTI

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Arboviruses spread by mosquitoes present a major challenge to global health. The lack of effective vaccines and specific medical treatments means control efforts are heavily reliant on the use of insecticides to target the mosquito vectors. Insecticide selection and resistance cause profound alterations in the normal physiology of vectors. There are concerns that this may modify the vector competence of mosquitoes for arboviruses, and potentially alter transmission. The insecticide selection pressure was removed from a strain of Aedes aegypti with metabolic insecticide resistance to temephos. After 10 generations, the transcriptome of this unselected strain was compared to counterparts that had been maintained under temephos selection. After a further 10 generations, vector competence analysis was conducted using oral infections and intrathoracic injections. RNA sequencing revealed widespread transcriptomic changes within a small number of generations in response to the removal of insecticide. A number of genes potentially involved in the antiviral immune response were depleted in the unselected strain, including antimicrobial peptides and potential activators of the Toll pathway. Subsequent vector competence analysis showed an increase in the dissemination of ZIKV from the midgut in the unselected strain. Following intrathoracic injection, the prevalence of salivary infection was significantly lower in the temephos-selected strain (5.3%) than the unselected strain (41.9%) at 10-days post-infection. These data suggest that metabolic insecticide resistance to temephos is associated with reduced vector competence for ZIKV. The marked difference in salivary infection following intrathoracic injection suggests the presence of salivary gland infection and/or escape barriers in the temephos selected strain. Further research will establish the nature of these barriers and whether temephos selection is associated with the persistent overexpression of immune genes.

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ANTIBIOTIC STEWARDSHIP USING THE EPOCT+ DIGITAL CLINICAL DECISION SUPPORT ALGORITHM IN PRIMARY CARE FACILITIES IN TANZANIA: A CLUSTER RANDOMIZED CONTROLLED TRIAL

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Excessive antibiotic use is common and a major contributor of antimicrobial resistance. We developed ePOCT+, a novel digital Clinical Decision Support Algorithm (CDSA) to guide health workers in the management of sick children in primary care. To evaluate the impact of the ePOCT+ CDSA on antibiotic prescribing and clinical cure compared to usual care, we conducted a pragmatic, open-label, parallel-group, cluster-randomized trial in 40 primary care facilities in 2 rural and semi urban areas of Tanzania (NCT05144763). Health facilities were eligible if they received at least 20 children per week, and were randomized 1:1 stratified by location, attendance rate, and level of care. We included children under 15 years seeking care for an acute illness at participating health care facilities. The intervention consisted of the use of ePOCT+, additional point-of-care tests (C-reactive protein, hemoglobin, pulse oximeter), mentoring, and data feedback. Integrated Management of Childhood Illness training was provided to health facilities in both groups. The co-primary outcomes were 1) an absolute reduction in antibiotic prescription by 25%, and 2) non-inferiority in terms of day 7 clinical failure (upper limit of the relative risk (RR) confidence interval at 1.3). Between December 2021 and October 2022, we included 23,593 cases in the 20 ePOCT+ health facilities, and 20,713 in the 20 usual care facilities. Antibiotic prescription in cases managed per-protocol was 23.2% in ePOCT+ facilities, and 70.1% in usual care facilities, corresponding to an absolute reduction of 46.9% (95% CI 45.9; 47.8). At day 7, additional medications were taken by 7.3% of cases in the ePOCT+ arm and 7.4% in the usual care arm. Per-protocol day 7 clinical failure in the ePOCT+ arm (3.7%) was non-inferior to the usual care arm (3.8%) [adjusted RR 0.97 (95% CI 0.85; 1.10)]. Unplanned re-attendance visits were less common in ePOCT+ facilities compared to usual care facilities (1.7% vs 2.9%). The use of the ePOCT+ digital CDSA allowed clinicians to safely reduce antibiotic prescription by a factor of 3 in near programmatic conditions.

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EFFECTIVENESS OF A CLINICAL DECISION SUPPORT ALGORITHM (EPOCT+) IN IMPROVING QUALITY OF CARE FOR SICK CHILDREN IN PRIMARY HEALTH FACILITIES IN TANZANIA (DYNAMIC PROJECT): RESULTS FROM A CLUSTER RANDOMIZED TRIAL

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The Integrated Management of Childhood Illness (IMCI) booklet, a paper-based guideline for managing sick children under five years, has shown to improve quality of care and reduce child mortality. However, compliance to IMCI remains a challenge. Electronic clinical decision support algorithms (eCDSAs) are a promising solution to improve compliance to IMCI. We performed a cluster randomized trial to evaluate whether the use of ePOCT+, a CDSA based on IMCI, increased quality of care compared to usual care among routine clinicians in primary health facilities in Tanzania.18 sampled health facilities were randomized 1:1 (9 intervention and 9 control). Children aged 2-59 months presenting for the first time for an acute illness were enrolled and consultations were observed by an independent clinical researcher. The intervention consists of the use of ePOCT+ with additional point of care tests (C-reactive protein, hemoglobin, pulse oximeter) and clinical mentorship. Primary outcomes measures were: percentage of children prescribed an antibiotic at initial consultation and mean score of major IMCI symptoms and signs assessed. A total of 450 consultations (225 in each arm) were observed between March and May 2022. The mean score of major IMCI symptoms and signs was 42% in intervention and 23% in control facilities ($p<0.001$). The use of ePOCT+ increased the proportion of consultations where history of convulsions (33% vs 7%) and mid upper arm circumference (60% vs 2%) were assessed compared to routine care clusters ($p<0.001$). However, there were no significant differences between the intervention and control arms for some measure as fever assessment (91% vs 87%; $p=0.148$) and height measurement (1.3% vs 0.4%; $p=0.315$). Proportion of consultations with an antibiotic prescribed was 37.3% in intervention facilities and 76.4% in control facilities ($p<0.001$). Using the ePOCT+, a clinical decision support algorithm based on IMCI, has significantly improved the quality of care for sick children in primary health facilities in Tanzania.

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MULTIMODAL VITAL SIGN DEVICES FOR RELIABILITY AND FEASIBILITY, USABILITY, AND ACCEPTABILITY IN A LOW-RESOURCE SETTING: A PRELIMINARY ANALYSIS

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Healthcare workers (HCWs) in low-resource settings often lack tools for screening and clinical decision-making. Emerging technologies integrating multiple vital signs may provide objective measurements. A prospective, observational, mixed-methods study was conducted at the Institute of Medicine, Nepal. Adults and children (1-75 years), admitted into in-patient departments, were enrolled (Aug-Dec 2022). Five investigational devices (IDs) were evaluated - Checkme Suit (A), MD905 (B), Portable Multiparameter (C), Neopenda (D), and VitalStream (E). Vital signs (oxygen saturation (SpO2), pulse rate (PR), temperature (T), blood pressure (BP), respiratory rate (RR)) were taken, along with Sp02 and PR from reference device Masimo Rad G, as a simultaneous 'spot-check' and repeated three times. Repeatability was estimated as pooled within-patient standard deviations. Content analysis was used to analyse 20 focus group discussions, exploring feasibility, usability, and acceptability of IDs. Of 498 enrolled patients, 71% were adults, 54% female, and the median age was 31 years. In adults, the following IDs showed good precision: SpO2[%], E (SD=0.79) and A (0.81); PR[bpm], A (2.84); T[°C], A (0.22) and C (0.27); systolic BP[mmHg], B (3.97) and C (4.48); diastolic BP[mmHg], E (2.79) and RR[rpm], E (2.92). In children, B had better precision than D. Bias was estimated as slope (target 1) and intercept (0) by Passing-Bablok regression. Among both age groups: for SpO2, no proportional bias (slope=1) was found for E, minor bias for A, B, and C and major bias for D. For PR, no bias was detected for all devices except D. Stakeholders identified preferred characteristics (comfort, speed, safety, reliability, accuracy, ease of use, portability, costs, durability), and noted shortcomings in each device, leading to recommendations for improvement. The findings highlighted the comparatively better performance of VitalStream and Checkme, enthusiasm for multimodal 'spot-check' devices, and identified areas for improvement. Multimodal devices hold promise in empowering HCWs to identify severe patients and support clinical decision-making.

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DEVELOPMENT AND EVALUATION OF A CLINICAL GUIDELINE FOR A PEDIATRIC TELEMEDICINE AND MEDICATION DELIVERY SERVICE: A PROSPECTIVE COHORT STUDY IN HAITI

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Despite the emergence of telemedicine as an important model for healthcare delivery, there is a lack of evidence-based clinical guidelines, especially for resource-limited settings. Our objective was to develop and evaluate a clinical guideline for a pediatric telemedicine and medication delivery service (TMDS). The guideline was derived from the in-person World Health Organization (WHO) Integrated Management for Childhood Illness guidelines. To evaluate our guideline, a prospective cohort study was conducted at a TMDS in Haiti. Children 10 years and younger whose caregiver contacted the TMDS during operating hours (6pm-5am) were enrolled. Incoming calls were received by Haitian providers who triaged cases as mild, moderate, or severe. Severe cases were referred to the hospital. For non-severe cases, a 'virtual' exam was performed to formulate an assessment and plan. For cases within the delivery zone, a driver and provider were dispatched to the home to conduct a paired in-person exam. The primary outcome was the performance of the virtual exam compared to the in-person exam (reference standard). A total of 391 cases were enrolled. The most common chief complaints were fever (44%; 142) and 'respiratory problem/cough' (17%; 54). Among 320 cases with paired exams, no general WHO danger signs were identified at the household; problem-specific danger signs were identified in 6 cases (2%). Cohen's kappa for the designation of mild cases was 0.78 (95%CI 0.69-0.87). Among components of the virtual exam, the sensitivity and specificity of a reported fever was 91% (95%CI 87%-96%) and 69% (62%-76%), respectively; the sensitivity and specificity of 'fast breathing' was 47% (95%CI 21%-72%) and 89% (85%-94%), respectively. Kappa for 'no' and 'moderate' dehydration indicated moderate congruence (0.69; 95%CI 0.41-0.98). At 10 days, 95% (273) of the 287 cases contacted were better/recovered. This study represents a formative step towards an evidence-based pediatric

telemedicine guideline built on WHO clinical principles. In-person exams for select cases were important to address limitations with virtual exams and identify cases for escalation.

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IMPACT OF A DIGITAL CLINICAL DECISION SUPPORT ALGORITHM ON ANTIBIOTIC PRESCRIPTION IN RWANDA: PRELIMINARY RESULTS FROM A CLUSTER NON-RANDOMIZED CONTROLLED TRIAL

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Children account for most of the antibiotics consumed in low-resource settings. To address overprescription, we developed ePOCT+, a novel Clinical Decision Support Algorithm (CDSA) aimed to guide health workers in outpatient consultations for sick children under 15 years of age. To evaluate its impact on antibiotic prescription (primary outcome), we conducted a pragmatic parallel-group cluster non-randomized trial (NCT05108831) in 32 primary health centers in Rwanda. In 16 health centers allocated to the intervention arm, the algorithm, adapted to the Rwandan guidelines, was deployed on tablets together with point-of-care tests (C-reactive protein, hemoglobin, pulse oximeter), while 16 health centers allocated to the control arm continued providing routine care and completing an electronic case report form in tablets without decision support. Between December 2021 and October 2022, we included 18,843 first-time consultations of children visiting for an acute illness and for whom data were captured electronically. Antibiotics were prescribed in 24.5% of children managed with ePOCT+, versus 70.5% receiving routine care (OR = 0.14; 95% CI: 0.13, 0.14). Antibiotic prescription varied among intervention health centers from 6% to 67%. Average uptake of the intervention was 75%, also ranging between 46% and 96%. Clinical cure at day 7 (secondary outcome) was non-inferior in the intervention arm according to the upper limit of the odds ratio confidence interval being below 1.3 (adjusted OR = 1.14; 95% CI: 1.01, 1.23). We showed that the use of the ePOCT+ digital CDSA can safely reduce antibiotic prescriptions in sick children in outpatient settings. We are further analyzing which contextual factors contribute to variable effectiveness across time and health facilities.

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ENVIRONMENTAL IMPACT AND MINERAL AND ENERGY REQUIREMENTS OF THE USE OF AN ELECTRONIC CLINICAL DECISION SUPPORT ALGORITHM TO MANAGE SICK CHILDREN IN TANZANIA: A LIFE CYCLE ASSESSMENT

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Digital health interventions are a promising way to improve quality of care in low resource settings, but their environmental impact is generally not considered. The objective of the present analysis was to measure the environmental impact of the DYNAMIC digital project, aimed at improving the rational use of diagnostics and medicines by clinicians at primary level in Tanzania using electronic clinical decision support algorithms. A Life Cycle Assessment (LCA) of the DYNAMIC project was carried out to calculate the greenhouse gas (GHG) emissions, the fossil energy and mineral resources use, and the damages on ecosystems and human health. At the time of data collection, the DYNAMIC project was implemented in 40 health facilities, allowing to treat 91'000 children per year. Its GHG emissions were 24.5 tons of CO2-eq per year, while 12.5 tons of CO2-eq were saved thanks to a decrease in antibiotic prescriptions. Medical supplies were the main source of GHG emissions (69%), followed by digital supplies and activities (20%), and finally logistics (11%, mainly transport for supervision visits). The fossil energy and mineral resources use of the project were 444 GJ and 86 kg per year. The damage on human health and ecosystems were 0.062 DALY and 12'000 PDF*m2 per year. This analysis highlights the environmental impact due to medical consumables like medicines and single use tests and demonstrates the environmental benefits of antibiotic stewardship initiatives. Digital tools had much lower impact on GHG emissions compared to medical consumables, as seen with other LCAs performed in high-income countries. Nonetheless digital tools account for a significant share of total mineral resource use.The 24.5 tons of CO2-eq emitted annually represents the annual emissions of 84 Tanzanians or 1.6 Americans. Our results should thus be interpreted while bearing in mind the principle of climate equity. The environmental impact of any health intervention should be considered along with other indicators like effectiveness or costs. Our results can help guide decision making for the implementation of other health projects, both in the global South and the global North.

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LEVERAGING DIGITAL MOBILE TECHNOLOGY TO INCREASE KNOWLEDGE OF TUBERCULOSIS DISEASE AND BRIDGE THE GAP IN TB CASE FINDING IN NIGERIA: A CASE STUDY OF THE NATIONAL TUBERCULOSIS CALL CENTRE

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Tuberculosis (TB) remains a huge public health concern as Nigeria is ranked sixth among the 30 high-burden TB countries in the world and first in Africa. Nigeria reported 204,000 TB cases in 2021 compared to the estimated 467,000 TB cases. Several factors have contributed to low TB case finding, including limited knowledge of the disease and available services. In 2015, USAID supported Nigeria to establish a TB call center with an 11-digit number. The call center serves as a digital hub to provide basic information on TB and refer clients to the nearest testing facility. In 2021, the National TB and Leprosy Control Program (NTBLCP) with USAID support through Breakthrough ACTION-Nigeria (BA-N) upgraded the functionalities of the call center. NTBLCP and BA-N replaced the 11-digit number with a short code, 3340, making it easier for people to remember; updated the list of TB testing centers, enabling prompt referrals for testing; added a call back feature to ensure clients went for a test; and added an unstructured supplementary service data (USSD) component, enabling self-screening and self-referral for testing when they dial *3340#. To increase awareness of TB and drive increased calls, a national, multi-channeled social and behavior change campaign, Check Am O!, encouraged anyone coughing for two weeks or more to call 3340 or dial *3340#. From October 2015 to June 2019, the call center received 149,118 calls and referred 5,976 callers to testing centers. After the start of the Check Am O! campaign and upgrades to the call center, there was a 530% (790,192 calls) increase in the number of calls received from January 2021 to December 2022. Agents referred 6,145 callers to testing centers, among which 760 tested positive for TB. National TB case notification increased by 50% from 2020 (138,591) to 2021 (207,785). The national TB call center has contributed to increased

access to correct TB information, increased use of TB testing centers, and increased TB case finding. Coordinating this service with a multi-channeled SBC campaign that uses simple, focused messaging is an effective way to increase the impact of the call center in improving access to TB services.

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REDUCING LOW BIRTH WEIGHT BY ADDING TWO DOSES OF AZITHROMYCIN TO THE INTERMITTENT PREVENTIVE TREATMENT OF MALARIA IN PREGNANCY WITH SULFADOXINE PYRIMETHAMIN: A RANDOMIZED CONTROLLED TRIAL IN BURKINA FASO

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Exposure during pregnancy to malaria and sexually transmitted infections is associated with adverse birth outcomes including low birth weight (LBW). Whether the adjunction of two doses of azithromycin to sulfadoxine-pyrimethamine during the intermittent preventive treatment of malaria in pregnancy would result in a reduction of LBW is unclear. We conducted a 2-parallel-groups, open-label randomized controlled trial involving pregnant women (16 to 35 years of age, and 12 to 24 weeks of gestation as confirmed by last menstrual period or fundal height) in rural Burkina Faso. Women were assigned in a 1:1 ratio either to receive azithromycin (1 g daily for 2 days) during the second and third trimesters of pregnancy plus monthly sulfadoxine-pyrimethamine (1,500/75 mg) (SPAZ) (intervention) or to continue receiving the routine monthly sulfadoxine pyrimethamine (1,500/75 mg) (SP) (control) under supervision. Primary outcome was a LBW (birth weight measured within 24 hours after birth < 2500 g). Secondary outcomes including stillbirth, preterm birth or miscarriage are reported together with safety data. A total of 992 pregnant women underwent randomization (496 per group), and 898 (90.5%) valid birth weights were available (450 in SPAZ and 448 in SP). LBW incidence was 8.7% (39/450) in SPAZ and 9.4% (42/448) in controls (p-value = 0.79). Compared with controls, pregnant women with SPAZ showed a risk ratio (RR) of 1.16 (95% confidence interval (CI): 0.64-2.08]) for preterm births, 0.75 (95% CI: 0.17-3.35) for miscarriage and 0.64 (95% CI: 0.25-1.64) for stillbirths. No treatment-related severe adverse events (SAEs) have been observed, and there was no significant difference in the number of SAEs (13.5% [67/496] in SPAZ, 16.7% [83/496] in SP, p-value = 0.18) or AEs (17.1% [85/496] in SPAZ, 18.8% [93/496] in SP, p-value = 0.56). Adding azithromycin to the IPTp-SP regimen in malaria endemic areas does not reduce the risk of LBW, as far as women receive a malaria prevention regimen early enough during pregnancy.

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THE UGANDA HOUSING MODIFICATION STUDY - A CLUSTER RANDOMIZED TRIAL EVALUATING THE IMPACT OF TWO TYPES OF HOUSING MODIFICATION ON MALARIA BURDEN IN UGANDA

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Once a key pillar of malaria control, housing modification remains underutilized in most endemic areas. A cluster-randomised trial to evaluate the impact of housing modification on malaria burden in Uganda is being conducted between October 2021 and July 2023. Sixty clusters in moderate to high malaria transmission areas in Jinja and Luuka districts were randomized 1:1:1 to three arms: 1) house screening: screening windows, eaves (if open), and ventilation openings, and patching holes in the walls; 2) eave tubes; and 3) control. These interventions were selected based on a pre-trial pilot of four different house modifications in 200 households. The trial is assessing impact on malaria incidence through a cohort of 0-5-year-old children from 1,500 households (25 per cluster) followed for 12 months; impact on malaria and anemia prevalence through three cross-sectional surveys; and changes in vector densities through repeated CDC light trap collections in each cohort household. Costing and qualitative evaluations addressed feasibility and acceptability. Housing modifications were installed in 2,042 houses in screening clusters and 1,964 houses in eave tubes clusters, reaching 92.2% and 88.3% intervention coverage, respectively, and showing that both interventions were acceptable and feasible to implement. Parasite prevalence in the baseline survey was 31.4% by microscopy in 6 month-14-year-old children; improved housing quality was associated with lower odds of parasitemia (prevalence ratio: 0.80 [95%CI 0.71-0.90]). While trial data collection is still ongoing, the pre-trial pilot findings of 75% (density ratio [DR]: 0.25 [95% CI 0.12-0.53]) and 55% (DR: 0.45 [95% CI 0.21-0.99]) reductions in Anopheles gambiae (s.l.) density in the screening and eave tubes arms, respectively, compared to the controls, are encouraging. Main trial results reporting the impact of house modifications on malaria incidence, prevalence, and vector density will be presented. The study will provide evidence about potentially valuable long term malaria interventions that could be important additions to the malaria prevention toolkit.

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INSECTICIDE CHEMICAL CONTENT AND BIOEFFICACY OF INSECTICIDE-TREATED NETS CONTAINING CHLORFENAPYR OR PIPERONYL BUTOXIDE OVER 24 MONTHS OF FIELD USE IN BURKINA FASO, RWANDA, SIERRA LEONE, AND BURUNDI

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New insecticide-treated net (ITN) typeshave been distributed through mass campaigns since 2019. Given their limited deployment todate, published durability monitoring (DM) data on new ITN types is sparse andpredominantly limited to field trials. The U.S. President's Malaria Initiative(PMI) VectorLink project supported National Malaria Programs to gatherempirical data on insecticide chemical content and bioefficacy of chlorfenapyr(CFP) and piperonyl butoxide (PBO)-synergist ITNs under natural conditionsafter 24 months of field use in Burkina Faso, Rwanda,

Sierra Leone and Burundi.Chemical content was measured as the percentage reduction in active ingredientsagainst the manufacturer's target dose and bioefficacy was measured with susceptible(sus.) and resistant (res.) mosquito strains using 24-hour mortality for PBOITNs with cone tests and 72-hour mortality for CFP ITNs with tunnel tests. InBurkina Faso, CFP and PBO content reduced by 67% and 84% in field samples,respectively, corresponding to sus. mosquito mortality of 93% and 94% and res.mortality of 51% and 26% after24 months. In Rwanda, CFP and PBO content in field samples reduced by 29% and54%, respectively, corresponding to sus. mortality of 82% for PBO samples (sus.mortality for CFP samples was not analyzed) and res. mortality of 53% and 51%,respectively, after 24 months. Over the same period in Sierra Leone, PBOcontent reduced by 57% and 66% in field samples of two PBO ITN brands,corresponding to sus. mortality of 47% and 80% and res. mortality of 4% and 9%,respectively. In Burundi, no chemical content testing was conducted but PBO sample sus. mortality was 100%and res. mortality was 95%, 24 months post-distribution. Insights intoinsecticidal effectiveness and chemical content of ITNs is necessary forstakeholders to determine which ITNs to procure, and how frequently. Mechanismsto capture this data should be included in the standard post-market monitoringguidance, which is currently under development, as part of the WHO ITNpre-qualification guidelines.

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THE RIPPLE EFFECT OF QUALITY IMPROVEMENT IN STRENGTHENING UPTAKE OF INTERMITTENT PREVENTIVE TREATMENT FOR THE PREVENTION OF MALARIA IN PREGNANCY: A CASE STUDY OF KAKAMEGA COUNTY, KENYA

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Malaria during pregnancy is associated with an increased risk of premature birth, low birth weight, and maternal and infant deaths. The World Health Organization recommends the use of sulphadoxine-pyrimethamine (SP) as intermittent preventive treatment (IPTp) for the prevention of malaria in pregnancy (MiP) in regions of moderate to high malaria transmission. The uptake of three doses of IPTp (IPTp3) in Kenya has remained low at 48% (KMIS 2020) compared to the 80% target. In Mumias East and Ikolomani sub-counties, Kakamega county, IPTp3 uptake was 8% and 9% respectively, in 2020. Between 2020 and 2022, the President's Malaria Initiative Impact Malaria (IM) project and Kakamega county integrated quality improvement (QI) methods in routine service delivery to improve ANC attendance and IPTp3 uptake and established quality improvement teams (QITs). IM supported the orientation of 24 QIT members from 16 health facilities (HF), representing 55% of the HFs in the 2 sub-counties. QITs identified bottlenecks associated with low IPTp uptake, including late 1st ANC attendance, poor IPTp documentation, poor defaulter tracing mechanisms, and a weak facility-community linkage system. To strengthen facility-community linkage, the QITs mobilized community health volunteers (CHVs) to support the early identification of pregnant women and defaulter tracing. QI coordinators mentored health workers on proper IPTp data capture in the ANC register and defaulter tracing. The QITs convened monthly monitoring meetings. QI coordinators held quarterly HF monitoring visits to review interventions implemented and IPTp performance. The s trengthened HF-community linkages led to an increase in pregnant women referred by CHVs to the HF from 3,937 in 2020 to 6,385 in 2022. Women attending 1st ANC before 12 weeks gestation increased from 4% to 15% in the same period. IPTp3 uptake improved from 9% in 2020 to 79% in 2022 in Ikolomani and 8% to 76% in Mumias East. Integration of QI in routine service delivery can contribute to improved uptake of preventative services, reducing the risk of morbidity and mortality.

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LLIN EVALUATION IN UGANDA PROJECT (LLINEUP2): IMPACT OF LONG-LASTING INSECTICIDAL NETS (LLINS) TREATED WITH PYRETHROID PLUS PYRIPROXYFEN VS LLINS TREATED WITH PYRETHROID PLUS PIPERONYL BUTOXIDE ON MALARIA INCIDENCE IN UGANDA: A CLUSTER-RANDOMIZED TRIAL

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Long-lasting insecticidal nets (LLINs) are the cornerstone of malaria control in Africa, but their effectiveness is threatened by pyrethroid resistance. In collaboration with the Ministry of Health, we embedded a cluster-randomized trial into Uganda's 2020-21 national LLIN distribution campaign to compare the impact of two newer generation LLINs: Royal Guard containing alphacypermethrin plus pyriproxyfen (PPF), an insect growth regulator, and PermaNet 3.0 containing deltamethrin plus piperonyl butoxide (PBO), a synergist. Overall, 64 clusters (target communities surrounding public health facilities termed malaria reference centers [MRCs]) were included, covering 32 districts in Uganda with a high malaria burden, where IRS is not being implemented. Clusters were randomised 1:1 in blocks of two by district to receive: (1) PPF LLINs (n=32) and (2) PBO LLINs (n=32). LLINs were delivered to study areas from November 2020 to March 2021. The evaluation includes health facility surveillance at the MRCs to generate continuous estimates of malaria incidence for each cluster, and cross-sectional community surveys in at least 50 randomly selected households per cluster (3200 households per survey) at 12- and 24-months after LLIN distribution. The primary outcome is malaria incidence over 24 months following LLIN distribution; secondary outcomes include LLIN coverage, parasite prevalence in children 2-10 years of age, and prevalence of anemia in children 2-4 years or age. Preliminary results after 22 months following LLIN distribution show no significant difference in malaria incidence between the PBO arm and PPF arms (469 vs 475 episodes per 1000 person-years; incidence rate ratio 1.04, 95% CI: 0.91-1.20, p=0.57). Final results, including secondary outcomes from the 12- and 24-month cross-sectional surveys, will be presented. Preliminary results from this innovative trial embedded within a national LLIN distribution campaign indicate that PPF and PBO LLINs are equally effective in Uganda.

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REDUCING MALARIA TRANSMISSION IN FOREST-GOING MOBILE AND MIGRANT POPULATIONS IN LAO PDR AND CAMBODIA: A STEPPED-WEDGE CLUSTER-RANDOMISED CONTROLLED TRIAL

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Countries of the Greater Mekong Sub-region aim to achieve malaria elimination by 2030. In the region, malaria is concentrated in high-risk areas and populations such as forest-going mobile and migrant populations (MMPs). However, routine protective measures such as long-lasting insecticidal nets do not prevent all infectious bites in these high-risk populations. Evidence for the effectiveness of a personal protection package tailored to forest-going MMPs which is acceptable, feasible, and cost-effective for reducing malaria transmission is required to inform the malaria elimination toolkit in the region. A personal protection package consisting of long-lasting insecticidal hammock net, insect repellent and health communication pamphlet was developed in consultation with relevant implementing partners from Cambodia and Lao PDR. An open stepped-wedge cluster-randomized controlled trial was conducted from March 2022 to February 2023 in 488 villages to evaluate the effectiveness of the personal protection package. Villages were randomized into 11 blocks, with blocks transitioned in random order from control to intervention states at monthly intervals, following a one-month baseline period. The primary outcome of the trial was the prevalence of Plasmodium spp. infection diagnosed by rapid diagnostic test. Difference in prevalence of malaria infection was estimated across intervention and control periods using generalized linear mixed modelling. In this presentation the primary analyses of this recently completed trial will be presented together with a summary of the acceptability, feasibility, and cost-effectiveness of the personal protection package intervention. Results will inform national and regional policy on the use of personal protection packages for the prevention of malaria in high-risk populations.

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DO ATTRACTIVE TARGETED SUGAR BAIT STATIONS REDUCE MALARIA BURDEN IN ZAMBIA? FIRST RESULTS FROM A PHASE III COMMUNITY-RANDOMIZED EFFICACY TRIAL OF ATSB IN WESTERN PROVINCE, ZAMBIA

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Attractive targeted sugar baits (ATSB) are a potential new class of vector control tool operating through an 'attract and kill' approach. ATSB contain a sugar source to attract Anopheles mosquitoes and a neonicotinoid, dinotefuran, to kill foraging vectors. A community-randomized controlled trial was designed to evaluate if the use of ATSB has an impact on reducing malaria (30% reduction in malaria burden over a two-year implementation period) and warrants recommendation by WHO. In Western Province, Zambia, 70 clusters of 250-350 households were assigned by restricted randomization to intervention or control in 1:1 ratio. All clusters received either indoor residual spray or insecticidal nets in accordance with national microplanning, serving as standard of care. Intervention clusters additionally had two ATSB installed on exterior walls of each eligible residential structure, with ATSB placement and physical condition monitored to ensure continued high coverage through the seasonal implementation period (December-June). The primary outcome is clinical malaria case incidence measured by a cohort, defined as fever (axillary temperature ≥37.5oC or reported fever in prior 48 hours) plus positive rapid diagnostic test (RDT) in children ≥12 months and <15 years in age. 4,562 children were recruited into the cohort and successfully cleared Plasmodium falciparum infections to begin follow-up (2,321 in December 2022, 2,241 in December 2023). Cohort participants were visited monthly for follow-up during the January-June transmission season. Incidence across study arms from December 2022 to June 2023 was 2.36 cases per person-year. The secondary outcome was prevalence of P. falciparum infection by RDT among participants ≥6 months measured by cross-sectional household surveys conducted during peak transmission season (March-April 2022 and 2023). 1,239 participants were tested for malaria in 2022, prevalence across study arms was 53.3%. Trials in Mali and Kenya to evaluate ATSB efficacy in other transmission environments will be completed in 2024. Cohort follow-up in Zambia will end in June 2023, enabling presentation of trial outcomes at ASTMH.

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MULTIPLE PLASMODIUM FALCIPARUM EARLY TRANSCRIBED MEMBRANE PROTEIN FAMILY MEMBERS ARE DIFFERENTIALLY EXPRESSED IN PEDIATRIC PATIENTS WITH SEVERE MALARIAL ANEMIA

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Plasmodium early transcribed membrane proteins (ETRAMPs) are a group of parasite membrane proteins located at the parasite-host interface which have been evaluated as novel malaria vaccine candidates. Although P. vivax ETRAMP11.2 (pvETRAMP11.2) and pvETRAMP4 have been shown to be highly immunogenic in animal models, no studies have reported the impact of their P. falciparum homologs on stimulating immune responses. Moreover, it is currently unknown if pfETRAMPs gene expression profiles differ according to disease severity in children with malarial anemia. To address this gap in knowledge, we performed transcriptomic analysis on P. falciparum in samples collected from a pediatric cohort (3-36 months) in western Kenya. Children were stratified into either severe malarial anemia [SMA, hemoglobin (Hb)≤6.0 g/dL, (n=20)] or non-SMA [(Hb>6.0 g/dL, (n=40)]. P. falciparum gene expression profiles were determined by next-generation sequencing (NGS) on peripheral whole blood samples collected prior to antimalarial treatment. NGS was conducted at a depth of >20 million high-quality mappable reads using the Illumina NovoSeq platform with reads then mapped onto a Kenyan isolate reference genome (pfKE01) using HTSeq. This revealed ~3200 distinct P. falciparum transcripts for which children with SMA had upregulation of pfETRAMP4 (log2foldchange= 1.92, P=0.003) and downregulation of pfETRAMP10.1 (log2foldchange= -0.32, P=0.016), pfETRAMP11.2 (log2foldchange = -0.51, P=0.048), pfETRAMP12 (log2foldchange= -0.61, P=0.046) and pfETRAMP14 (log2foldchange= -0.50, P=0.042). Given the importance of the ETRAMP family in erythrocyte invasion, parasite development, and virulence, these findings support further exploration of their role as potential novel drug targets and vaccine candidates for the treatment and prevention of malaria, particularly in the context of severe disease. It remains to be determined if the differential expression of ETRAMPS in children with SMA is due to different immune responses and/or inherent properties of the infecting parasites.

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PROTEOMICS ANALYSIS REVEALS ALTERED HOST PATHWAYS SPECIFIC TO SEVERE MALARIA IN BENINESE CHILDREN.

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In 2020, 80% of malaria deaths occurred in children under five years old, vulnerable to severe forms of the disease like cerebral malaria (CM) and severe malaria anemia (SMA). Although specific parasite variants contribute to the disease progression, the host-parasite interaction leading to severe malaria remains poorly characterized. To study severe malaria's pathogenesis, an untargeted proteomic analysis was conducted using clinical isolates of children attending health facilities in southern Benin during the malaria transmission peak. The study included 278 clinical samples as a secondary analysis of two cohorts, including 122 CM, 135 uncomplicated malaria (UM), 21 SMA, all infected by Plasmodium falciparum. In addition, 50 non-infected (NI) children were included as a control group. The mass spectrometry analysis of a subset of samples revealed three plasma proteome clusters (NI, UM, and SMA+CM) identified through a principal component analysis, and proteins differentially abundant were a signature of CM vs.UM. Transferrin Receptor protein was identified in infected mature erythrocytes (with a significant increase in CM samples, p= 0.012). Furthermore, iron homeostasis (p <0.01) and ferroptosis signalling pathways (p=0.011) were over represented in CM vs SMA differentially abundant proteins. In addition, CM and SMA samples showed an overrepresentation of ubiquitination and protein degradation by proteasome pathways compared with UM samples (p=0.033). The plasma protein analysis showed a higher abundance of seven subunit of the circulating 20S proteasome in CM samples compared with UM, and four of these units were also more abundant in SMA. Further confirmatory analyses are ongoing in the entire sample cohort (n=278) and will be presented at the conference. The results suggest an increase of erythroid precursors invasion by parasite causing CM, and that iron metabolism plays a role in the clinical presentation of pediatric malaria in endemic areas. Overall, this study provides an innovative approach to study and insights into the pathogenesis of severe malaria and highlights potential targets for therapeutic intervention.

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ROLE OF PLASMODIUM FALCIPARUM HEMOZOIN-ASSOCIATED BIOMOLECULES IN THE PATHOGENESIS OF CEREBRAL MALARIA

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One of the hallmarks of cerebral malaria, a severe complication of Plasmodium falciparum infection, is the adhesion of P. falciparum-infected red blood cells (iRBCs) to the microvasculature of the brain, which is frequently accompanied by the weakening of the junctions between endothelial cells lining the blood-brain barrier (BBB), resulting in vasogenic edema. Our lab is focused on identifying the mechanisms through which P. falciparum-infected RBCs are able to disrupt the BBB. We have observed that iRBCs (intact or lysed) disrupt intercellular junctions of human brain microvascular endothelial cells (HBMECs) in vitro. Removing hemozoin, a heme crystal that is formed during the blood stage of the parasite's life cycle, eliminates the iRBC lysates' ability to disrupt intercellular junctions in HBMECs. Furthermore, natural hemozoin isolated from P. falciparum-iRBCs is able to disrupt intercellular junctions in HBMECs, suggesting that hemozoin may carry the ability to induce the loss of barrier function in the brain endothelium. We also observed that, while natural hemozoin actively induces endothelial barrier disruption, commercially-available synthetic hemozoin does not have this effect. Since natural hemozoin is bound to a variety of biomolecules including proteins, lipids, and DNA released from P. falciparum-iRBCs, while synthetic hemozoin is not, we hypothesize that the biomolecules associated with natural hemozoin are required for the endothelial barrier disruption. We aim to determine the contributions that hemozoin-associated biomolecules make in the cell signaling events that lead to the disruption of endothelial junctions. Further elucidating the mechanism behind cerebral malaria may lead to the development of better therapeutics which could drastically drive down the high morbidity and mortality rates of this disease.

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EXPRESSION PROFILES OF DBLA DOMAINS OF VAR GENES FROM PLASMODIUM FALCIPARUM PARASITES CAUSING CLINICAL MALARIA OR PROMOTING ASYMPTOMATIC INFECTIONS

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In Mali, the vast majority of malaria cases occur during the wet season. During the dry season, mosquitoes are rare, thereby interrupting malaria transmission. Nevertheless, Plasmodium falciparum can persist in individuals without symptoms at low parasitaemias through the 6-month dry season. Our lab has described that dry season asymptomatic carriers harbour blood stage parasites that are further along in the erythrocytic cycle than parasites collected from individuals with clinical malaria. Longer circulation of infected erythrocytes promotes more effective splenic clearance of parasitized cells in the dry season, and highlights their less efficient cytoadhesion. How this is achieved seasonally remains unknown. Cytoadhesion is largely mediated by P. falciparum erythrocyte membrane protein 1 (PfEMP1) expressed in a monoallelic fashion by the multigene family var. We aimed to explore var gene expression to better understand the dry season low cytoadhesion phenotype, characterize the PfEMP1s present on infected erythrocytes that become more easily cleared in the spleen, preventing high parasitaemias, and provide insight to the evolutionary selection process driving it. With parasites collected from subclinical and clinical infections of Malian donors, we sequenced RT-PCR amplified DBLα expression- tags located in the N-terminal of var genes, and used the Varia algorithm to predict the var genes' domain composition, such as the Cysteine-rich Interdomain Region (CIDR). Our findings confirm previously published profiles from non-severe malaria cases dominated by DB0Lα and CIDR domains of CD36- binding PfEMP1 found in group B/C var genes. The dry season parasite population appears to be a mixture of CD36- and EPCR- binding PfEMP1 and dominated by fewer var genes. Across all the timepoints ICAM-1 and CD36 binding var genes were most abundant. We are now investigating whether number and type of var genes expressed throughout the year correlate with number or particular parasite haplotypes, and whether var expression level varies during the year, to identify trends in the expression profiles of PfEMP1 in seasonal transmission setting.

7206

ELEVATED URIC ACID PREDICTS MORTALITY AND COGNITIVE IMPAIRMENT IN UGANDAN CHILDREN WITH SEVERE MALARIA

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Elevated uric acid levels have been reported in children with severe malaria (SM), but the relationship of elevated uric acid levels with SM pathogenesis and outcomes is not well understood. We investigated the role of uric acid in SM pathogenesis in two populations of Ugandan children with SM using a test and validation approach. In the test cohort, platelet-free plasma uric acid was analyzed in 372 children aged 18 months to 12 years enrolled with SM (Cohort #1). In the validation cohort, serum uric acid was analyzed in 595 children aged 6 months to 4 years enrolled with SM (Cohort #2). Each cohort enrolled community children without SM (Cohort #1, n=128; Cohort #2, n=118). Uric acid levels at enrollment were significantly higher in children with SM compared to community children, with hyperuricemia (uric acid >7mg/dL) present in a quarter of all children with SM (15% in Cohort #1, 36% in Cohort #2) but 0% in community children. Hyperuricemia was more common in children who died vs. survived (Cohort #1, 36% vs. 13%, p<0.01; Cohort #2, 81% vs. 32%, p<0.001), and was associated with coma, acidosis, severe anemia, and severe acute kidney injury (AKI). Xanthine oxidase, the enzyme responsible for uric acid production, was positively correlated with uric acid in children with SM (rho: 0.41, p<0.001) but not community children (0.04, p=0.67). In children with severe AKI, uric acid levels remained elevated at 24 hours (p=0.12), whereas in children without severe AKI, levels dropped significantly (p<0.001). Mechanistically, elevated uric acid was strongly associated with markers of hemolysis, AKI, endothelial activation, and acidosis, but not parasite density or biomass. Among survivors, elevated uric acid was independently associated with worse long-term cognition in children <5 years of age across both cohorts. Elevated uric acid is associated with increased mortality and worse cognition in children with severe malaria. Clinical trials evaluating medications that reduce uric acid as adjunctive therapy for children with severe malaria should be considered to improve survival and protect neurodevelopment in survivors.

7207

CONSERVED SUBGROUPS OF PLASMODIUM FALCIPARUM RIFIN ANTIGENS PREDOMINATE IN CEREBRAL MALARIA CASES FROM MALI AND MALAWI

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Cerebral malaria is the deadliest manifestation of Plasmodium falciparum infection. Central to its pathogenesis are parasite-derived antigens displayed on infected red blood cells that enable cytoadherence in the microvasculature. These antigens belong to diverse multi-gene families, the largest of which are the RIFINs. Our preliminary data showed that parasites expressed more RIFIN transcripts during cerebral malaria vs. uncomplicated malaria in Malian children. Here, we investigated RIFIN transcript diversity in cerebral malaria cases from two distinct African regions. We hypothesized that certain RIFIN transcripts from West African (Mali) and East African (Malawi) infections share high sequence identity, suggesting important roles in pathogenesis. We collected blood from Malian (n=22) and Malawian (n=10) children with retinopathy-confirmed cerebral malaria and matched uncomplicated controls. For each sample, we conducted RNA sequencing, assembled de novo parasite transcriptomes, and identified mRNA transcripts encoding surface antigens. We performed a multiple sequence alignment of transcripts from cerebral infections and visualized relationships with a principal component analysis. The average amino acid identity shared between any two RIFIN transcripts was 44%. We identified two large clusters corresponding to the A-RIFIN and B-RIFIN groups, each with similar distributions of transcripts from Malian and Malawian cases. Highly expressed RIFIN transcripts formed two smaller, conserved subgroups. One subgroup included RIFINs expressed only in Mali and shared ~93% sequence identity. The other subgroup contained transcripts from both Mali and Malawi, sharing ~99% identity, but diverged significantly from the majority of sequences along the first principal component. Although parasites in cerebral malaria infections expressed a diversity of RIFIN variants, conserved subgroups predominated. These RIFINs may be promising candidates for vaccine development. Next, we will define additional RIFIN subgroups based on sequence similarity and compare expression levels in cerebral vs. uncomplicated malaria.

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STOOL MICROBIOME IN UGANDAN CHILDREN IS ASSOCIATED WITH DIFFERENTIAL MALARIA OUTCOMES

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Gut microbiota in mice modulates the severity of malaria by regulating the humoral immune response to Plasmodium. It is presently unknown if gut microbiota also impacts the severity of malaria in humans. This study sought to assess if the composition of the gut microbiota differentially affects the development of severe malaria in Ugandan children infected with P. falciparum. We sequenced the bacterial 16S rRNA gene in over 500 stool samples from <5-year-old Ugandan children with five clinically distinct severe malaria presentations (prostration, severe malaria anemia, multiple seizures, respiratory distress, and cerebral malaria), and healthy community children (consisting of both P. falciparum negative and asymptomatic P. falciparum positive children). When assessing alpha diversity, asymptomatic and community children had greater richness and evenness compared to children that developed severe malaria. Beta diversity analysis demonstrated significant dissimilarity in stool bacteria communities between each severe malaria subgroup and asymptomatic children. Differential abundance testing revealed a single bacteria species as consistently enriched in all severe malaria subgroups. Additionally, longitudinal analysis over twelve months revealed specific bacteria were enriched in the community children that subsequently developed severe malaria. Ongoing studies include the investigation of bacterial biochemical pathways between groups and assessing the causative potential of the differential microbiome communities towards severe malaria using gut microbiome humanized mice. Our data provide the first demonstration that specific gut bacteria are associated with the severity of malaria in African children.

7209

PROJECT "HEMOGLOW": THE DEVELOPMENT OF GENETIC TOOLS FOR THE STUDY OF MOSQUITO HEMOCYTES

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Immune cells, known as hemocytes, are central to mosquito cellular and humoral immune responses that include phagocytosis, the establishment of immune memory, and the recognition and killing of malaria parasites. Yet,

despite their importance, studies of mosquito hemocytes have been limited by a lack of genetic resources that have restrained their characterization to morphological properties of size and shape. Recent single-cell studies have characterized mosquito immune cell populations with new and increased resolution, establishing a set of universal or subtype-specific marker genes that can define mosquito immune cell sub-populations. With the intent to develop genetic tools and resources to improve our understanding of mosquito immune cell function, we have now generated transgenic Anopheles gambiae expressing fluorescent markers under the regulation of promoters that drive universal hemocyte or granulocyte-specific gene expression. Additional oenocytoid-specific lines are still under development. Moreover, experiments are currently under way to use these promoters for the development of a binary Q system in mosquito hemocytes with promise for genetic ablation, overexpression studies, or hemocyte-specific gene-silencing. Together, our experiments will provide valuable new genetic resources for the mosquito hemocyte community that will significantly advance our understanding of Anopheles immune cell biology, while serving as the foundation for future studies to better define the contributions of hemocytes to malaria parasite killing.

7210

SCALED PRODUCTION OF A FEMALE-SPECIFIC LARVICIDAL YEAST DIET TO FACILITATE MASS-REARING OF MALE MOSQUITOES

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Sex-sorting prior to mass release of male mosquitoes is critical for several population-based mosquito control technologies, including the sterile insect technique. However, methods of sex-sorting that can be scaled and implemented globally in multiple species of mosquitoes have not been established. We demonstrated that yeast strains expressing shRNA targeting mosquito GGT genes facilitate sex sorting and generation of fit Aedes, Culex, and Anopheles gambiae males. Replacement of the nutritional yeast component of larval mass rearing diets with heat-inactivated dried yeast resulted in female-specific larval death, yielding production of fit males and 5 male:1 female ratios in adults. While these studies successfully demonstrated proof of concept, the global deployment of this strategy to mass rearing facilities worldwide requires scaled production of the yeast, which is not feasible with the laboratory yeast strains used in our pilot studies. To address this, Cas-CLOVER, an RNA guided dimeric nuclease system, was used in combination with piggyBac transposase to generate a robust commercial-ready yeast strain with multiple integrated copies of an expression cassette for production of shRNA targeting the Culex spp. GGT gene. shRNA production levels in this robust yeast strain were confirmed to be several fold higher than that of the initial lab strain, facilitating efficient sex sorting with a fraction of the amount of dried yeast used in the initial studies. Large-scale fermentation facilitated kilogram-scale production of the yeast, which was heat killed and dried. shRNA levels were maintained during this process, which is being further optimized in preparation for global deployment of the yeast larvicides. The results of this study indicate that production of female-specific RNAi yeast larvicides can be scaled to facilitate global implementation of population-based control strategies that require releases of sterile or genetically modified adult males. Ongoing efforts to generate additional commercial-ready strains that facilitate sex-separation in other species of mosquitoes will be presented.

7211

CHARACTERIZATION OF THE MOSQUITO SPOROZOITE-ASSOCIATED SALIVA PROTEINS: TWO POTENTIAL MALARIA PARASITE TRANSMISSION-BLOCKING TARGETS

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Plasmodium relies on numerous mosquito-derived host factors when engaging its intimate interactions with the vector's midgut, hemolymph, and salivary glands. Mosquito saliva primarily facilitates blood feeding but can also affect the malaria parasites transmission, yet mosquito salivary proteins' function remains fully characterized. A general screen of the mosquito saliva proteins associated with Plasmodium sporozoites while moving out of the mosquitoes was established, and two specific sporozoite-associated mosquito saliva protein 1 (SAMSP1) and AgSAP were identified through this screen; SAMSP1 plays a role in facilitating Plasmodium infection in mice, and AgSAP has immunomodulatory activity. Using CRISPR/Cas9-mediated gene editing, we have generated knockout mosquitoes lacking SAMSP1 and AgSAP and used them for functional assays in the mosquito midgut and salivary gland stages. Both SAMSP1 and AgSAP knockout mosquitoes have yielded a significant reduction of P. falciparum oocysts and sporozoite loads. Using RNAi-mediated gene silencing, we are confirming the agonist function of SAMSP1 and AgSAP in the mosquito midgut and salivary glands. Co-feeding of the polyclonal antibodies of SAMSP1 has shown a significant reduction of P. falciparum oocysts loads, but no differences were observed when co-feeding with AgSAP IgGs. The effect of SAMPS1 on oocyst loads suggests that it may be ingested together with the gametocytes by the mosquito and there affects parasite infection of the midgut. Using these knockout mosquitoes we will elucidate this hypothetical mechanism of SAMPS1 host factor function.

7212

CHROMOSOMAL INVERSIONS IN AEDES AEGYPTI ARE ASSOCIATED WITH GEOGRAPHICAL ORIGIN, BEHAVIOR, AND RESISTANCE TO PATHOGENS

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Chromosomal inversions play a fundamental role in evolution and have been shown to be associated with the epidemiologically important traits in malaria mosquitoes. However, they have never been characterized in the major vector of arboviruses Aedes aegypti because of the poor structure of its polytene chromosomes. In this study, we applied a Hi-C proximity ligation approach to identify chromosomal inversions in 20 strains of Ae. aegypti including world-wide population from 13 countries across the tropics, two old laboratory colonies, and the closely related species Ae. mascarensis. The study identified 23 multi-megabase inversions with size variations between 5.2 and 55 Mb and uneven distribution along the chromosomes. Most of the inversions were located in the 1q and 3p chromosomal arms. The inversions were highly associated with the geographical origin of the strains and were more abundant in the African strains than in the non-African, 15 versus 3 inversions, respectively. Among African inverions, 2 inversions were found in multiple strains and spread all over the African continent, 4 inversions were discovered only in West Africa and other African inversions were rare, found in one or in two strains. All chromosomal inversions, including the one specific for Ae. mascarensis, were polymorphic. Some of the inversions were shown to be associated with genomic locations of chemoreceptor genes and quantitative trait loci

to different infections. Thus, our results suggest existence of a large pool of structural variations in the Ae. aegypti genome potentially involved in the adaptation to humans and pathogenesis in this mosquito.

7213

TARGETING PLASMODIUM IN THE MOSQUITO VECTOR: VULNERABILITIES AND OPPORTUNITIES FOR MALARIA CONTROL

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Malaria, one of the world's deadliest diseases, is caused by Plasmodium parasites that are vectored to humans by the bite of Anopheles female mosquitoes. Despite massive control efforts, malaria remains a major global public health burden. The emergence of parasite resistance to drugs and mosquito resistance to insecticides represent major hurdles for malaria control, stressing the need for the development of novel strategies to fight this deadly disease. In recent years, the development of novel Anopheles genetic tools has opened the path towards new strategies to control malaria by targeting the parasite in the vector. Plasmodium has to complete a complex infection cycle within the mosquito, involving multiple developmental transitions and interactions with mosquito tissues and host factors. Each one of these stages and interactions provide specific opportunities for transgenic interference with the parasite's infection cycle that could result in transmission-blocking. While the invasive stages of Plasmodium infection in the mosquito midgut epithelium may be the most studied, the earlier stages in the blood bolus along with the later oocyst and sporozoite stages also present vulnerabilities that can be exploited to block infection. Here we present and discuss approaches, with their pros and cons, for targeting the various Plasmodium stages in the mosquito using genome editing and antibody -based approaches.

7214

FUNCTIONAL GENOMIC ANALYSIS OF TRANSCRIPTIONAL ENHANCERS IN THE MALARIA VECTOR ANOPHELES COLUZZII

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Transcriptional enhancers are noncoding regulatory elements that are responsible for almost all regulated gene expression in eukaryotes. The role of enhancers in vector phenotypes has barely been examined, but differential activity of enhancer likely plays a role in natural phenotypes such as insecticide resistance, parasite susceptibility, behavior, or adaptation to ecological conditions. We generated a genome-wide catalog of 3300 functional enhancers in the African malaria vector, Anopheles coluzzii, and filtered them genetically to identify a panel of candidate enhancers with the potential to influence susceptibility for Plasmodium falciparum infection. The activity of selected candidate enhancers was modified by CRISPR/Cas9 or by depletion of enhancer RNAs in Anopheles cells and whole mosquitoes. At least one enhancer identified in the screen regulates expression of a gene with large effect on P. falciparum infection rates. Results will be presented on enhancer function on gene expression and parasite infection.

7215

PREMONITION BARCODE: USING THE MITOGENOME FOR MOSQUITO SPECIES IDENTIFICATION AND SURVEILLANCE

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Over the last few decades, mosquito vectors have expanded their geographic range; because of their medical importance a reliable and accurate strategy for species identification is necessary for implementation of control strategies for those associated with disease transmission. Despite advancements in molecular techniques, identification of taxa belonging to cryptic species complexes have remained problematic. DNA barcoding has been traditionally used to generate reference barcodes from the cytochrome oxidase unit I (COI) gene and the ribosomal DNA internal transcribed spacer 2 (ITS2) region, which have both shown to be limited in rectifying species classification. However, expansion of sequencing strategies, including capture of the complete mitogenome, have proven useful in providing more comprehensive phylogenetic information when compared to individual COI and ITS2 gene sequences. Here, we used genome skimming to recover the mitochondrial genomes of mosquitoes retrieved and identified from a Premonition's Biological Weather Station (BWS) deployed in Harris County (Houston), Texas. Individual mosquito specimens were sequenced, and the raw reads were obtained using Illumina Miseq V2 chemistry; construction was executed using the NOVOPlasty assembler with related species. We generated mitogenomes for Aedes aegypti, Culex quinquefasciatus, Ae. albopictus and Anopheles crucians mosquito species which was also putatively identified by the Premonition BWS. The mitochondrial genomes produced in this study not only speciated but separated the mosquito specimens into individual clades. This study demonstrates that skimming for the mitogenome can be used for species identification and simultaneous taxonomic classification rectification for multiple mosquito species, as well as provide a source of new useful genetic barcodes.

7216

AGE AND PARASITEMIA EXPLAIN MOST OF THE VARIATION IN HOST AND PARASITE GENE EXPRESSION AMONG MALIAN CHILDREN INFECTED WITH PLASMODIUM FALCIPARUM

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Plasmodium falciparum caused ~600,000 deaths in 2021, primarily in young children. In Bandiagara Mali, malaria transmission is seasonal; children experience 2 malaria episodes per season, on average. However, even in the same transmission area, the parasitemia and number of symptomatic infections vary between children, and the host and parasite factors contributing to this variation are incompletely understood. We characterized host and parasite transcriptomes from 136 blood samples from children symptomatic for falciparum malaria and generated a total of 85 million reads per sample, on average, enabling analyses of 2484 Plasmodium and 9205 human genes. We used gene expression deconvolution to estimate the proportion of immune cells and parasite stages in each sample and corrected our differential gene expression analyses for differences between children. Parasitemia and host age

explained most of the variation in host and parasite gene expression, while few genes were associated with the number of symptomatic infections in the study period, COI or sex. Gene expression differences associated with parasitemia were driven by differences in cell composition. Higher parasitemia infections had more neutrophils and ring-stage parasites and fewer T-cells and trophozoites, suggesting parasitemia-dependent T-cell suppression and/or parasite sequestration. Similarly, parasite genes associated with the child's age resulted from differences in stage composition, with older children having proportionally more male gametocytes. By contrast, the host gene expression associated with age was not completely explained by differences in immune cell composition, suggesting true transcriptional differences. In particular, many genes involved in innate response (TLR and NLR signaling) were more expressed in younger children while genes involved in adaptive immunity (TCR and BCR signaling) were higher in older children. These analyses contribute to our understanding of the pathogenesis of P. falciparum and can provide insight for targeted prevention and treatment strategies based on age and/or parasitemia of infected children.

7217

A FOURTH LOCUS IN THE PLASMODIUM FALCIPARUM GENOME ASSOCIATED WITH SICKLE HEMOGLOBIN

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Malaria causes worldwide morbidity and mortality and has been a strong selective force on the human genome. Why some individuals develop life-threatening severe malaria while others experience mild or asymptomatic infection is incompletely understood. Heterozygosity for sickle haemoglobin (HbS) confers the strongest known genetic protection against severe malaria. A recent study identified genetic variants in three Plasmodium falciparum regions, termed Pfsa1-3, that were associated with HbS in severe malaria cases from Kenya and The Gambia. Here, we investigated parasite associations with haemoglobin variants in people with mild malaria in northern Ghana. Blood samples were collected for three years and underwent both human β-globin genotyping and P. falciparum whole genome sequencing. 1,368 samples were available for analysis after quality control filtering. HbS was found in approximately 3% of people, while the west African haemoglobin variant, HbC, was more common (approximately 23%). We replicated the previously identified associations with HbS at Pfsa1 and Pfsa3. The Pfsa2+ allele was absent from this population. A fourth locus, which we term Pfsa4, was also associated with HbS. The Pfsa4 association was not apparent in the severe cases from Kenya and The Gambia, but replicated convincingly in a published sample of mild malaria from Mali. The Pfsa4 mutation lies in the gene FIKK4.2, which encodes a serine/threonine kinase that is exported into the red blood cell (RBC) membrane and is thought to affect RBC rigidity and adhesion. The Pfsa1-4 loci vary widely in frequencies across Africa and are absent in Asia. Pfsa4 is generally absent or very low frequency in east Africa and much higher frequency in west Africa, while Pfsa2 shows the inverse pattern. The Pfsa1-4 loci are also highly correlated with each-other to varying degrees in multiple populations in Africa and, unexpectedly, in Colombia. We did not identify significant parasite associations with HbC. These findings suggest new functional avenues for exploration and add new complexity to the emerging picture of association between human and co-evolving parasite genomes.

7218

MALARIA PARASITE RELATEDNESS IS UNDERESTIMATED WHEN USING SPARSE MARKER DATA FROM INBRED POPULATIONS

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Malaria genomic epidemiology is increasingly recognised as a tool for public health. Identity-by-descent (IBD), which captures likeness derived from common ancestors, is a useful concept for malaria parasites because they sexually recombine. Analyses of malaria parasite relatedness based on IBD are important for generating results on spatiotemporal scales relevant to disease control. Relatedness estimates can be computed based on sparse genotypic data, including data on panels of SNPs (a.k.a. molecular barcodes) or microhaplotypes (a.k.a. amplicon sequencing panels), which can be generated at the scale of public health efforts. However, there are systematic differences between estimates based on sparse data compared to gold-standard whole genome sequencing (WGS) data, including the over-representation of zero-valued estimates. To better understand these differences, we mathematically interrogate models of relatedness and construct a tailored simulation framework. We show how sparse data can yield systematic underestimates of pairwise relatedness in settings with elevated relatedness across the malaria parasite population, due to the partial encoding of average population relatedness within sample allele frequencies. We propose a reinterpretation of maximum likelihood relatedness estimates based on sparse data, and practical diagnostics for identifying and correcting potentially problematic scenarios. Elevated relatedness across a parasite population is often found in pre-elimination settings. This is because elimination efforts often lead to fewer infectious mosquito bites, fewer multiclonal infections, bottlenecks in parasite diversity, and thus fewer opportunities for effective parasite recombination. Our results call for immediate investigation of the practical consequences of systematic underestimation of relatedness in pre-elimination settings for all applications in malaria genomic epidemiology that use relatedness directly or indirectly, including molecular surveillance and genetic-based recrudescence classification in therapeutic efficacy studies.

7219

MODELING THE EFFECTIVENESS OF GENOMIC SURVEILLANCE AT DETECTING GENETICALLY DISTINCT MALARIA PARASITES POPULATIONS

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Genomic surveillance of malaria is becoming increasingly common in sub-Saharan Africa and has the potential to enable tracking additional features of malaria parasite populations compared to using rapid diagnostic tests or microscopy on their own. Currently, genetic data is being used to monitor drug resistance markers, but it also has the potential to be used to differentiate between local and imported infections based on genetic similarity. We are using a diverse set of stochastic, agent-based transmission models with varying complexity and characteristics to explore the relationship between prevalence, importation intensity, sample size, and sequencing depth in a generalizable way. These simulated transmission trees are then processed using GENEPI, a software package that models the evolution of genetic diversity in the malaria parasite population. Our findings show that the model pipeline can help identify prevalence and importation regimes where it is more feasible to differentiate between local and imported infections. Additionally, the model can help us to find the limits of identifying genetically distinct parasite populations using variant panels or whole genome sequencing. Finally, this framework can also be used as a tool for identifying relevant genetic features and summary statistics that capture key transmission characteristics.

7220

MEASURING CHANGES IN PLASMODIUM FALCIPARUM POPULATION SIZE AND STRUCTURE IN RESPONSE TO SEQUENTIAL MALARIA CONTROL INTERVENTIONS

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The diversity of Plasmodium falciparum within human hosts requires parasite population size be defined in terms of parasite variation rather than the number of infected hosts. To calculate population size, we arrive at a definition of parasite variation known as multiplicity of infection (MOIvar), based on the hyper-diversity of the var multigene family to measure within-host diversity. Using this approach, we track changes in parasite population size and structure from baseline and through sequential malaria interventions by indoor residual spraying (IRS) and the seasonal malaria chemoprevention (SMC) in an area characterized by high-seasonal malaria transmission in northern Ghana. Deep sampling of the DBLα-encoding region of var genes by targeted amplicon sequencing was completed on asymptomatic P. falciparum isolates at baseline (2012), during IRS (2014), post-IRS (2015) and during SMC (2017) from ~2,000 individuals of all ages at each time point. Following IRS, which reduced transmission intensity by >90% and decreased parasite prevalence by ~40-50%, significant reductions in var diversity, MOIvar, and population size were observed across all ages. These changes, consistent with the loss of diverse parasite genomes, were short lived and 32-months after IRS was discontinued and SMC was introduced, var diversity and population size rebounded in all age groups except for the younger children (1-5 years) targeted by SMC. By measuring population size, we show that despite major perturbations, the parasite population remained very large and retained the var population genetic characteristics of a high-transmission system (high var diversity; low repertoire similarity) demonstrating the resilience of P. falciparum to short-term interventions in high burden countries of sub-Saharan Africa.

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UNRAVELLING PLASMODIUM FALCIPARUM GENETIC DIVERSITY USING TARGETED AMPLICON DEEP SEQUENCING TO GUIDE ELIMINATION INTERVENTIONS IN SOUTH AFRICA

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The WHO recently acknowledged the progress made by South Africa towards halting local malaria transmission. However, persisting pockets of residual transmission have halted progress toward elimination. This study explored the feasibility and value of incorporating parasite genomic data into routine malaria surveillance data to provide evidence for decision-making by NMCPs. Dried blood spots and positive malaria rapid diagnostic tests were routinely collected from healthcare facilities in South Africa's three malaria-endemic provinces, KwaZulu-Natal, Mpumalanga, and Limpopo, from 2020-2022. These samples were sequenced at the National Institute for Communicable Diseases, using a 274-target amplicon sequencing panel (Multiplex Amplicons for Drugs, Diagnostics, Diversity, and Differentiation Haplotypes using Targeted Resequencing, MAD4HatTeR). The panel includes antimalarial drug and diagnostic resistance targets, vaccine targets, and diverse microhaplotypes. During this pilot project, we successfully sequenced 500 samples predominately from the eliminating districts within KwaZulu-Natal and Mpumalanga. No evidence of drug or diagnostic resistance was detected, with limited genetic relatedness detected between pairs of infections of samples collected in KwaZulu-Natal and Mpumalanga. There was more clustering of parasite isolates collected in Limpopo, compared to KwaZulu-Natal and Mpumalanga, confirming local transmission in Limpopo, and limited local transmission in KwaZulu-Natal and Mpumalanga. This assisted the program with more accurate case classification and intervention selection to reduce residual transmission and emphasizes the need to strengthen malaria control efforts in Limpopo if South Africa is to eliminate malaria. This pilot study showed that it was feasible to incorporate genomic surveillance into routine malaria surveillance and generate data that is useful to NMCP in their evidence-based decision-making process. For sustainability, it is essential that there are adequate funding resources to support the sequencing platform and skilled genomic and bioinformatics specialists.

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RISK AND SIZE OF AEDES-BORNE DISEASE OUTBREAKS ARE POORLY PREDICTED BY CLIMATE-BASED SUITABILITY INDICES

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The recent geographical expansion of Aedes mosquito-borne diseases (ABDs) is a global health threat. Quantifying these pathogens' epidemiology and identifying at-risk populations are key steps toward preparing for future ABD outbreaks. Data from past outbreaks should be central to informing these efforts, but leveraging these data toward generalizable conclusions is often difficult. Outbreak data are context-dependent and take various forms (e.g., a time-series of cases or retrospective serology data), precluding straightforward comparisons. In this presentation, we approach this problem from two angles, using chikungunya virus (CHIKV) as an example. First, we show how outbreaks with different types of data can be compared directly through the framework of Bayesian inference and mathematical modeling. We use this approach to estimate several measurements of outbreak risk and potential size, such as the basic reproduction number (R0), for 87 CHIKV outbreaks. Second, we test whether these risk estimates can be predicted using local, pre-outbreak information, including demographic factors and previously published climate-based indices of suitability for ABD transmission. Our results suggest that climate-based indices may approximate where outbreaks can occur, but do not predict R0, outbreak risk, or potential outbreak size. More broadly, we illustrate the importance of combining a biologically realistic model with various data sources when quantifying the risk of ABD transmission.

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REDUCED DENGUE INCIDENCE FOLLOWING LARGE-SCALE RELEASES AND ESTABLISHMENT OF WMEL WOLBACHIA IN AEDES AEGYPTI MOSQUITOES IN THREE COLOMBIAN CITIES

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The introduction of the wMel strain of Wolbachia into Aedes aegypti mosquitoes reduces their capacity to transmit dengue and other arboviruses. Randomized and non-randomized studies in multiple countries have shown reductions in dengue incidence following field releases of wMel-infected Ae. aegypti. We present here the public health outcomes from phased, large-scale releases of wMel-Ae. aegypti mosquitoes throughout the contiguous cities of Bello, Medellín and Itagüí in the Aburra Valley, Colombia, with a combined population of 3.3 million people. Pilot wMel releases were conducted in Bello in 2015-2016, then staged city-wide adult releases throughout the three cities between May 2017

and December 2020, with supplementary egg releases in some areas. Prevalence of wMel in the Ae. aegypti population over time was monitored via adult mosquito trapping during and after releases. By the last monitoring in July 2021-April 2022, wMel was stably established at a high level (>80% prevalence) throughout Bello and Itagüí and at a moderate-to-high level (>60%) in 11/18 release areas in Medellín. The public health impact of the wMel releases was evaluated to July 2022 using interrupted time series analysis of notified dengue cases in the three cities, and a prospective case-control study in outpatient clinics in 4 comunas in Medellín (2019-21). Stable introduction of wMel into local Ae. aegypti populations was associated with a significant reduction (94-97%) in notified dengue incidence in each city, compared to ten years pre-release, after adjusting for seasonal trends. A causal association between wMel deployments and reduced dengue incidence was supported by the results of the case-control study, which showed a 47% reduction in the incidence of virologically-confirmed and presumptive dengue cases wMel-treated versus untreated neighborhoods.These results from the largest contiguous implementation of Wolbachia mosquito releases to-date highlight the operational feasibility and real-world effectiveness of wMel deployment in large urban settings, and the reproducibility of the public health benefit across different ecological settings.

7224

THE IMPACT OF INTEGRATED VECTOR MANAGEMENT ON THE INCIDENCE OF DENGUE IN URBAN MALAYSIA: THE IDEM CLUSTER-RANDOMIZED CONTROLLED TRIAL

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For dengue control, the World Health Organization recommends cost-effective and sustainable integrated vector management (IVM). Dengue is the communicable disease with the highest incidence in Malaysia. In the country's capital, Kuala Lumpur and Putrajaya, we carried out a large cluster-randomised trial of an IVM strategy. Each cluster was a locality, i.e., an urban housing development with shared facilities and one or more medium- or high-rise apartment blocks. 280 localities were randomised either to control, i.e., routine control activities, or to an IVM strategy consisting of (1) targeted outdoor residual spraying with K-Othrine Polyzone, (2) auto-dissemination devices with the active ingredients of pyriproxyfen and Beauveria bassiana and (3) community engagement. Dengue is a notifiable disease in Malaysia, and the primary outcome of the trial was incidence of dengue reported to the e-Dengue national surveillance system. The baseline population of the trial localities was 903,834, the intervention arm representing 23% (447,153) of the population of Kuala Lumpur and Putrajaya. Entomological outcomes, including ovitrap index, larvae density, adult density from sticky ovitraps, and mosquito insecticide susceptibility, were measured in 12 localities in each arm. From June 1, 2020 to December 31, 2022, 3907 cases were recorded in e-Dengue from people resident in the trial localities. We were able to continue trial activities during the COVID-19 pandemic, despite movement restrictions, although this coincided with much lower reported dengue incidence. Initial analysis indicates that dengue incidence was lower in the intervention arm, although with a relatively small rate ratio that was not statistically significant. This study shows how public health surveillance can be used to efficiently assess public health interventions in large randomized trials.

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ASSESSING AUTO-DISSEMINATION STATIONS AS A CONTROL TOOL FOR AEDES AEGYPTI IN THE RIO GRANDE VALLEY, TEXAS, USA

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Novel mosquito control intervention methods are needed to reduce the transmissions of Aedes-borne viruses as only weak evidence exists for the effectiveness of current control practices. Autodissemination, in which the adult mosquitoes themselves spread a larvicide to aquatic environments, has been effective in lab and small-scale trials, but studies evaluating efficacy at larger spatial scales are lacking. We conducted a cluster randomized control trial using autodissemination stations (ADS) loaded with pyriproxyfen (PPF) in eight neighborhoods in the Lower Rio Grande Valley, Texas, USA. Adult Aedes aegypti surveillance was conducted before, during, and after the intervention using BG Sentinel 2 traps. Water was collected from the field to measure PPF concentration and for larval bioassays in the laboratory. Lastly, human exposure to Aedes bites was measured using a Bitemark assay, which is an ELISA-based test measuring human IgG antibodies to the Ae. aegypti Nterm-34kDa peptide. We achieved an average of 77% coverage (percent of homes with ADS) in our intervention neighborhoods. Our preliminary results suggest that the intervention was successful at reducing adult Aedes mosquito abundance by up to 70%. PPF concentration in field-collected water was generally below detectable limits and laboratory larval bioassays showed no difference in survival between reference and intervention arms. Differences in exposure to human Aedes bites between intervention and reference arms are under analysis. To our knowledge, our results are the second large scale field study to show evidence of ADS as an effective tool for Aedes mosquito population suppression.

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POOLING THE POOLS: REDUCING COSTS OF MOLECULAR ARBOVIRAL SURVEILLANCE WITHOUT LOSS OF SENSITIVITY IN DENGUE ENDEMIC AREAS

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Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) assays are effective tools for detecting transmission of vector borne diseases. They are extremely useful for simultaneous detection of zika, dengue and chikungunya viruses, to identify specific locations with ongoing transmission and enable health officials to target their efforts to control the spread of vector borne diseases when the mosquito was captured in surveillance traps. Molecular surveillance of mosquitoes can also complement human disease surveillance considering human clinical cases may take more complicated logistics and longer times to be reported. However, the excessive costs and low frequency of positive detections in mosquitoes is a limitation, particularly in lower income endemic areas. Positive mosquitoes are rare if compared to human positive detection; even in areas with high incidence, typically less than 1% of the collected mosquitoes test positive for arbovirus resulting in an extremely excessive cost/detection and mass trapping efforts, with too little actionable information obtained to make the effort cost effective. Normally, mosquitos are grouped into "pools" from the same geo-coded trap. We developed an approach to evaluate 900 mosquito pool samples instead of 90 per PCR every week and reduce costs by developing a "super pool" with 10 individual pools. If negative, the cost of testing each individual pool is eliminated. If positive, then each pool must be individually evaluated. We demonstrate the super pooling technique developed for use in Puerto Rico to test 900 mosquito pools weekly with a cost reduction estimation of 98% without affecting results,

maximizing the use of the procedure invested time, and minimizing reagents consummation. It is shared how the technique was validated, how it is used in practice, and how the "all-in" costs of this technique compared to single pool testing is possible to be reduce. A large surveillance testing program is not necessarily practical with the traditional approach, but it becomes more practical with super pooling.

7227

USE OF MACHINE LEARNING TO IDENTIFY NOVEL MOSQUITO AND TICK REPELLENTS

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Vector-borne diseases, such as malaria and dengue fever, kill over half a million people annually. Currently available repellents for personal or household protection are limited in their efficacy, applicability, and safety profile. To address this issue, we developed a machine-learning-driven high-throughput method for the discovery of novel repellent molecules. Our approach involved digitizing a large, historic dataset containing ~19,000 mosquito repellency measurements. We then trained a graph neural network (GNN) to map molecular structure and repellency. The GNN was able to learn the complex relationships between molecular structure and repellency, allowing us to predict the efficacy of new molecules. To test our method, we selected ~400 candidate molecules to test in parallelizable behavioral assays. We quantified repellency in multiple species and conducted follow-up trials with human volunteers. Here we show that our method was able to identify novel molecules with high efficacy against multiple species. We further expanded the hits identified in our initial screening by testing analogous compounds and identified additional active molecules. Through this process, we discovered several novel repellents that exhibit greater potency than DEET. Our approach also led to the identification of several repellent molecules that demonstrate activity against mosquitoes, ticks, and fleas, suggesting their broad-spectrum effectiveness.Additionally, we applied a similar machine learning-driven approach to identify tick repellents specifically. We trained ML models on tick repellency data, tested a selection of compounds, and achieved a hit rate of 57%, further demonstrating the utility and versatility of our high-throughput method for the discovery of novel repellent molecules. Our method has several advantages over traditional methods of discovering mosquito repellents. It is faster and more cost-effective than traditional methods, allows for the screening of large numbers of compounds simultaneously, and can be used to predict the efficacy of new molecules before they are synthesized or tested in vivo.

7228

CHROMOBACTERIUM SPECIES PANAMA (CSP_P) PELLET FORMULATIONS: A NOVEL BIO-LARVICIDE FOR MOSQUITO VECTOR CONTROL

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The development of novel biopesticide to control vector-borne diseases, is urgently needed due to emerging resistance against currently used chemical insecticides. Here, we have formulated a larvicide pellets containing non-live Chromobacterium species Panama (Csp_P) which are eco-friendly, cost-effective, with prolonged water-stability and residual activity. Using Csp_P pellet formulation, significant larval mortality was observed against Aedes aegypti, Anopheles gambiae, Anopheles stephensi and Culex quinquefasciatus within 48 hrs post-exposure. Interestingly, upon sub-lethal dose of Csp_P pellet exposure, significantly reduced and delayed pupation was noticed compared to the control pellet exposed group. Additionally, Csp_P exposed larvae reaching the pupal stage would not develop into adults. Notably, Csp_P pellets are irreversibly detrimental to the larvae that fail to develop into adults. Altogether, our results show that our Csp_P pellet formulation is effective at killing larvae of multiple mosquitos' species and could be developed into a new vector control tool.

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DRONES AND DENGUE: PILOTING THE USE OF UNMANNED AERIAL VEHICLES TO MAP TRASH DISTRIBUTION AND DENGUE VIRUS RISK IN RURAL AND URBAN KENYA

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The incidence of dengue and chikungunya, viruses transmitted by Aedes aegypti mosquitoes, has increased exponentially in the past 50 years and is projected to continue increasing with climate change. Trash, a favored breeding ground for Ae. aegypti, is a critical mediator of this increasing threat; however, research on trash is limited by inadequate techniques to quantify trash distribution and exposure. We hypothesized that high resolution aerial imaging from unmanned aerial vehicles (UAVs) could be used to map trash distribution, quantify trash exposure, and identify high-risk trash microclimates. We piloted the use of UAVs to map trash in rural and urban communities in Kenya and developed a trash classification scheme based on trash appearance and Ae. aegypti risk. We validated the trash identification by ground truthing and assessed the benefits and limitations of the use of UAV imaging for trash identification over ground methods. In our pilot UAV flights, conducted in two sites in Kenya, we identified over 1800 trash piles in the urban site and over 1300 piles in the rural site. The majority of trash sites were small household piles (41%) and the greatest proportion of trash by area consisted of trash scattered in the grass (43%) and trash collection centers (15%). The rural site had a significantly higher proportion of trash mixed with vegetation and deposited in partially completed building sites and decreased evidence of burning trash compared to the urban site. We generated a trash exposure score for individual households and identified trash microclimates in both communities, conferring differential risk for Ae. aegypti-vectored viruses, dengue and chikungunya. As the global population expands alongside the consumption of non-biodegradable materials, solid waste, particularly plastics, create increasing environmental and human health problems. The validation of a reproducible, quantifiable measure of trash exposure opens the door for rigorously evaluating the relationship between trash and a variety of infectious diseases as well as designing and measuring much needed trash interventions.

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DENGUE, CHIKUNGUNYA, AND MALARIA IN KENYA; CO-EXPOSURE AND CO-INFECTION STATUS

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In Kenya, malaria is a long standing well recognized public health problem, whereas arboviral illnesses such as dengue (DENV) and chikungunya (CHIKV) are presumed to be underrecognized. Periodic seroprevalence surveys are therefore necessary to quantify the burden of DENV, CHIKV, and malaria in the population and assess the effectiveness of public health interventions. For this prospective cohort study, we recruited and followed 4534 individuals from Kisumu (central-eastern Kenya) and Ukunda (south-western Kenya) between 2019-2022 and analyzed the exposure and co-exposure status for dengue, chikungunya, and malaria.

In this cohort, 22.8% (1038) participants were seropositive for dengue and 21.4% (972) participants were seropositive for chikungunya based on IgG ELISA test results. Acute arboviral infection was rare; PCR results showed 0.06% (3) participants with an active chikungunya infection and 0.7% (31) participants with active dengue infection and no acute DENV-CHIKV co-infections. Malarial microscopy results showed 15.5% (707) malaria positive participants, three of whom were co-infected with DENV. Amongst the cohort, 0.6% (27) participants were co-exposed to all three infections with 1.5%-9% participants being exposed to more than one infection at the same time. Among the people having exposure to more than one infection, the majority were females, between 18-60 years of age residing in Kisumu. When analyzing the co-seroconversions, 2.2% (31/1379) participants co-seroconverted for DENV and CHIKV in 2020, followed by 2.3% (62/2660) participants in 2021 and 1.9% (7/370) in 2022. Preliminary analysis indicates that older age (OR: 1.04 [95% CI:1.02, 1.06]), presence of water containers and livestock in the house ((OR: 2.87 [95% CI:1.22, 6.25]), (OR: 3.37 [95% CI:0.98, 8.87])), and going to school (OR: 0.27 [95% CI: .06, 0.78]) are significantly associated with co-exposure to all three infections. The results of the study suggest that Kenyans are highly likely to be exposed to arboviruses and malaria over the course of their lifetime and that the mosquito borne infections continue to represent a public health threat in Kenya.

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INCREASING MALARIA CASES IN THAILAND'S WESTERN BORDER PROVINCES

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In February 2020, Thailand became the second country, after China, to report a case of coronavirus disease 2019 (COVID-19). One year later, in February 2021, a political crisis erupted in neighboring Myanmar. In response to the local context, Thailand installed strict movement policies that gradually receded. Since March 2022, malaria cases have resurged, contradicting years of progress and coinciding with the country's biggest peak in COVID-19 cases. This study utilized a Seasonal Autoregressive Integrated Moving Average (SARIMA) time series analysis to assess malaria trends in this changing context, using fiscal year 2019 (FY19) as a baseline. The analysis included all malaria cases from FY19 to FY22 in the national database (n = 21,606). In FY22, 8,548 malaria cases were reported: a 95.6% increase since the previous year and 46.2% since FY19 ($p < 0.05$). Nearly all (94.4%) cases were reported in six border provinces, with 60.5% of FY22 cases in Tak and 17.2% in Mae Hong Son. Thailand's seminal 1-3-7 surveillance strategy showed minimal drops in adherence over the study period: Day 1 (87.6% in FY19 vs. 85.3% in FY22), Day 3 (95.4% vs. 97.5%), Day 7 (87.3% vs. 84.4%); these drops were not statistically significant. SARIMA results of t-tests (paired by month) showed a significant increase in mean incidence during the high transmission season (March to September) in FY22 compared to the previous year: in Tak, FY22 mean incidence increased by 253.3 cases per month and in Mae Hong Son they increased by 39.5 cases per month. Thailand's success in maintaining 1-3-7 surveillance is attributed to both a strong community health worker network and stringent domestic movement restrictions. Relaxations of international border restrictions began in January 2022 for in-demand workers; concurrent changes in population movement across the Myanmar border and behaviors could contribute to these changing epidemiological results. The June 2022 peak in malaria cases is limited to border provinces only, so malaria authorities are considering novel cross-border initiatives such as bilateral foci and active case detection to mitigate the outbreak.

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TRANSLATING CONTINUOUSLY COLLECTED ANTENATAL CARE MALARIA PREVALENCE INTO TRENDS OF COMMUNITY TRANSMISSION AND CLINICAL INCIDENCE — BURKINA FASO, MOZAMBIQUE, AND NIGERIA, 2020-2022

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Malaria surveillance data collected at antenatal care (ANC) are less prone to treatment-seeking bias compared to surveillance during outpatient visits. They also have advantages over data collected in demographic health surveys, as they are continuously collected and can achieve greater geographic granularity. While ANC malaria prevalence estimates malaria burden in pregnancy and correlates well with prevalence in children under 5 years old, estimation of general community transmission and incidence from this data source requires additional analytical methods. We sought to develop a tool to translate continuously collected prevalence data from ANC surveillance to trends in community malaria transmission. Malaria surveillance by rapid diagnostic test among pregnant women at first ANC visit was conducted as a sub-study of the New Nets Project in 82 health facilities from 10 districts across Burkina Faso (BF), Mozambique (MZ), and Nigeria (NG) between September 2020 and December 2022. We incorporated particle Markov chain Monte Carlo (pMCMC) into an existing malaria model to infer trends in entomologic inoculation rate (EIR). Among 50,098 women tested over 28 months, 23.6% (n = 11,813; 95%CI 23.2–24.0%) tested positive for malaria. Initial EIR ranged from 9 infectious bites per person per year (ibpppy; 95%CI 5.7–12.9) in Changara, MZ to 2,637 ibpppy (95%CI 561–4,756) in Asa, NG. Seasonal variation of estimated EIR patterns depended on location. For example, in Banfora, BF, following an EIR of 0.001 ibpppy (95%CI 0.0–0.5) at the end of the dry season in June 2021, EIR peaked in July 2021 at the onset of rainy season (80 ibpppy; 95%CI 22–212). In contrast in Ejigbo, NG where malaria burden is less seasonal, EIR did not fluctuate but rather declined steadily from 73 (95%CI 35–278) to 11 ibpppy (95%CI 2.5–29) over two years. Our pMCMC approach flexibly recaptured malaria dynamics from locations of varying transmission levels and seasonality patterns. With this framework, ANC surveillance data can help inform malaria intervention activities, such as monitoring chemoprevention impact, within the general community even at a sub-regional level.

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ASSESSING HISTORY OF ACCEPTABILITY AND COVERAGE WITH MASS DRUG ADMINISTRATION (MDA) FOR LYMPHATIC FILARIASIS TO INFORM RE-START OF MDA 6 YEARS POST-ELIMINATION

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Belitung District in Bangka-Belitung Province Indonesia stopped mass drug administration for lymphatic filariasis (LF) in 2010. Following three rounds of transmission assessments, the district achieved LF elimination status in 2017. It was later revealed that LF transmission was ongoing, and Belitung qualified for the use of ivermectin, DEC and albendazole (IDA) as per WHO's alternative treatment strategy for LF elimination. To inform the first round of IDA treatment in 2022, an acceptability study was carried out in June 2022 in 20 villages. 16 villages were identified via probability proportionate to size sampling and 4 LF-endemic villages were purposively included in the sample. Only individuals aged 18 years and older were included in the sample with one person per household. Within 444 households invited to participate, 44 individuals refused. A total of 400 participants were included in the final analysis. Results included: 5.5% had never heard about LF; 48.4% reported that they didn't know the cause of LF (worms); 43.3% did not know the transmission route for LF (mosquitoes); 39.4% reported that they had never taken treatment for LF (never treated) and 37.6% reported taking treatment once. Recommended messages derived from the survey results included promoting: the safety and effectiveness of the MDA treatment; ancillary benefits of LF MDA (scabies, intestinal worms); importance of taking MDA for the benefit of the whole community. Results and suggested messages were presented to 73 district stakeholders in July ahead of the October 2022 MDA. Results from the consultations included: identify local resources to support MDA; revisit the occurrence of adverse events; reinforce directly observed treatment; recommend refresher training prior to MDA for health staff; consider urban characteristics to adjust MDA; work with community leaders to reduce number of households who may refuse MDA. Research revealed the importance of using evidence from a rapid and timely community assessment to inform socialization and implementation of MDA. Survey results can be used to create momentum within districts and communities towards an effective MDA.

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BUILDING THE CAPACITY OF COMMUNITY INFLUENCERS TO INCREASE THE EQUITY AND IMPACT OF UGANDA'S TRACHOMA RESPONSE

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The Uganda MOH identifies and overcomes gender equity and social inclusion (GESI)-related barriers to the uptake of trachoma preventive medicine in Uganda through building the capacity of community influencers. The goal of the approach is to reach populations, like nomadic pastoralists, who have historically been missed by past mass drug administration (MDA), and by reaching them with MDA, accelerate trachoma elimination efforts. To improve medicine access and acceptance among these "hard to reach" groups, the Uganda MOH, with support from USAID's Act to End NTDs | East (Act | East) program, has implemented targeted behavior change (BC) activities in villages with the highest burden of trachoma. The MOH trains district officials to supervise BC teams comprised of Village Health Teams (VHTs), local elders and religious leaders A root cause analysis follows via focus group discussions and interviews with a selection of the community who missed the previous MDA to identify the key barriers to MDA uptake. The district officials validate the results of the root cause analysis with the influencers, and coach on addressing the root causes through concrete behavior change and social mobilization actions, tailored to the community's needs and the influencers' positions of trust and authority. The Uganda MOH and Act | East also provide training materials in the local language and coach MDA supervisors on how to make trachoma MDA more accessible and therefore more equitable. In 16 villages with some of the highest prevalence of trachoma, 68 (40 M; 28 F) community influencers have been trained on GESI-integrated BC and supported to implement interventions for improving MDA uptake. These efforts have contributed to village-level MDA coverage improvements from below 55% in 2020-21 to 80% and above in 2022, representing a total of 13,513 people in 2021 and 2022 (Source: MOH). Results from January 2023 implementation in 8 additional villages will be available in April 2023. This evidence-based methodology in Uganda can inform other health and development decision makers about the power of community influencers in increasing the equity of NTD health services.

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CITIZENS CAN HELP TO MAP PUTATIVE TRANSMISSION SITES FOR SNAIL-BORNE DISEASES

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Schistosomiasis is a snail-borne disease that affects over 200 million people globally, 90% living in Sub-Saharan Africa. However, the lack of malacologists presents a major challenge to implementing the WHO recommendations on snail control to supplement drug treatment towards disease elimination. Therefore, we adopted a citizen science approach to snail monitoring. A network of 25 trained citizen scientists (CSs) collected snail data at 73 water contact sites around southern Lake Albert (Uganda), on a weekly basis for 20 months. The quality of this data was assessed by comparing it to the data collected by an 'expert' malacologist that visited the same sites monthly. The binary agreement in the presence/absence of Biomphalaria, Bulinus and Radix snails reported by the expert and CSs ranged between 70% and 86% (900 reports) with an average of 17% false negatives (site wrongly defined as snail-free). The agreement for Biomphalaria and Radix increased with an increase in snail abundance, while false negatives decreased when considering the cumulative number of snails collected by citizens per month. Site type significantly predicted binary agreement, which was lowest at lake sites (55%) and highest at spring sites (99%) with variations across genera. The CS and expert data showed similar temporal trends in snail abundance and despite the expert recording higher snail abundance than the CSs, the relative abundance is consistent across site types. The match between the top 15 sites with the highest Biomphalaria spp. abundance identified by both CS and the expert is consistently high (>70%) and increases over time. The agreement in presence/absence and the congruence in relative abundances demonstrate the potential of citizen science to map putative schistosomiasis transmission sites. Benefits of the citizen science approach beyond data collection include financial cost, informal learning and enhanced community participation.

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PATTERNS OF HEALTH SEEKING BEHAVIOUR AND TREATMENT PRACTICES FOR FEBRILE CHILDREN FOLLOWING THE INTRODUCTION OF RTS,S/AS01 MALARIA VACCINE IN GHANA

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Ghana has expanded RTS,S/AS01 malaria vaccine implementation programme. We assessed introduction of the vaccine on health-seeking behavior and treatment practices for febrile malaria children. Series of household surveys were conducted in 66 clusters in six regions of Ghana. A baseline survey was carried out prior to vaccine introduction in 2019, followed by midline and endline household surveys conducted November 2020 and March 2022 after vaccine introduction respectively. The survey data were summarized into frequencies and proportions. A total of 7795, 7915 and 8993 children were enrolled in the baseline, midline and endline household surveys respectively. Proportion of children with recent fever was comparable in the surveys, implementing areas at baseline 24.3%, midline 21.7% and 22.7% endline, and non-implementing areas; baseline 20.5% midline 18.4% and 21.9% at endline. A similar trend was noted among those who sought advice or treatment for fever, implementing areas at baseline 71.6%, midline 71.5% and 62.6% endline, and in non-implementing areas; baseline 71.6.% midline 75.8% and 71.4% endline. Little differences was observed in those tested in the surveys, implementing areas; baseline 38.3%, midline 35.8% and 28.9% at endline and in non-implementing areas; baseline 42.1% midline 44.8% and 33.6% at endline. Proportion of children treated for fever was nearly same in the surveys, in implementing areas; baseline 84.7%, midline 81.7% and 82.9% at endline and in non-implementing areas; baseline 86.5% midline 84.4% and 84% at endline. Artemisinin-based combination was the most used drug for febrile children and it was almost same in the surveys; implementing areas at baseline 13.4%, midline 25.1% and 9.7% at endline and non-implementing areas; baseline 10% midline 21.1% and 9.1% endline. There was little to no impact on health-seeking behavior or health worker provision of care following the introduction of the malaria vaccine.

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OPERATIONAL PERFORMANCE AND ACCEPTABILITY OF A PROGRAMMATIC MASS DRUG ADMINISTRATION CAMPAIGN FOR MALARIA IN SOUTHERN MOZAMBIQUE: A CROSS-SECTIONAL SURVEY

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Mass Drug Administration (MDA) to reduce transmission of malaria in low transmission settings was recommended by the World Health Organization in 2022. Given that achieving high population coverage, of at least 80%, and good adherence to the antimalarials are critical aspects of MDA campaigns, National Malaria Control Programmes (NMCPs) need to develop programmatic delivery strategies and assess the real-world implementation challenges to optimize them. In December 2022 and January-February 2023, two rounds of programmatic MDA (pMDA) with dihydroartemisinin-piperaquine were conducted by the Mozambican NMCP in the administrative post of Chidenguele (district of Manjacaze, Gaza province), which has an estimated population of around 60,000 people. A cross-sectional community survey was then conducted to evaluate the operational feasibility, acceptability, and penetration of the pMDA delivery strategy. 770 individuals were selected through a multistage cluster sampling. After obtaining informed consent, a standardized questionnaire was administered. Preliminary data show that 61.6% (474/770) of households reported having been visited by a pMDA team during the first round, whereas the household visitation coverage for the second round was 89.1% (686/770). For those that were visited during round 2, 82.9% (569/686) reported having taken the medication, and 96.1% (547/569) of those reported having completed the full treatment course. 23.2% (159/686) of participants reported drug-related side effects, of which 25.2% (40/159) resulted in the participant having to seek care at the nearest health facility. 91.3% (703/770) of participants thought that taking the medication regardless of malaria infection status was acceptable, and 84.2% thought that the MDA campaign could help reduce the malaria burden in the community. Final results will be available to be presented at the time of the ASTMH conference.

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WILL A LACK OF FABRIC DURABILITY BE THEIR DOWNFALL? IMPACT OF TEXTILE DURABILITY ON THE EFFICACY OF NEXT-GENERATION LONG-LASTING INSECTICIDAL NETS AGAINST MALARIA PREVALENCE AND INCIDENCE: A SECONDARY ANALYSIS FROM A CLUSTER-RANDOMIZED TRIAL IN TANZANIA

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Dual insecticides nets have been developed to counteract the reduced efficacy of standard nets due to widespread pyrethroid resistance. These nets have demonstrated superior efficacy in controlling malaria and recently constitute half of the nets distributed in Africa. However, data on their protective efficacy once they develop holes is limited. This study presents results from a randomized controlled trial (RCT) on textile conditions of the three next-generation nets Interceptor G2 (Alpha-cypermethrin + Chlorfenapyr), Olyset plus (Permethrin + piperonyl butoxide (PBO)) and Royal Guard (Alpha-cypermethrin+ Pyriproxyfen) over 3 years in Tanzania. The study assessed the association between malaria prevalence and textile condition in 4994 children (<15 years) and 5060 nets from 3284 households using cross-sectional surveys at 12, 24, and 36 months post-net distribution. We further assessed the association between malaria case incidence and the textile condition in 6161 children (<11 years), 4631 nets from 4994 households over two years using a cohort study. After one year of follow-up, Interceptor G2 and Olyset plus, regardless of their physical conditions, provided better protection (against malaria case incidence) than a good-standard LLIN. In year 2, children sleeping under good Interceptor G2 had lower malaria case incidence of 0.16 per child-year (IRR 0.49, p=0.006) compared to those sleeping under good-standard LLIN (0.34 per child per year). Sleeping under an LLIN was always more protective than not sleeping under a net against malaria infection prevalence, regardless of net type, conditions, or age. Non-users of nets in households with at least half of the sleeping spaces covered by study nets had added protection benefits compared to those living in houses with fewer sleeping spaces covered by nets (OR 0.69, p=0.003). Physical conditions degraded in all the nets but were more pronounced in Olyset Plus. Torn interceptor G2 or Olyset Plus offered superior protection than good standard LLIN in year 1. Interceptor G2 LLINs were consistently effective against malaria incidence and were physically durable.

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TRENDS IN ANTENATAL CARE VISITS AND INTERMITTENT PRESUMPTIVE TREATMENT IN PREGNANCY IN SUB-SAHARAN AFRICA. IMPLICATIONS OF WHO POLICY

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In 2016, The World Health Organization (WHO) recommended a minimum of eight antenatal care (ANC) visits during pregnancy with the first visit in the first trimester. However, the implementation and impact of this policy on malaria in pregnancy remain unclear. This study explores the relationship between ANC and intermittent presumptive treatment in pregnancy (IPTp) in sub-Saharan Africa from 2017-2022. The analysis included thirteen countries (Benin, Burundi, Cameroon, Gambia, Ghana, Liberia, Madagascar, Mauritania, Mozambique, Senegal, Sierra Leone, Uganda, Zambia) with a recent (2017-2022) demographic health survey (DHS) or malaria indicator survey (MIS). Bivariate associations explored sub-group trends in the percent of women with 1) 4+ ANC visits; 2) 8+ ANC visits; 3) Early ANC (first visit in less than four months of pregnancy); 4) IPTp 3+ (three or more doses of sulfadoxine/ pyrimethamine (SP) or Fansidar) during pregnancy. Meta-analysis explored correlations between these indicators across all countries. The national average of women with at least 4 ANC visits was 61% across all countries (ranging from 29% in Senegal to 91% in Ghana). However, the national average of women with at least 8 ANC visits was 10% (well below 10% in ten countries). An average of 44% of women attended their first ANC visit in the first trimester while 36% of women received at least three doses of SP/Fansidar (ranging from 10% in Mauritania to 61% in Ghana). There was a higher correlation between IPTp3 and 4+ ANC visits across the study countries- 0.58 compared to between IPTp3 and 8+ ANC visits (0.37). It is clear that the recommended 8+ ANC visits are far from being achieved and a review of its feasibility is needed as countries are still striving to achieve early ANC and 4+ ANC visits. Strategies to increase ANC visits in sub-Saharan Africa may include the use of home- and/or community-level ANC service delivery models, demand-generation interventions to increase early and frequent ANC visits as well as supply-side interventions to improve the quality of facility-based ANC. Commitment from both government and non-government stakeholders remains crucial.

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SEASONAL MALARIA CHEMOPREVENTION EFFECTIVENESS IN NORTHERN MOZAMBIQUE, RESULTS FROM A CLUSTER RANDOMISED CONTROL TRIAL

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Seasonal malaria chemoprevention (SMC) prevents malaria caused by Plasmodium falciparum in high-transmission areas. It involves administering antimalarial medicines intermittently during the transmission season. We conducted a cluster randomised control trial in Nampula province, Mozambique, from January to April 2022 to investigate the effectiveness of SMC in reducing malaria incidence in eligible children aged 3-59 months. The study was conducted in Nampula province, Mozambique, with one control and one intervention arm. 190 clusters were selected at the community level, with 76 in the intervention arm and 114 in the control arm. One eligible child was randomly selected from 15 households in each cluster, and a questionnaire and blood sample were collected after informed consent. Proportions of children with Rapid Diagnostic Test (RDT)-confirmed malaria were compared between control and intervention arms using Chi square tests and ORs. Survival analyses were performed for time to first RDT-confirmed malaria case, with random-effects models accounting for recurrent malaria events during follow-up. The study included 1,338 eligible children aged 3-59 months, with 628 in the control arm and 710 in the intervention arm. Children in the control arm had more than double the odds of RDT-confirmed malaria fever compared to the intervention arm, OR 2.29 [95%CI 1.85–2.59 (p<0.001)]. The Cox proportional hazards models showed a significant reduction of 69%, HR 0.31 [95% CI 0.26-0.37 (p<0.001)], in the hazard of RDT-confirmed malaria cases in the intervention district compared to the control district. After covariates adjustment, the random-effects model showed an 83%, HR 0.17 [95% CI 0.13–0.21 (p<0.001)], reduction in rates of confirmed malaria cases in the intervention district. One year after the pilot implementation in Mozambique, this study found that administering SPAQ through SMC was effective, with up to 83% estimated protection. While effectiveness is high in Mozambique, we require chemoprevention efficacy results, due in June 2023, to define future effectiveness and therefore sustainability of the intervention in the future.

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ADAPTING THE MASS ACTION AGAINST MALARIA APPROACH FOR MALARIA PREVENTION AND MANAGEMENT AT THE HOUSEHOLD LEVEL: IMPLEMENTATION LESSONS FROM FIVE HIGH BURDEN REGIONS IN UGANDA

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Since 2019, Uganda has experienced a sustained increase in malaria cases, with 74 districts reporting upsurges above normal expected levels in 2022, 16% of which have reached epidemic level. The USAID PMI Uganda Malaria Reduction Activity, implemented by JSI, works with the Ministry of Health to strengthen capacity of malaria prevention and ownership of health at community and household levels in five highest burden regions. The implementation framework is guided by the Government of Uganda's Mass Action Against Malaria (MAAM) multisectoral approach for eliminating malaria at all levels. Effective implementation requires gaps in malaria prevention, management, and control strategies at community and household levels to be addressed. We adapted MAAM for implementation at household level by equipping them with the knowledge to own and put specific malaria prevention measures in place and achieve a malaria free status. In collaboration with local leaders and village health team members, we used national HMIS data and health facility outpatient registers to map most affected villages and assess households for specific malaria transmission drivers to address. Malaria champions were established in each household to reinforce accountability. From September 2022 to January 2023, 2,515 households in four upsurge districts were assessed. Only 35% of assessed households knew at least three ways to prevent malaria, 52% had one mosquito net for every 2 people, and 84% of pregnant women and children under five slept under mosquito nets. Only 30% of pregnant women reported receiving the recommended three doses of intermittent preventive treatment for malaria. First round follow up visits suggest improvements, 70% of households knew three or more ways to prevent malaria, 80% of pregnant women received three doses of IPTp and 80% reported sleeping under mosquito nets. Effective and sustainable malaria elimination strategies require active engagement by the affected individuals. Empowering households to own the process of preventing, managing, and controlling malaria in their communities can help the GOU realize MAAM's vision of a malaria free Uganda.

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EVALUATION OF NEW, INSECTICIDE-TREATED NET PRODUCTS, META-ANALYSIS OF OBSERVATIONAL STUDIES, AND ECONOMIC EVALUATIONS FROM FIVE SUB-SAHARAN AFRICAN SETTINGS

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Standard insecticide-treated nets (ITNs) have been the main vector control tool for malaria in sub-Saharan Africa (SSA), but their effectiveness is currently limited by widespread pyrethroid resistance. New, dual active ingredient (AI) ITN products treated with multiple insecticides, synergists, or juvenile growth inhibitors have shown great effects in small entomological studies and clinical trials, but little is known about their effectiveness and cost-effectiveness at scale in field settings. We conducted observational studies and economic evaluations of dual AI ITN deployment in five settings in SSA (Burkina Faso, Nigeria, northern and western Mozambique, and Rwanda). Interceptor G2® ITNs (IG2; BASF AG), which combine alpha-cypermethrin and chlorfenapyr; Royal Guard® (RG; Disease Control Technologies, LLC), which combine alpha-cypermethrin and pyriproxyfen; and piperonyl butoxide (PBO) ITNs were deployed. Standard ITNs were also deployed in all settings as a comparator to dual AI ITNs. Observational studies followed district level difference in differences approaches for estimation of the average treatment effects. Incidence rate ratios (IRRs) and variance estimates were combined in a pooled random effects meta-analysis framework. Dual AI ITNs were protective relative to standard ITNs across all settings with an IRR of 0.60 (95% CI: 0.47-0.77). IG2 ITNs were more protective (IRR 0.57 in comparison to standard nets) than PBO ITNs (IRR 0.85 in comparison to standard nets). Effect models were used to calculate cases averted and costs per case, death, and disability-adjusted life year (DALY) averted in each setting. IG2 ITNs were the most cost-effective intervention across the studies, though a switch from standard ITN to any dual AI ITN is likely to be highly cost-effective in most settings with a willingness to pay threshold of ≤1x gross domestic product per capita per DALY averted. Dual AI ITNs offer the potential to greatly improve the impact of malaria programs but will be more costly in the near term than standard ITN deployment.

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PODOCONIOSIS: CLINICAL SPECTRUM AND MICROSCOPIC PRESENTATIONS

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Podoconiosis is a skin Neglected Tropical Disease (skin NTD) that causes lymphoedema, and affects barefooted subsistence farmers in some tropical countries. The clinical presentation and histopathologic correlates of podoconiosis have been understudied. Here, we systematically document the clinical and histopathologic spectrum of podoconiosis. This is a cross-sectional study in Durbete, Ethiopia from February 2018 to October 2019. Dermatologists performed a patient history, physical examination, filariasis test strip, and skin biopsy for histopathologic examination. The results were summarised and a descriptive statistical analysis and Wilcoxon rank sum test with continuity correction was done. We recruited 289 patients for the study, 178 (61.6%) had stage 1 or 2 podoconiosis, and 111(38.4%) stage 3 to 5 podoconiosis. 188 (64.1%) had a family history of podoconiosis. In 251 (86.9%) patients, both legs were affected by podoconiosis and in 38 (13.1%) only one leg was affected. 220 (77.5%) patients had warty lesions, 114 (39.4%) had nodules. The median number of episodes of Acute Dermato-Lymphangio-Adenitis (ADLA) reported by the patients in the last three months was 2 (interquartile range (IQR) 1–4). Increased episodes of ADLA were significantly associated with stage 3–5 podoconiosis (P = 0.002), while burning pain in the feet was more common in stage 1 or 2 podoconiosis. Stage 3–5 disease was histopathologically characterised by epidermal and dermal thickening, verrucous acanthosis, inflammatory cell infiltrates (predominantly lymphoplasmacytic), dilated andectatic and a reduced number of lymphatic vessels, eccrine ductal hyperplasia, and sclerosis such as thickened collagen bundles. In conclusion, we provide a detailed description of the different clinical patterns, associated clinical findingsand the histopathologic spectrum of podoconiosis at different stages of the disease. Our observations should serve as a guide to classifying patients with podoconiosis for prognosticassessment and treatment decision.

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THROMBOSIS AND ORGAN DYSFUNCTION IN SNAKEBITE ENVENOMING: TIME TO REDEFINE VENOM INDUCED CONSUMPTION COAGULOPATHY?

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The mechanism of venom-induced consumption coagulopathy (VICC) in viper envenoming is due to procoagulant venom toxins mediated consumption coagulopathy resulting in bleeding. Classical features of disseminated intravascular coagulation- systemic microthrombi and end-organ failure are absent. However, it remains unknown if this is uniformly so for different snake species. Here we report a series of 3 patients with Echis envenoming from desert regions of Rajasthan, India who presented with venom-induced consumption coagulopathy but had evidence of thrombosis leading to organ dysfunction along with bleeding. We report findings from an ongoing prospective study in patients with Echis envenoming after ethical approval. Clinical features, antivenom use, and coagulation parameters were collected. Post-mortem biopsies from the heart, lung, kidneys were collected after informed consent. Of 23 admitted with Echis envenoming in 2022, 19 had VICC, of whom three developed thrombosis and organ dysfunction. All 3 had coagulopathy, serious bleeding: hematuria in all, muscle hematoma in patients 1 and 3, and low serum fibrinogen. All needed intensive-care admission, transfusion support. All received 30 vials of Indian polyvalent antivenom with persistent bleeding suggesting

antivenom non-responsiveness. Patients 1 and 3 had acute kidney injury. Patient 3 had thrombotic microangiopathy. Patient 1 developed left arm deep venous thrombosis which resolved by day 12. Patient 2 developed intestinal obstruction and 3 had abdominal compartment syndrome with gangrenous bowel loops. Patient 1 was discharged on day 14 while the others expired. Post-mortem renal and lung histopathological samples from patients 2 and 3 and part of resected gangrenous intestine sent intraoperatively (patient 3) showed extensive fibrin microthrombi in vessel walls. Renal injury is frequently reported in the context of thrombotic microangiopathy in snakebites. To our knowledge, this is the first report of non-renal end-organ damage (lung and intestines) in snakebite envenoming suggesting that the currently accepted definition of VICC needs to be reconsidered.

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THE RELEVANCE OF REPORTING LEPROSY RELATED DISABILITY AT THE COMPLETION OF MULTI-DRUG THERAPY: A FIVE-YEAR RETROSPECTIVE ANALYSIS OF DISABILITY IN PERSONS AFFECTED BY LEPROSY AT ALERT HOSPITAL ETHIOPIA

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Leprosy is one of the neglected tropical diseases associated with significant morbidity in endemic regions. Leprosy causes disability affecting the daily activities and social participation of affected individuals. Understanding the prevalence and trend of leprosy-related disability throughout the world and accuracy of disability data counted by WHO is crucial in guiding efforts to be made towards the targets set by WHO to be achieved by 2030. Our study aims to show the prevalence and trend of leprosy related disability and critique the reliability and usefulness of WHO Leprosy related disability data based on the data from ALERT hospital in Ethiopia. We did a mixed method study with a 5-year retrospective analysis of outcomes of newly diagnosed leprosy patients at ALERT Hospital in Ethiopia from 2016 to 2020. A comparative review and analysis of leprosy related G2D (Grade 2 Disability), globally, regionally, and in Ethiopia using WHO data was also done. In addition, we conducted semi- structured interview of health workers and professionals working in the field of leprosy at various organizations. The total number of newly diagnosed leprosy cases at ALERT hospital between January 2016 and December 2020 were 1032 and among those patients who had completed treatment the prevalence of G2D was 33% at diagnosis and 23% at completion. The trend of G2D among newly diagnosed leprosy patients shows no decline globally for the past 20 years, while it is increasing in Africa and stable in the Southeast Asian and American regions where majority of leprosy patients are found showing the gap in early case detection and effective patient management. The interview has also shown gaps in the completeness and quality of disability data reported to WHO and how disability is counted. Leprosy related G2D among newly diagnosed patients is not declining worldwide and even increasing in endemic regions like Ethiopia. More training should be given to health professionals in assessing disability. WHO shoulder consider counting disability at the end of MDT to know the impact of interventions and prospective studies are needed in assessing disability progression post treatment.

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PATHOGENESIS OF ACUTE KIDNEY INJURY IN LASSA FEVER

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Lassa fever (LF) is an endemic viral hemorrhagic fever in West Africa, with Nigeria being one of the main foci. The most common complications of severe LF are acute kidney injury (AKI) and neurological involvement. AKI often requires hemodialysis - which is often not available in resource-limited settings - and is an important cause of mortality in LF. The pathogenesis of AKI in LF is not well understood, both micro-bleeding and inflammation, as well as secondary causes have been discussed as potential mechanisms. Hence its management remains challenging. We are conducting a prospective, clinical, observational study with the aim to explore the underlying pathophysiological mechanisms of AKI in LF and to ultimately improve patient management. Adult patients with RT-PCR confirmed LF hospitalized at the Irrua Specialist Teaching Hospital in Edo State, Nigeria, with laboratory diagnosis of AKI according to KDIGO criteria were enrolled and followed prospectively. Secondary causes of AKI such as pre- and postrenal failure, as well as pre-existing chronic renal disease and pre-disposing conditions (history of diabetes mellitus, hypertension, among others) were assessed. Study visits included clinical examination, recording of clinical parameters such as vital signs and fluid input/output, laboratory testing (including HbA1c and Cystatin C) and point-of-care ultrasound examination. We here report the findings of the first 51 patients with AKI. The mean age of the case series was 41.7 years (±15.8 years). Most of our patients exhibited signs of severe LF. Ultrasound findings showed marked hyperechogenicity of kidneys in affected patients, similar to findings in other virus-associated nephropathies, such as HIV-associated nephropathy (HIVAN). Furthermore, we observed marked proteinuria and gross hematuria and elevated inflammatory markers in the cohort. Cystatin C- based estimates of GFR correlated well with clinical course and serum creatinine. Pre- and postrenal failure were excluded, along with preexisting diabetes. The overall results indicate a possible inflammatory etiology of AKI in LF.

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TRYING TO UNMASK THE HIDDEN CAUSES OF IMPORTED FEVER WITH NEW GENOME SEQUENCING: A MULTICENTER PROSPECTIVE COHORT STUDY

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Although acute undifferentiated febrile illnesses (AUFI) are the leading cause for hospitalization in returning travelers, up to 45% of them remain undiagnosed even at referral centers. Metagenomic next-generation sequencing (NGS) has been proposed as a promising tool, but evidence of its usefulness in AUFI is limited. Prospective multicenter cohort study of travelers with AUFI after international travel (November 2017-November 2019). NGS was performed in sera samples of travelers with AUFI and results were compared with those obtained by standard diagnostic methods (SDM). 507 returned travelers with AUFI were included, 165(32.5%) of them presented with severe disease and 133(26.2%) remained undiagnosed by SDM at the end of the follow-up. NGS allowed the identification of potentially pathogenic microorganisms in 172(33.9%) samples: 136 samples that tested positive by SDM and 36 additional samples. NGS resulted negative in 222(43.8%) samples that resulted positive by SDM. 113(22.3%) samples resulted negative by SDM and NGS.NGS allowed the identification of microorganisms in 27/133(20.3%) undiagnosed cases and 5/26(19.2%) severe undiagnosed cases. The most common identifications obtained by NGS in patients undiagnosed by SDM were Pseudomonas aeruginosa (n=7), Enterovirus B (n=3), Aspergillus

spp. (n=3), Hepatitis B virus (n=2), Bordetella spp. (n=2), Burkholderia spp. (n=2), primate erythroparvovirus 1 (n=2), Penicillum spp. (n=2), amongst others.NGS showed additional identifications in 29/374(7.8%) cases already diagnosed by SDM. In conclusion, NGS from sera might be useful for the diagnosis of selected cases of imported fever non-diagnosed by SDM. However, the interpretation of NGS results poses a great challenge from a clinical perspective. The evaluation of NGS in plasma and whole blood samples could improve the diagnostic performance of metagenomic NGS techniques in febrile travelers. 1

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MALSCORE: AN INNOVATIVE TOOL TO PREDICT MALARIA IN PATIENTS WITH IMPORTED FEVER TO START EARLY TREATMENT.

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Fever after international travel is one of the most common conditions for seeking health care. Plamodium falciparum malaria is the leading cause of fever and also the deadliest imported disease. Nonetheless, its presentation is commonly undistinguishable from other benign and self-limited conditions, and microbiological diagnosis can be challenging in non-referral centers. This can lead to delayed diagnosis of malaria and late initiation of treatment, which worsens patients' clinical outcomes. Therefore, new tools are needed in order to rapidly detect patients at risk of malaria. We conducted a nested study within a prospective multicenter cohort study of international returning travelers or recently arrived migrants with fever, attending three European Travel Clinics and/or Hospitals, from November 2017 to November 2019. The objective of this study is to build a predictive model to identify suspected malaria cases that should be treated promptly. For this purpose, a machine learning approach was used, using demographic characteristics, clinical and laboratory variables as features of the model. A total of 765 patients with fever were recruited and 95 (12.4%) malaria cases were diagnosed. The median age was 36 years (IQR: 28-47), and 133(17.4%) went visiting friends and relatives. Out of a total of 97 features, we built an xgboost model with only six features to predict suspected cases of malaria: visiting friend and relatives, Africa as a travel destination, platelet value, C-reactive protein, bilirubin value and respiratory symptoms. The model showed an AUROC of 0.94 (CI 95% 0.91-0.97) in the cross-validation with the training set (80%), and an AUROC =0.97 with the test set (20%). Also, a sensitivity of 100% (CI 95% 96.15-100) and specificity of 80% (95% CI 77.05-83.08) was obtained. With only 6 variables that are easy to obtain through anamnesis or basic laboratory results, the predictive model is an accurate resource to detect malaria cases in patients with imported fever. This tool could be easily scalable to a digital application and could help clinicians without access to microbiologic tests to start empiric antimalarial treatment.

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DIAGNOSTIC TOOLS AND ALGORITHMS AT THE POINT OF CARE TO SAFELY REDUCE ANTIBIOTIC PRESCRIPTIONS FOR ACUTE FEBRILE ILLNESS MANAGEMENT

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Antimicrobial resistance (AMR) is a growing public health threat. Strategies are needed to reduce unnecessary use of antibiotics, a known driver of AMR. We hypothesized that point-of-care tests and diagnostic algorithms could reduce antibiotic prescriptions without compromising clinical outcomes in patients with fever. We conducted a two-arm, open-label, randomized controlled trial in three African and two Asian countries. The intervention included a diagnostic algorithm to guide antibiotic prescription, based on Selected Rapid Diagnostic Tests (RDTS). The control arm used standard care. Primary outcomes were antibiotic prescribing on the day of presentation, and clinical status after seven days. From September 2021 to September 2022, we enrolled 11,664 participants. 30% were children aged <5 years, 47% were female, and 47% presented with respiratory symptoms. Antibiotics were prescribed for 29.4% of patients. The intervention significantly reduced antibiotic prescriptions for patients with: negative malaria RDT at African sites (absolute risk difference (ARD) [95%ci] -32.5% [-38.6%, -26.4%], P-Value <0.001), respiratory Symptoms (-9.3% [-12.0%, -6.5%], P-Value: <0.001), and no vaccination against COVID-19 (-28.1% [-32.4%, -23.9%], P-Value: <0.001). Conversely, there were significantly more antibiotic prescriptions for patients with positive malaria RDT (ARD: 11.2% [6.3%, 16.0%], p-value <0.001), non-respiratory symptoms (7.2% [4.9%, 9.4%], p-value: <0.001), and unknown COVID-19 vaccination status (14.8% [12.5%, 17.1%], p-value: <0.001). African and Asian settings varied in disease epidemiology and antibiotic prescribing. The intervention significantly reduced antibiotic prescribing in Burkina Faso (-24.9% [-30.6%, -19.2%], p-value <0.001) but significantly increased it in Uganda and three regions of India. Overall, 11,243 (99%) had favourable outcomes at day 7 with no significant differences among sites. Diagnostic tests and algorithms have the potential to safely reduce antibiotic prescribing for sub-populations with fever. However, their use must be tailored to local epidemiology.

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IDENTIFICATION OF TARGETS OF PROTECTIVE ANTIBODY RESPONSES AGAINST PLASMODIUM VIVAX MALARIA USING A MULTIFUNCTIONAL ANTIBODY PROFILING APPROACH

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A need for highly effective malaria vaccines has been made more urgent following stalled progress in reducing the global burden of malaria since 2015. While advances in Plasmodium falciparum malaria vaccine development have seen the recent approval of the RTS,S vaccine, very limited progress has been made towards development of a P. vivax vaccine. No vaccines for P. vivax have completed testing for efficacy in malaria-endemic settings and limited candidates are in the discovery pipeline. P. vivax is the most widespread Plasmodium species and a major cause of malaria outside Africa, with over 3 billion people at risk of infection with. A major challenge to developing a P. vivax vaccine is a limited knowledge of the targets of protective immune responses. Antibodies play a major

role in acquired immunity to malaria and likely act through three major mechanisms: direct inhibition of host cell invasion, recruitment and activation of complement, and interactions with Fcγ-receptors to promote phagocytosis or killing by immune cells. However, knowledge of functional antibody mechanisms in P. vivax immunity is very limited. To address this, we developed novel high throughput multiplex assays to identify the targets of functional antibodies against P. vivax that interact with complement and Fcγ-receptors. In a longitudinal cohort study of 1-3-year-old children from PNG, we measured antibody magnitude (IgG, IgG subclasses and IgM) and functions (complement fixation, FcγR binding and opsonic phagocytosis) to 30 P. vivax antigens. Using these approaches, we identified known and novel antibody targets and specific functions associated with protection against clinical P. vivax malaria. Using statistical modelling approaches we identify important combinations of antigen-specific functional antibodies that may provide maximal protection against P. vivax malaria. Our findings identify promising antigens for prioritisation in P. vivax vaccine development, and a knowledge of target-specific functional immune responses that are most important for protective P. vivax immunity.

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ANTIBODY AND CELLULAR RESPONSES TO IN UTERO MALARIA EXPOSURE IN INFANTS

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Antibody-producing B cells and CD4+ T cells are key in control of malaria infection. Transplacental transfer of maternal-origin antibodies is essential for protecting the infant from pathogens encountered during the initial months of life. CD4+ T follicular helper cells (TFh) help generate protective B cell and antibody responses. Placental malaria and antimalarial chemoprevention may affect this response by altering exposure to malaria antigens. We assessed antibody responses to 25 malaria antigens from Ugandan infants born to mothers with and without placental malaria using a Luminex multiplex bead array. We also assessed the frequency and phenotype of circulating follicular helper T cells and B cells for these infants. Antibody concentrations decrease significantly from birth to six months for all malarial antigens and appear to increase from 6 months to 12 months for all except CSP, tetanus toxoid and AMA1. Antibody responses to EBA181, HSP40 and SEA were associated with a lower incidence of malaria in the first six months of life. Etramp5, GLURP, HYP2 and SBP1 emerged as markers of exposure. At one year of age, Th1 were the most abundant TFH subset while naïve B cells were the most abundant B cell subset. Symptomatic malaria in pregnancy was associated with lower Th2/Th17-like TFh at one year of age, and there was a strong positive correlation between Th2-like TFh, and Th2/Th17-like TFh, with antibody levels to all tested malaria surface antigens. We also found an inverse relationship between the frequency of atypical memory B and follicular helper T cells of infants at age one year. These data suggest important relationships between in utero malaria exposure and infant TFh and B cell responses.

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SEX HORMONES, CD8+T CELLS, AND THE LIVER: HOW THE ENDOCRINE-IMMUNE INTERFACE ALTERS MALARIA LIVER-STAGE VACCINE OUTCOMES

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Sex bias in parasitic infections is a well-documented phenomenon. Males experience higher severity and/or prevalence to almost all known parasitic infections compared to females. Despite such strong sex-specific phenotypic differences, the influence of host sex on immune responses to parasites is understudied. This is the case for malaria, where the impact of host sex may modulate the host response to each stage of the Plasmodium life cycle. This is especially relevant during liver-stage infection since the liver is one of the most sexually-dimorphic organs in vertebrates. By studying Plasmodium yoelii (Py) rodent malaria parasites in both male and female mice, and through the use of in vivo sex hormone manipulation models, we show sex and sex hormones are dramatic mediators of immune responses to both wild-type malaria sporozoite challenge and vaccination with live-attenuated sporozoites. We demonstrate that female mice experience heightened type I and II interferon signaling in response to liver stage infection after wild-type Py sporozoite challenge. We further demonstrate that androgens suppress and estrogens promote host inflammation and innate immune responses to Py infection. This same trend is also recapitulated following immunization with live-attenuated Py sporozoite vaccines. Finally, we demonstrate that sex hormones skew memory CD8+ T cell frequencies following live-attenuated Py sporozoite vaccination, resulting in sex-divergent protection outcomes. This result demonstrates sex-specific effects on liver resident memory CD8+ T cell, a critical correlate for protective liver stage vaccines. Sex hormone modulation on host response to sporozoites adds an endocrine perspective to our understanding of innate and adaptive immune responses to Plasmodium in the liver. This work further emphasizes the importance of considering biological sex and the endocrine-immune axis when studying parasite infection and immunity.

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INDUCTION OF LIVER-RESIDENT MEMORY CD8+ T CELLS AND PROTECTION AGAINST MALARIA AT EXOERYTHROCYTIC STAGE BY MRNA-CONTAINING LIPID NANOPARTICLES

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Malaria is a febrile disease caused by Plasmodium parasites, and one of the important life-threatening infectious diseases in the world. Right after entering the human body by mosquito bite, Plasmodium sporozoites invade hepatocytes and proliferate (liver-stage), followed by the development of symptomatic blood-stage. Recent studies showed that resident memory T cells (TRM) in liver play a critical role in liver-stage malaria protection. Although RTS,S was recommended by WHO as a malaria vaccine in 2021, its efficacy is moderate. Therefore, more effective vaccine is required. Recently, mRNA contained lipid nanoparticles (LNPs) was approved as a vaccine platform. In this study, we aimed to develop liver TRM inducing malaria vaccine based on mRNA contained LNPs (mRNA-LNPs). We utilized pH-sensitive lipid LNPs, which contains third generation SS-cleavable pH-Activated Lipid-like Material (ssPalm) that enhances endosome disruption and mRNA release to the cytosol and promotes efficient protein production. Single dose intravenous injection of ovalbumin (OVA) mRNA LNPs induced antigen-specific cytotoxic T lymphocytes (CTLs) efficiently in a dose-dependent manner in the liver. Furthermore, five weeks after the immunization, TRM were generated in the liver. Finally, we immunized mice intramuscularly twice with LNPs containing mRNA encoding P. berghei ANKA (PbA) circumsporozoite protein (CSP), and examined protection against PbA sporozoite. Sterile immunity was induced in 70% of the immunized mice. These results demonstrate that mRNA-LNPs is a promising liver-stage malaria vaccine platform.

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ONCE YOU'VE HAD MALARIA YOU'LL NEVER FORGET (OR WILL YOU?): THE MEMORY B CELL AND PLASMA CELL RESPONSE TO PLASMODIUM REINFECTION

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Malaria is caused by parasites in the genus Plasmodium, with symptoms caused by rounds of parasite growth and rupture inside red blood cells. Clearance of blood stage parasites is driven by a germinal center response that yields plasma cells (PCs) capable of producing high affinity antibodies and memory B cells (MBCs), which can respond during subsequent infections. After years of repeated infection some people develop clinical immunity to malaria, but why this varies between individuals is poorly understood. An emerging modulator of the germinal center response against Plasmodium is the gut microbiome. Curiously, mice that are genetically identical but with differing gut microbiomes (Taconic (Tac), and Charles River (CR)) show drastic differences in their susceptibility to nonlethal P. yoelii 17XNL. Tac mice, which are protected from severe disease, generate a stronger germinal center response against P. yoelii compared to CR. When challenged with a lethal secondary P. berghei ANKA infection, Tac mice demonstrate heightened survival, suggesting that the gut microbiome also influences immune memory. Characterization of immune memory demonstrated that Tac mice generate more MBCs than CR mice during P. yoelii infection, but there is no difference in the number of PCs produced. We next investigated whether Tac mice generate more P. yoelii-specific PCs, however no differences were observed, suggesting that memory PCs do not contribute to the heightened survival against P. berghei seen in Tac mice. To test this further, we depleted individual memory cell subsets from P. yoelii-immune Tac mice and then challenged them with P. berghei. We discovered that depleting MBCs made previously protected Tac mice susceptible to P. berghei challenge, but depleting PCs did not. This indicates that MBCs are necessary for protection against reinfection with Plasmodium, while PCs and circulating antibodies play a lesser role.

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NEUTRALIZING AND INTERFERING HUMAN ANTIBODIES DEFINE THE STRUCTURAL AND MECHANISTIC BASIS FOR ANTIGENIC DIVERSION

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Defining the protective modes of antibody protection and the methods of pathogen immune evasion are crucial to the development of protective and durable vaccines. Merozoite Surface Protein-1 (MSP-1) is a key malaria vaccine antigen that has achieved limited clinical success due to poor understanding of antibody-mediated neutralization of this protein. In addition, MSP-1 is a prototypical example of an antigen that displays "antigenic diversion", an immune evasion phenomenon wherein the action of neutralizing antibodies is prevented by non-neutralizing antibodies that enable parasite survival. However, the structural and mechanistic bases for antigenic diversion have not yet been defined. We investigated a panel of MSP-1-specific naturally acquired human monoclonal antibodies through a combination of structural biology and biophysics tools, and parasite neutralization to study the complex interplay between neutralizing and non-neutralizing antibodies during natural infection. One of these antibodies potently neutralized parasites, whereas the others had minimal or no effect. We therefore determined the co-crystal structures of MSP-1 with neutralizing and non-neutralizing antibodies. This human antibody epitope map revealed a novel potent and strain-transcending epitope that overlaps with the epitopes of non-neutralizing interfering antibodies. Strikingly, the non-neutralizing interfering antibodies outcompete the neutralizing antibodies, which facilitates parasite survival. Overall, these findings demonstrate the structural and mechanistic basis for a parasite immune evasion mechanism through naturally acquired neutralizing and interfering human antibodies to MSP-1 elicited by antigenic diversion. The findings are highly relevant to malaria vaccine and therapeutic antibody development. This work is currently being leveraged to design potent and durable malaria interventions through structure-guided vaccine design.

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STRUCTURE GUIDED MIMICRY OF AN ESSENTIAL PLASMODIUM FALCIPARUM RECEPTOR-LIGAND COMPLEX ENHANCES CROSS NEUTRALIZING ANTIBODIES

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Invasion of human red blood cells (RBCs) by Plasmodium falciparum (Pf) merozoites relies on the interaction between two parasite proteins, apical membrane antigen 1 (AMA1) and rhoptry neck protein 2 (RON2), making it an attractive vaccine target. However, clinical trials with recombinant AMA1 alone (apoAMA1) did not provide protection, likely due to inadequate levels of functional antibodies. Stabilizing AMA1 in the receptor-ligand bound conformation using RON2L, a 49 amino acid peptide from RON2, confers superior protection against P. falciparum malaria by enhancing the proportion of neutralizing antibodies. Here, we engineered chimeric antigens by strategically replacing the AMA1 DII loop that is displaced upon ligand binding with RON2L. The structure of one of the fusion chimeras (Fusion-FD12) was determined to 1.55 Å resolution and found to mimic the receptor-ligand complex. Interestingly, Fusion-FD12 immune sera neutralized parasites more efficiently than apoAMA1 immune sera despite having an overall lower anti-AMA1 titer, suggesting improvement in antibody quality. Furthermore, immunization with the fusion chimera enhanced antibodies targeting conserved epitopes on AMA1 resulting in greater neutralization of non-vaccine type parasites. Identifying epitopes of such cross-neutralizing antibodies will help in the development of an effective, strain-transcending malaria vaccine. Our fusion protein design can be expanded to cover polymorphisms in AMA1 to effectively neutralize all P. falciparum parasites.

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VERTICAL AND HORIZONTAL TRANSMISSION OF MICROSPORIDIA MB IN ANOPHELES ARABIENSIS: EFFECT ON LIFE HISTORY TRAITS

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Microsporidia MB is a naturally occurring symbiont in Anopheles arabiensis that inhibits the development of Plasmodium and is also avirulent. Microsporidia MB is transmitted vertically, from mother to offspring, and horizontally through mating. These characteristics are expected to promote its spread through mosquito populations, enhancing the potential of Microsporidia MB as a candidate for the development of a symbiont-mediated malaria transmission blocking strategy. However, in depth understanding of Microsporidia MB transmission patterns is required for mass production of mosquitoes, a pre-requisite for mosquito release, and for robust estimates from theoretical models on Microsporidia MB spread in the natural populations following release. Iso-female lines originating from field collected Microsporidia MB - infected and uninfected females were compared for various life history traits from the egg to adult stage. Bioassays were conducted on first filial generation mosquitoes to determine the effect of diet type and quantity on Microsporidia MB prevalence and density. Microsporidia MB -infected and uninfected males were compared individually and in groups for mating competitiveness. Larval development time of Microsporidia MB -infected An. arabiensis is shorter compared to uninfected mosquitoes. Diet type and quantity influences the density

of Microsporidia MB. Microsporidia MB -infected adults have a higher mating rate compared to uninfected mosquitoes. In general, Microsporidia MB -infection has a positive effect on the development of An. arabiensis mosquitoes. Microsporidia MB -infection is influenced by diet type and quantity. Diet can, therefore, be manipulated to rear highly infected mosquitoes. Microsporidia MB is inherently able to spread in mosquito population due to higher mating rate making it a promising candidate for malaria transmission blocking strategy.

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CHARACTERIZING ANTIBODY RESPONSES TO MOSQUITO SALIVARY ANTIGENS OF THE SOUTHEAST ASIAN MALARIA VECTORS WITH A HUMAN CHALLENGE MODEL OF CONTROLLED EXPOSURE

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Measurement of antibody titers directed against mosquito salivary antigens in blood samples has been proposed as an outcome measure to assess human exposure to vector bites. However, only a handful of antigens have been identified and the specificity and longitudinal dynamics of antibody responses are not well known. Therefore, we conducted a world-first clinical trial of controlled exposure to mosquito bites striving to identify and validate biomarkers of exposure to bites of Southeast Asian malaria mosquito vectors. This trial was an exploratory factorial randomized controlled trial of controlled exposure to mosquito bites with 10 arms corresponding to different species (Anopheles dirus, An. maculatus and An. minimus) and biting levels (35 or 305 bites in total over 6 weeks). Blood samples were collected from study participants (n = 210) before, during and after mosquito challenges (17 weekly measurements per participant in total). Candidate peptides were identified from the published literature and with antigen prediction algorithms using mosquito DNA sequence data. Antibody titers against candidate peptides were determined in participants samples with high-throughput ELISA. Quantification of the antibody response profile over time (including an estimate of the decay rate) and the effect of biting level and species on the antibody response was estimated using longitudinal modeling. Preliminary analyses indicate that antibody levels against Anopheles salivary peptides were boosted during and after mosquito biting challenges, but decayed overall over the course of the study. This research generates important knowledge on species-specific antigens for vector sero-surveillance and evaluation of vector-control interventions in the Greater Mekong Subregion.

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ANOPHELES SALIVARY ANTIBODY BIOMARKERS ASSESS THE EFFECTIVENESS OF PERSONAL INSECT REPELLENT AND IDENTIFY FOCI OF MALARIA TRANSMISSION IN SOUTHEAST MYANMAR

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Innovative approaches for vector surveillance are urgently needed to advance the malaria elimination agenda, as current tools are inefficient and insensitive. Human antibodies to Anopheles salivary proteins have the potential to serve as biomarkers of vector and malaria exposure, and could be used as surrogate outcome measures in vector-control intervention effectiveness trials and to identify focal areas of ongoing transmission. However, evidence for these applications are limited. Antibodies to Anopheles salivary proteins and transmission-stage malaria parasites were measured by ELISA in 14,128 samples collected over 15 months from 111 villages in Southeast Myanmar as part of a stepped-wedge cluster randomised controlled trial of personal repellent effectiveness. We quantified the effect of repellent on anti-Anopheles salivary antibodies (as a serological biomarker of biting exposure) overall and for high-risk populations (migrants and forest goers). A Bayesian geostatistical modelling framework was used to generate spatially continuous predictions of malarial and anti-Anopheles salivary antibody seroprevalence, as a proxy for malaria transmission. Reduced antibody levels to Anopheles salivary proteins were observed after transition to repellent, particularly in migrants and forest dwellers, compared to village residents. Temporal and geospatial analysis revealed that antibodies to Anopheles salivary and parasite transmission-stage proteins followed seasonal trends in vector abundance and malaria transmission and varied over small spatial scales. Joint modelling of anti-Anopheles and parasite antibody seroprevalence identified potential foci of ongoing transmission. These findings suggest antibodies to Anopheles salivary proteins could be an informative vector-control trial outcome measure and support their use as a serosurveillance tool to measure vector exposure and identify foci of malaria transmission.

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WIDE AND SUSTAINED LONG-TERM TARGET EFFICACY OF AN INJECTABLE LONG-ACTING IVERMECTIN FORMULATION AGAINST PLASMODIUM VECTORS IN THE FIGHT AGAINST MALARIA

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Recent biological and behavioral changes of Anopheles result in impaired effectiveness of insecticidal nets in the prevention of malaria. Mass drug administration of ivermectin to humans as a systemic insecticide could help the vectors control. However, the efficacy of this strategy is hampered by the short duration of efficacy as approved ivermectin remains at mosquitocidal plasma concentrations only for few days after administration, and thus requires repeated dosing to achieve full coverage of transmission period. Long-Acting Ivermectin Formulations (LAIFs) that deliver ivermectin at mosquitocidal plasma concentrations for more than one month could be a substantial advantage in the fight against malaria.In the IMPACT project, three LAIF candidates targeting 2-to-3-months sustained mosquitocidal

efficacy, were formulated using BEPO® technology and injected to calves. Efficacy against An. gambiae was determined through survival experiments, and the PK/PD properties of ivermectin and its metabolites were characterized using nonlinear mixed-effects modelling. A lead formulation was selected and further tested in Burkina Faso. Calves were exposed to wild Anopheles using a "Greco-Latin Square" design representing 72 night-calves per month for 3 consecutive months. In addition, in vitro experiments were used to characterize the mosquito-lethal effects of treated calve plasma on the primary Southeast Asian malaria vectors; An. dirus and An. minimus. Data showed PK/PD properties compatible with a sustained exposure to ivermectin and the 3"-O-demethyl ivermectin metabolite for at least 3 months after a single injection. During this time period, wild Anopheles from 10 species in Western Africa and colony-reared An. dirus and An. minimus from Southeast Asia that fed on treated calves were 3 to 10 times more likely to die than those fed on control-animals. Dose-response models will compare susceptibility between species and resistance backgrounds, and help to understand metabolite effects. Our results will provide crucial data on this innovative LAIF with promising epidemiological relevance towards a phase-1 trial in humans.

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INFLUENCE OF ANOPHELINE BITING PREFERENCES ON THE PLASMODIUM FALCIPARUM HUMAN INFECTIOUS RESERVOIR IN WESTERN KENYA

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The human infectious reservoir of Plasmodium falciparum malaria parasites is governed in part by mosquito biting preferences. Understanding biting bias in a natural setting would inform precise targeting of interventions to efficiently interrupt transmission. In a high transmission setting in Western Kenya, we enrolled a longitudinal cohort of 75 households in 5 villages to quantify vector biting bias under natural conditions. To do so, we collected resting mosquitos from households using vacuum aspiration weekly from July 2020 - September 2021 and matched human short tandem repeat (STR) genotypes between mosquito blood meals and cohort individuals. Among 1,065 freshly-fed female anopheline mosquitos, 780 (73%) returned human alleles, among which 657 (84%) were single-source and 123 (16%) were multi-source blood meals. To enable matching of both single- and multi-source blood meals, we developed a reproducible pipeline to match participants to mosquito blood meals using weight-of-evidence likelihood ratios for all mosquito-human pairs. This approach yielded 729 directly observed natural biting events, 685 (94%) of which were matched to participants living in the household where the mosquito was collected. We observed a strong signal of biting bias, with 20% of cohort participants accounting for 85% of all biting events and a Gini index coefficient of inequality of 0.82 (95% CI: 0.79 - 0.85). Pinpointing blood meals to individuals on specific days allows us to explore both static and dynamic factors that may drive biting preference or bias, including age, gender, household size, and bed net use. Importantly, longitudinal observations can reveal the contribution of malaria infection and duration to biting preference since an individual's infection status changes over time. Taken together, these results elucidate factors leading to increased likelihood of receiving mosquito bites, which will ultimately provide insight into precisely targeting individual, household-based, and vector control interventions.

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ASSESSING THE STATISTICAL POWER OF A SEMI-FIELD EXPERIMENT: TESTING SINGLE AND COMBINED INTERVENTIONS AGAINST MALARIA VECTOR ANOPHELES ARABIENSIS

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Vector control remains one of the most efficient strategies against malaria. Semi-field experiments are a very good first way of understanding the impacts of potential new vector controls before going to the field. However, the design of the semi-field experiment is critically important to ensure the outcomes are measurable and robust. One of the best ways to assess this is by power analysis. Assessing a study's statistical power can help avoid wastage of resources, ethical concerns or promising control methods being prematurely dismissed. We developed a power analysis framework to assess how many semi-field chambers, the frequency of sampling and sampling size that a semi-field setting would provide enough power to determine the impact of the interaction between two tools, here pyriproxyfen (PPF) and the widespread long-lasting insecticidal net (LLIN) against malaria vector Anopheles arabiensis. We estimated power across a range of semi-field experimental design objectives and scenarios including testing LLIN alone and the interaction between LLIN and PPF by analysing more than 1000 simulated data sets per scenario using generalized linear mixed-effects models. Power was estimated as a proportion of the simulated data sets in which the null hypothesis was rejected. Although power increased with the increasing number of chambers, sampling frequency and mosquitoes to be sampled, the number of chambers was the dominant factor determining power relative to all other design choices. We also noted that the target effect size has a large impact on power, highlighting that careful and rational choice of this parameter value is critical to achieving realistic power estimates. The higher the effect sizes, the higher the power to quantify the interaction between LLIN and PPF with minimal resources. In our case study, a minimum of 4 chambers per treatment for high interaction effect size between LLIN and PPF should be considered. However, high variance among chambers was noted to contribute to the decreases in power, highlighting the importance of making conditions similar among chambers, e.g., by rotating treatments and samplers among chambers.

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SEMI-FIELD EVALUATIONS OF THE IMPACT OF NOVEL BITE PREVENTION INTERVENTIONS ON ANOPHELES MINIMUS LANDING AND KEY LIFE HISTORY TRAITS IN THAILAND

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The downward trend in the global malaria burden has stalled. Malaria vector control largely relies on indoor residual spraying (IRS) and insecticide treated nets (ITNs), which target mosquitoes resting and feeding indoors. As outdoor biting is increasingly prominent, interventions that target outdoor resting/biting mosquitoes and complement IRS and ITNs are needed. This semi-field study evaluated three transfluthrin- and one metofluthrin-based volatile pyrethroid spatial repellents (VPSRs), as well as etofenprox-treated

clothing for their protective efficacies against two pyrethroid-susceptible Anopheles minimus strains at two research sites in Thailand (Armed Forces Research Institute of Medical Sciences (AFRIMS), Kasetsart University (KU)). A block-randomized crossover design was applied; the intervention and control were randomly assigned to one of two chambers for a block of four days, and switched for a second block of four days. Human landing catches (HLCs) collected mosquitoes for the 6-hour replicates, and backpack aspirations collected remaining mosquitoes after 6 hours. The impact of these interventions on mosquito landing, immediate knockdown, post-exposure blood feeding, and 24-hour mortality was estimated. Preliminary results indicate that most interventions prevented in excess of 50% landing when new (data analysis to be completed by June 2023). All VPSRs, etofenprox-treated forest ranger uniforms and civilian clothing (long trousers), and the combined intervention (VPSR1 + treated civilian clothing (long)), suggest the potential to offer community protection by preventing diversion to nearby non-users through mosquito disarming. Treated civilian clothing (short trousers) did not reduce landing, but did reduce post-exposure blood feeding success and increase 24-hour mortality, also suggesting the potential to provide community protection by disarming and preventing diversion. This study suggests that using SFS with multiple endpoints that extend beyond mosquito landing may help to understand the total effect of the interventions in the community.

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HIGH-RESOLUTION ANALYSIS OF TRANSLATIONAL REGULATION DURING LIFE CYCLE TRANSITIONS IN *TOXOPLASMA GONDII*

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Protein expression can be regulated through cis and trans factors acting on mRNA and translation machinery. This regulation allows cells to fine-tune expression of specific factors in response to environmental cues. The transcriptome of the Apicomplexan parasite *Toxoplasma gondii* represents a challenge to canonical models of translational regulation in eukaryotes as its 5′ UTRs are several times longer than most other characterized species and the vast majority of 5′ UTRs harbor at least one, if not several, upstream AUGs. These unusual features may be maintained in *Toxoplasma* because they confer regulatory information important for gene expression across the parasite life cycle. To understand how the parasite utilizes translational regulation across both the tachyzoite and bradyzoite stages, we performed high-resolution ribosome profiling on *Toxoplasma* and human host cells. Combining these data with bioinformatic approaches, we have characterized transcript features that contribute to translational efficiency. By comparing tachyzoites to parasites exposed to short-term stress, as well as fully-differentiated bradyzoites, our data reveal a new timeline for activation of the bradyzoite gene expression program. Finally, we identified a cohort of translationally-regulated factors whose expression changes across the tachyzoite-to-bradyzoite transition, including many uncharacterized proteins whose functions may provide new insight into bradyzoite biology. Together, this work expands both our molecular framework for gene regulation in *Toxoplasma* as well as determinants of translation that shape the gene expression program of chronic stages.

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CRYPTOSPORIDIUM REMODELS HOST MICROVILLI THROUGH AN EXPORTED VIRULENCE FACTOR

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The intestinal parasite *Cryptosporidium* is a leading cause of diarrhoeal disease, contributing to early childhood morbidity and mortality. Like other members of the phylum Apicomplexa, *Cryptosporidium* has secretory organelles containing proteins that are exported into host cells following parasite invasion. For *Cryptosporidium*, the identity and function of the vast majority of these proteins is unknown. Using a bioinformatics approach, we first identified a putative host-exported protein with serine repeats, which we epitope tagged at the endogenous locus. With a combination of super-resolution and expansion microscopy we discovered that this protein localises to the parasite's secretory dense granule organelles prior to host-cell invasion, and then within the host microvilli following invasion. To determine the function of this MicroVilli Protein (MVP) we used yeast-2-hybrid screening, detecting interacting partner EBP50; a scaffold protein known to facilitate F-actin recruitment and control microvilli dynamics. Microvilli elongation is commonly seen in *Cryptosporidium* infected epithelial cells, but the mechanism for this was previously unknown. Parasites deficient in MVP have moderately attenuated growth yet show a complete lack of elongated host microvilli during infection. It is known that the *Escherichia coli* virulence factor MAP also interacts with EBP50, driving cell surface membrane protrusions and displacement of the NH3 sodium transporter contributing to diarrhoeal symptoms. While MVP has C-terminal homology with MAP, there does not appear to be evidence of a horizontal transfer event. This suggests a convergent evolution between bacteria and parasite that may contribute to diarrhoeal symptoms during infection.

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A SKIN-ON-CHIP ORGANOID MODEL TO UNRAVEL THE DEVELOPMENT OF DERMAL TRYPANOSOMES

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Trypanosoma brucei, a protist responsible for Human African Trypanosomiases, is an extracellular parasite that complete its complex life cycle in two hosts: a tsetse fly vector that transmits it to the mammalian host during a blood meal. The fly deposits metacyclic trypomastigotes, a cell cycle arrested stage, into the skin dermis. From there, the parasites enter the blood and lymphatic system which forms the primary reservoir for the development of infection. Experimental infections in animal models and field studies in human have recently shown that *T. brucei* maintains a population in the extra vascular dermis that remain transmissible to tsetse flies. Thus, the skin represents as an important anatomical reservoir for these parasites. To characterise the adaptations of dermal trypanosomes (proliferation, differentiation, transmissibility, motility), their interactions with the dermal environment, as well as their exchanges with the vascular compartment, we developed an in-house skin-on-chip (SoC) model based on the reconstruction of a vascularized human skin tissue within a microfluidic chamber. This skin model shows a tissue organization and a cell polarity mimicking human skin and recapitulating some of its physiological properties. The SoC remains viable for 8 days making it a suitable model for live imaging of fluorescent parasites and quantification of key biological functions with high reproducibility. For instance, first experiments showed marked differences in motility of the parasites in the dermal niche.

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DYNAMICS AND SIGNALING OF MITOCHONDRIAL MRNA U-INDEL EDITING DURING *T. BRUCEI* DIFFERENTIATION

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Twelve of the 18 mitochondrially encoded mRNAs in *T. brucei* must be post-transcriptionally modified by insertion/deletion of uridine residues (U-indel editing) to establish an open reading frame that is competent for translation on mitochondrial ribosomes. Here, we investigated changes in total and edited mRNAs in pleomorphic *T. brucei* at various times during the differentiation from long slender bloodstream form (BSF) to procyclic form (PCF). We found that, for most mRNAs, the abundances of total

and edited mRNAs increase modestly in stumpy forms and return to near slender BSF levels in PCF. In contrast, when stumpy BSF parasites are transitioned to PCF medium, the four cytochrome mRNAs (*COI*, *COII*, *COIII*, and *CYb*) are upregulated. Using droplet digital PCR, we quantified precise numbers of total and edited molecules per cell, allowing us to calculate editing efficiencies. Interestingly, while *COII* and *CYb* mRNAs exhibit increased editing efficiencies during differentiation, *COI* and *COIII* mRNAs are upregulated primarily by changes in total abundance. These increases in cytochrome mRNAs were also reflected *in vivo* during tsetse fly midgut infections, thus demonstrating this is a physiologically relevant event. We also found that a decrease in temperature is a key differentiation cue that sensitizes the parasites to other biomolecular triggers such as RDK1 depletion. We propose a working model in which temperature serves as a sensitizing trigger for the pathways governed by RDK1 to upregulate the abundance of the edited and never-edited cytochrome mRNAs during BSF-to-PCF differentiation.

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