Technical consultation on the malaria rebound phenomenon

Report on a virtual meeting,
22–23 March 2022

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SUMMARY

On 22–23 March 2022, a WHO technical consultation was convened by the Global Malaria Programme to discuss the malaria rebound phenomenon. The aims of the technical consultation were to: 1) define what is meant by the rebound phenomenon and understand its determinants; 2) understand the potential public health significance of the rebound phenomenon; and 3) clarify expectations (e.g. study design, duration of follow-up) for evaluation of the rebound phenomenon during product development.

Experts reviewed key issues with respect to the definitions of rebound and related terms. A review of the evidence from malaria rebound evaluations was discussed to inform understanding of the determinants of the extent of rebound, and the pros and cons of different study designs and analytical approaches. The aim of this discussion was to agree on good practices and a consistent approach to rebound evaluations and analyses across studies. The experts concluded with a discussion of the public health relevance of rebound, including implications for the evaluation of rebound for current and future interventions, approaches to the management of rebound within the public health system, and implications of rebound evaluations for the timing of policy recommendations.

Key conclusions of the meeting

1. The participants agreed on a proposed definition of rebound as a period of increased malaria risk after time-limited protection from malaria (i.e. after chemoprevention, vaccination or vector control), relative to individuals of the same age from the same population who did not receive the intervention. A review and formalization of this definition and other associated terms (e.g. age-shift, delayed malaria, resurgence) should be undertaken by the malaria terminology committee.

2. Although the available evidence suggests that rebound is a real, measurable phenomenon, evaluations have shown that the extent of the rebound has not outweighed the benefits of the intervention, and it does not appear to be of a frequency or magnitude to warrant serious concern about current interventions. Nevertheless, the risk of rebound should be considered where new interventions or new strategies for the use of existing interventions are evaluated (see point 4 below).

3. The cumulative impact (intervention period plus post-intervention rebound follow-up period) is the best measure of an intervention's effect. Assessment of cumulative impact should consider, if possible, all available data, including clinical malaria and more severe outcomes, such as severe malaria, hospitalization or death.

4. Clinical trials should be designed to assess cumulative impact in key settings where rebound could best be measured and might occur (e.g. long-term application of interventions, starting at young ages, highly effective intervention(s), areas of moderate to high transmission). Donors should be encouraged to fund such assessments.

5. Available studies on rebound are limited by the heterogeneity of methods and end-points used. Standardized methodology (end-points, analytic methods, including cumulative end-points during the intervention and follow-up period, etc.) should be used for rebound evaluations of new interventions in trial settings. This will enable data to be consolidated across trials for meta-analyses.

6. The period of rebound may vary depending on how abruptly protection stops. Assessment of rebound in the year following discontinuation of chemoprevention may be more appropriate to detect rebound than with a vaccine, where protection wanes more gradually.

7. Policy recommendations for highly effective interventions should consider the cumulative benefit of the intervention. Evidence on rebound could be accrued during the immediate period (first year) following discontinuation of the intervention in parallel with the policy formulation process.

8. The deployment of highly effective interventions should not be delayed. Longer periods of follow-up (over one year) to assess rebound with new, highly effective interventions with gradually waning protection could occur following policy recommendation through continued follow-up of clinical trial participants. If there was marked rebound in the first year after the intervention was stopped, an extended period of follow-up for more than one year would be indicated to document the duration of the rebound. How best to balance the availability of longer term follow-up evidence on rebound with prompt recommendation and deployment of highly effective interventions should be considered on a case-by-case basis, taking into account the characteristics of the intervention and the available evidence generated during the evaluation trial and by other relevant studies.

9. Currently, there is limited evidence to inform if, when, and how interventions should be stopped. These decisions should consider the cumulative impact achieved by the intervention, which will reflect not only the biological aspects of the intervention or combination of interventions, but also issues such as changes in transmission, health system characteristics, and human behaviour. It would be useful to develop a package of tools, including modelling approaches, for programmes to evaluate when and how to withdraw interventions, as well as how and where to assess rebound risk, and to identify potential options for amelioration, if needed.

1. BACKGROUND

The malaria rebound phenomenon has been variably defined, but is broadly considered to be the period of increased risk of malaria following time-limited protection (e.g. by chemoprevention, vaccination or vector control), relative to individuals of the same age who did not receive the intervention. Although an interesting immunological phenomenon, its public health importance is unclear. A better understanding of the determinants and characteristics of the rebound phenomenon can help to guide evaluations of new products and strategies for malaria control. This meeting focused on the rebound phenomenon following temporary prevention of clinical disease (e.g. through chemoprevention, vaccines, etc.), as distinct from the age-shift in malaria that results from long-term reduction of exposure (e.g. through implementation of insecticide-treated nets [ITNs] or other effective methods of vector control).

1.1 Aims

- Define what is meant by the rebound phenomenon and understand its determinants.
- Understand the potential public health significance of the rebound phenomenon.
- Clarify expectations (e.g. study design, duration of follow-up) for the evaluation of the rebound phenomenon during product development.

1.2 Objectives

- Review existing evaluations of the rebound phenomenon and draw attention to differences in definition, degree and duration of protection, and the approaches to measuring and analysing the phenomenon.
- Agree on a definition of the rebound phenomenon.
- Agree on key issues related to the rebound phenomenon in the design of studies evaluating new strategies or interventions.
- Consider when and to what extent rebound could be a public health problem.
- Consider approaches to ameliorate the effects of rebound in public health practice.

The meeting was not intended to review rebound from an immunological perspective, but rather to focus on clinical and epidemiological features. Participants included scientists, public health practitioners, modellers and product developers. The list of participants can be found in Annex 1. Prof Kevin Marsh chaired the meeting.

2 WELCOME AND OPENING REMARKS

The Global Malaria Programme Director Dr Pedro Alonso welcomed the participants. Dr David Schellenberg, Global Malaria Programme scientific advisor, then reviewed the meeting aims and objectives, as well as the agenda for topics to be covered during the two half-day sessions (Annex 2).

3 DEFINITIONS

The proposed definition of rebound as a **"period of increased malaria risk after time-limited protection from malaria (e.g. after chemoprevention, vaccination or vector control), relative to individuals of the same age from the same population who did not receive the intervention"** was accepted by the consultative group. It was noted several times during the meeting that the occurrence of rebound does not mean that an intervention is not useful. Rather, one must consider the cumulative impact during both the intervention phase and the follow-up phase to assess overall benefit.

The increased risk observed in the intervention group relative to the comparison group during the post-intervention period may be a combination of the waning efficacy of the intervention (e.g. the immune response following vaccination) and the earlier and more rapid acquisition of naturally acquired immunity (NAI) in the comparison group over time as a result of exposure and infection. The apparent rate of decay of efficacy will vary for different clinical (e.g. severe versus uncomplicated disease) and non-clinical (e.g. parasitological or immunological) end-points.

The group noted the potential need for more precision around some of the terms used in the proposed definition of rebound. For example, the term "protection" might need further specificity (e.g. protection from *Plasmodium falciparum* blood-stage infection), and "risk" might need to be modified as "risk of clinical disease". This definition is well suited to a clinical trial context (individual risk), but perhaps less well suited to situations in which communities benefit from indirect effects, for example, by mass drug administration (MDA) or indoor residual spraying (IRS).

Other terms have been used to describe a situation of increased risk of malaria following cessation or interruption of protection; all have some degree of similarity in that the protected group experiences delayed or impaired acquisition of NAI. Examples include:

- time-limited interventions, such as seasonal malaria chemoprevention (SMC) or perennial malaria chemoprevention (PMC), where abrupt stoppage of the intervention (antimalarial drug) is planned at a certain age. The protective effect of the drug disappears relatively quickly, over a period of weeks, and a period of increased risk (rebound) could result when the intervention is discontinued.

- time-limited interventions with more slowly declining efficacy, such as vaccines or monoclonal antibodies, where protection may wane over months to years

These first two scenarios are illustrative of rebound and have also been termed **"delayed malaria"** or an **"age-shift"** in malaria, as the increased risk of clinical manifestations occurs in the protected individual at a later age than in those who were unprotected, and thus had more malaria earlier in life and developed NAI more rapidly. The onset, duration and magnitude of the increased risk may vary with abrupt cessation (antimalarial drugs) versus more slowly declining protection (vaccines or monoclonal antibodies).

- accidental or unplanned cessation of programme delivery

In this third scenario, an intervention that has been applied to the whole population for a period, such as a vector control programme or MDA, is abruptly withdrawn in the context of continued availability of vectors and transmission potential. This can

then result in an increase in malaria incidence in the whole population to similar levels as before implementation of the intervention. This phenomenon has been termed **"resurgence"** and it is distinct from rebound. Resurgence has occurred after both planned (e.g. discontinuation of MDA or IRS programmes) and unplanned (interruption or dramatic reduction of programme service delivery due to financial constraints) circumstances, and is a major public health concern *(1–3)*.

Noting the interest in adding precision to the definition of rebound and considering its relation to other terms such as "age-shift", "delayed malaria" and "resurgence", the participants suggested that the World Health Organization (WHO) malaria terminology committee should further discuss and refine these definitions.

4 EVIDENCE REVIEW

4.1 Overview

A full evidence review was conducted, of which a summary of the key points is provided here (the full text is available at https://zenodo.org/record/6952029#.YukBsHZByUk).

The evidence review indicated that, with current interventions (chemoprevention, vaccines), the available data, although somewhat limited due to the heterogeneity of end-points and methods, suggest that rebound occurs infrequently and, when present, does not appear to have a measurable cumulative negative impact. Overall, the evidence review provided reassurance with respect to current interventions, while also highlighting areas for improvement in study design, methods and analyses to evaluate rebound in the context of new tools and/or strategies.

Included in the evidence review were research studies of malaria interventions conducted in endemic areas that had a control or comparison group that did not receive the intervention. Included studies also had a follow-up period post-intervention in both the intervention and comparison arms that was greater than one month in duration. Randomized controlled trials and non-randomized studies were included, as well as modelling studies.

A total of 50 studies, reported in 67 publications, met the inclusion criteria. There was substantial heterogeneity of key parameters among the studies, such as the study design, age groups included, duration of application of the intervention, duration of follow-up, outcomes assessed, and methods of measurement used to ascertain those outcomes. This heterogeneity precluded the possibility of assessing the evidence through a meta-analysis.

Among these 50 studies, six drug-based studies and two vaccine studies provided some evidence of a rebound effect for uncomplicated clinical malaria. Three of the drug-based studies evaluated chemoprophylaxis, one evaluated PMC, and two evaluated SMC. Three drug-based studies reported a significant rebound of severe malaria: two after chemoprophylaxis and one after PMC. However, in the chemoprophylaxis study with long-term follow-up, the cumulative rate of severe malaria was lower in the children who had received chemoprophylaxis during the first year of life than in those who had not received the intervention. Two follow-up studies of RTS,S AS01 vaccination documented a statistically significant increase in the incidence of clinical malaria in older children during extended follow-up: one during the fifth year after the last dose of the vaccine for the group of children who had

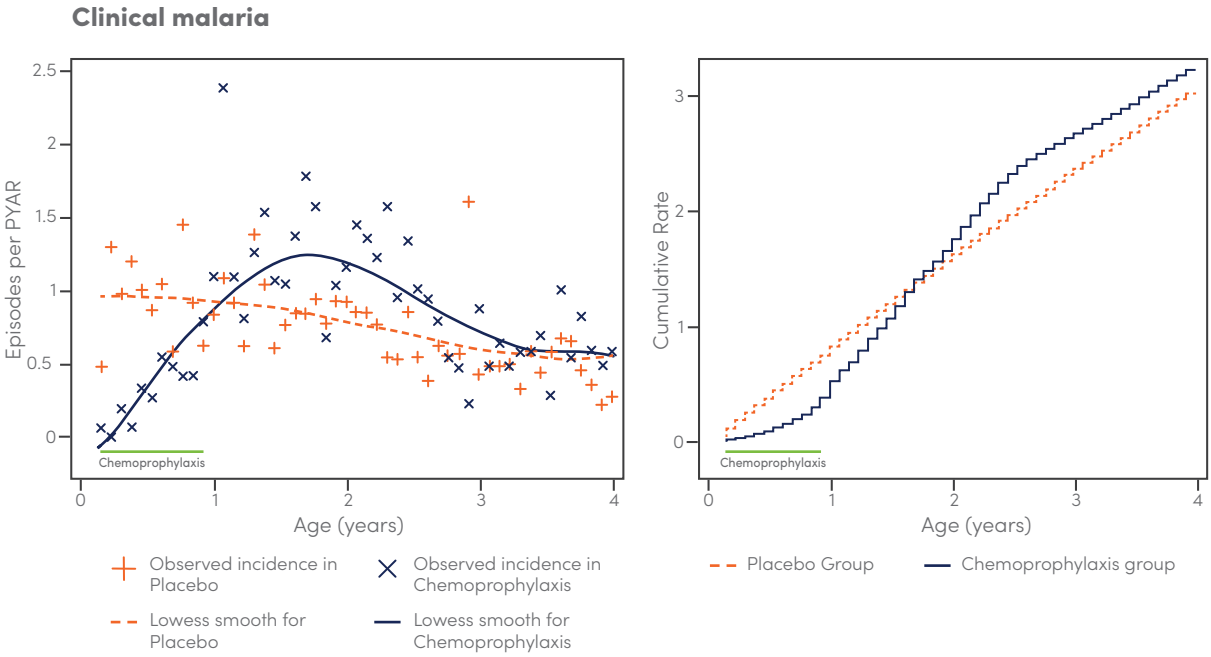
higher-than-average exposure to malaria, and the other during the four to seven years post-vaccination in the study site with the highest transmission intensity. Nevertheless, a cumulative benefit was still observed across the entire seven-year follow-up in the latter study, and no statistically significant rebound of severe malaria was observed in the RTS,S/AS01 studies. Several other drug-based or vaccine studies found a non-significant increased risk of clinical malaria, severe malaria or mortality during the post-intervention period. In general, the number of severe events in these studies was small, and the studies were not powered to detect rebound.

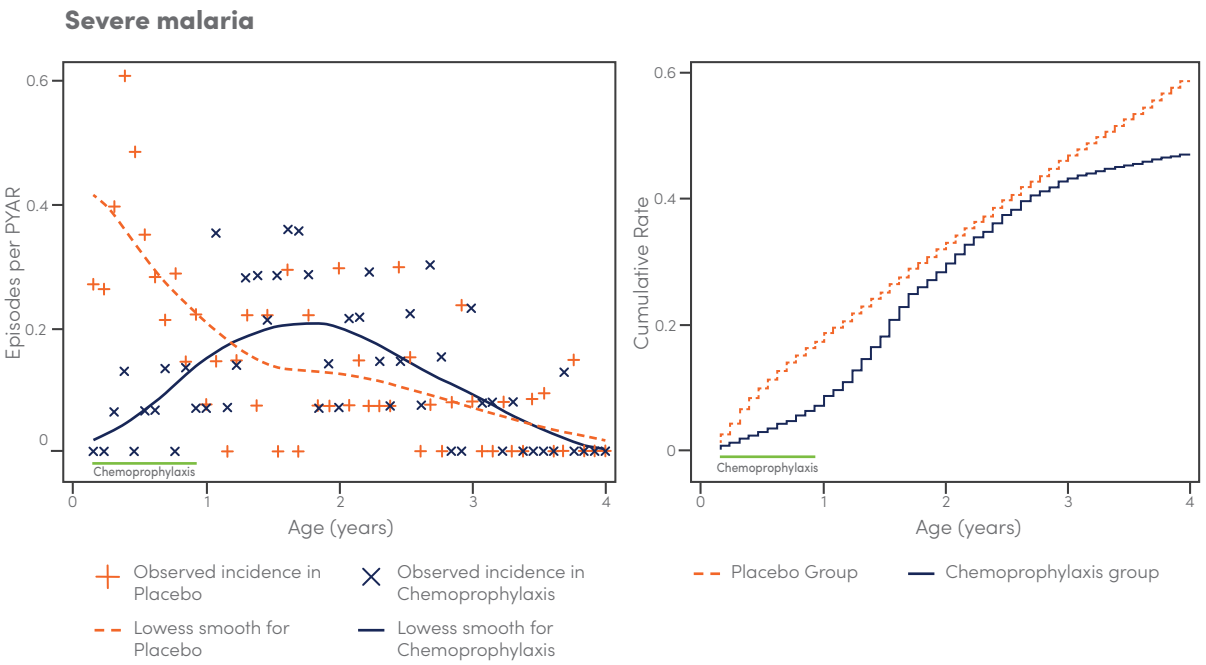
One IRS study documented resurgence following discontinuation of the intervention in Uganda, and one MDA study targeting *P. falciparum* in a setting with *P. vivax* documented an increase in *P. vivax* (but not *P. falciparum*) following the intervention. Neither of these scenarios is considered rebound.

4.2 Cumulative impact

An important consideration is the issue of cumulative or net benefit, which assesses not only the follow-up period, but also the preceding period when those receiving the intervention are afforded protection by the intervention. This is illustrated by the findings from a study of chemoprophylaxis in Tanzanian infants *(4–5)*. Fig. 1 illustrates the incidence of both clinical malaria and severe malaria (upper and lower figures on the left) in the intervention and placebo groups. The incidence of both clinical and severe malaria is suppressed dramatically during the period of chemoprophylaxis (horizontal line parallel to x-axis). After cessation of chemoprophylaxis, the incidence becomes higher in the intervention group for a period and then returns to levels similar to the comparison group. The upper and lower figures on the right show the cumulative incidence of clinical malaria and severe malaria over the whole period (intervention + follow-up). The cumulative incidence in the intervention group compared to the control group does not differ significantly for clinical malaria or severe malaria.

Fig. 1. Risk periods and cumulative incidence in infancy, chemoprophylaxis study, United Republic of Tanzania (adapted from *(5)*)





Although the cumulative incidence of both uncomplicated and severe malaria does not differ significantly between the intervention and control groups over the whole period, the point estimate for severe malaria is lower in the intervention group; those children were substantially protected from malaria early in life when they were most vulnerable, and severe disease and death would have been more frequent. As children age, they experience these severe outcomes less frequently. Even though an intervention group may have somewhat lower NAI than the comparison group at the time the intervention is stopped, they are older, which reduces the subsequent risk and number of events of severe disease and death. Understanding the timing of when rebound occurs can inform measures to reduce its clinical impact.

The approach of assessing rebound in the context of overall net impact is valuable, but has been used in only a very small number of studies. Methods for improved assessment of rebound are discussed in the next section.

4.3 Heterogeneity of studies

Given the heterogeneity of study designs, methods and measurements, it was not feasible to combine evidence across studies for more robust analysis of the factors associated with increased likelihood of rebound. However, considering that impairment of NAI is closely linked to the risk of rebound, it was considered likely that factors that enhance protection (and thus impair the development of NAI in the intervention group) would increase the risk of rebound. These factors include greater intervention efficacy, longer duration of protection, higher force of infection (transmission intensity), and younger age of the protected group.

Important potential modifiers were often not well measured or documented in the available studies; these included parameters such as transmission intensity, and the coverage of other interventions (e.g. case management, vector control, other prevention activities that may have been implemented individually or in combination) in the intervention and control arms.

It was noted that the reported end-points and their definitions varied widely across studies. Evaluation of more serious outcomes in rebound studies, such as severe disease or death, was often lacking due to limited sample size. Severe disease or mortality end-points are challenging to measure in all but very large studies due to their decreasing frequency over time as children become older. Therefore, a relatively large population would be needed to assess these outcomes, and studies powered to detect differences between intervention and control groups during the intervention period will usually be underpowered to detect significant differences in less frequent severe disease and death outcomes in older children. Other issues related to rebound study design and analytic methods are discussed in the next section.

5 STUDY DESIGN APPROACHES AND METHODS FOR EVALUATING REBOUND

5.1 Challenges in design and analysis

Many of the published studies on malaria rebound pose challenges for both individual and collective interpretation of the studies. These challenges include the following:

Multiple comparisons: Often studies have exploratory end-points beyond the primary end-point for which the original study was powered. Unless the p-values are adjusted for multiple comparisons, there is the possibility that any observed "significant" associations are spurious and could be due to chance alone.

Consistency of end-points: Definitions of end-points or outcomes such as clinical malaria or severe malaria may vary between studies, and outcomes captured might vary within a study between the intervention period and the follow-up rebound period.

Rebound studies are often powered to detect a difference in clinical (uncomplicated) malaria, as a relatively common outcome for which the definition is often similar/comparable across studies. Outcomes such as severe malaria and its contributing syndromes are more variably defined. Severe malaria and death occur much less frequently as children age and thus require larger sample sizes (and more costly studies) to ensure sufficient statistical power.

If a severe disease or death outcome is a primary trial end-point, then the sample size calculation should be powered to demonstrate the difference between intervention and control groups during the intervention period (demonstration of efficacy of the intervention). Such a study would then presumably be able to detect a similar-sized but opposite rebound effect during the follow-up period However, because the incidence of severe disease or death is much lower in the follow-up period due to the changing patterns of disease by age, it is unlikely that any observed rebound will negate the observed benefits of the intervention. As an example, in a chemoprophylaxis study in Gambia, children receiving chemoprophylaxis from 3 months to 5 years of age had a significantly lower mortality risk during the intervention period than children who received a placebo, based on nearly 600 deaths (261 deaths in the intervention group and 315 deaths in the placebo group). In the year after stopping chemoprophylaxis, only 16 deaths occurred (11 in the intervention group and 5 in the placebo group), a difference that was not statistically significant. Over the course of the eight years of intervention and follow-up, there was an overall significant 15% reduction in mortality in the intervention group compared to the placebo group, demonstrating a cumulative benefit in averting deaths *(6)*.

When calculating the sample size of studies that include an evaluation of rebound, it is important to accommodate expected increases in loss to follow-up, given the longer follow-up duration, and the higher number of statistical tests.

Selection bias: Trials to evaluate efficacy are usually randomized at enrolment to distribute confounding between the intervention and control groups, and make the groups comparable at baseline. However, follow-up for a rebound evaluation often starts long after baseline randomization and considers only the "rebound period". This potentially results in a population for the analysis that differs substantially from the baseline population and where the intervention and control arms differ as a result of the non-random distribution of confounders, including past exposure to malaria, or non-random discontinuation of the trial.

5.2 Considerations for research study design

General: In the context of the evaluation of a completely new tool or approach, rebound is considered a safety issue and should be included in the overall study design and plan.

Plan for a rebound evaluation from the beginning of the intervention trial: This should include ensuring sufficient power to assess the efficacy of the intervention, a planned duration of follow-up during the rebound evaluation, use of the same end-points in the intervention and rebound periods, and an analytic approach to measure relative risk over time and cumulative net impact.

Analytic approaches for measuring relative risk and cumulative impact over time: As detailed in the previous section and illustrated in Fig. 1, assessment of an intervention is best done by considering the net or cumulative effect of the intervention during the period of the intervention and any rebound period. The cumulative incidence of the primary end-point during the entire evaluation period (intervention period + follow-up period) provides the estimate of overall benefit. The measurement of relative risk during specific time periods during the intervention and control arms highlights the intervals when rebound might occur after cessation of the intervention, thus informing a targeted approach to reduce risk, if needed.

Detailed discussion of appropriate statistical methods is beyond the scope of this report. However, suggested approaches for analyses over time include piecewise models or survival analysis with time-dependent estimates. In the United Republic of Tanzania study, a piecewise model with short follow-up duration intervals (four weeks) was used over the four-year study period *(5)*. The investigators used Poisson regression for each piece and included multiple episodes of clinical malaria since randomization. An autoregression component was employed in which, for each group, the risk in a period was dependent on the risk in the preceding period, all within the context of a Bayesian framework.

Duration of follow-up: The duration of planned follow-up for rebound evaluation may vary depending on the type of intervention assessed. For example, with drug-based interventions where the protective effect wanes quite rapidly, a shorter duration of follow-up may be sufficient, compared to interventions where the protective effect wanes more slowly, as might be seen with vaccines or monoclonal antibodies. It may be reasonable to plan for a minimum of one year of follow-up, but be prepared to continue follow-up if rebound is detected in the initial period, until the risks in both the intervention and control group have stabilized. As noted below in the section "Public health considerations – rebound evaluations and timing of policy recommendations",

this does not necessarily imply a delay in a policy recommendation for a potentially valuable new intervention.

The costs of initial rebound evaluation should be budgeted for within the initial efficacy study costs and should be borne by the study funder or sponsor. In cases of extended follow-up for rebound, the costs may need to be shared among public and private partners.

End-points: Standard end-points with consistent definitions facilitate meta-analysis across trials. These could include definitions for clinical and severe malaria, as defined for other large multi-site intervention trials *(7)*. Although there is a well-accepted WHO definition of severe malaria, it requires competent clinicians and considerable laboratory testing capacity; in some settings, an alternative definition using hospital admissions with confirmed malaria has been adopted *(8)*. It is advisable to use the same end-points and surveillance methods to detect end-points in both the intervention period (for efficacy) and the extended follow-up period (for rebound evaluation). Evaluation of multiple end-points (severe malaria, clinical malaria, anaemia) may help to establish biological plausibility; for example, finding an increase in severe malaria without a concurrent increase in clinical malaria would be unusual.

Cost-effectiveness: Cost-effectiveness estimates from intervention trials rarely include data on cumulative impact. Cost-effectiveness may be impacted substantially if considered across the cumulative intervention and post-intervention period. This suggests the need to rethink the role and approach to cost-effectiveness analysis in the evaluation of malaria interventions.

Number of trials: An ideal study of a new tool or approach would be large enough to collect data on cumulative impact over a sufficient length of time, accommodating multiple statistical tests and increased loss to follow-up. Given the importance of transmission intensity in understanding both efficacy and rebound, such a study could occur at several sites with different transmission patterns and intensity, but would need to be adequately funded.

It may be more feasible to conduct several smaller, separately funded studies, but it would be critical to ensure a consistent approach to study design, end-point definition and surveillance methods in order to enable consolidation of data across sites and facilitate meta-analysis and robust estimates of cumulative impact and cost-effectiveness.

5.3 Considerations for programmatic evaluations

Research evaluations of rebound and the overall cumulative impact are appropriate for the evaluation of new tools or approaches, especially those expected to be at high risk of substantial rebound. However, the reviewed evidence suggests that, with currently deployed interventions, rebound occurs infrequently and, when present, does not have a measurable cumulative negative impact. When interventions and strategies likely to have modest efficacy are being considered, it may be useful to consider the feasibility of a programmatic evaluation of rebound.

Given the design challenges inherent even in controlled research settings, it is important to acknowledge that evaluation of rebound in programmatic settings is even more challenging, and there is no ideal approach. Such evaluations may be confounded by issues such as health system access and performance, coverage of

the intervention being evaluated, type of intervention, coverage and impact of other interventions deployed, seasonality and other variables. Particularly considering the impact of seasonality and rainfall on malaria, a "before-after" evaluation of rebound is a risky proposition unless some sort of control group can be identified. It may be helpful to measure malaria risk in a different age group to that receiving the intervention, during both the pre- and post-intervention periods.

Another approach is to use a case-control design, assessing exposure to the intervention in cases of clinical or severe malaria, and comparing this to exposure in controls during the rebound evaluation period. The level of exposure to – or protection afforded by – an intervention (e.g. the number of cycles of SMC or doses of vaccine) could be considered as part of a "dose-response" analysis. Case-control evaluations are relatively less costly, but pose challenges, as they may be particularly prone to selection bias and confounding due to associations between receipt of the intervention and survival, or access to care.

Finally, an approach that relies on routine data such as hospitalization with confirmed malaria to assess the frequency of end-points during the rebound evaluation period may be considered. Although this approach is also potentially challenging due to data quality, health system access and supply chain issues, it may be improved by using the same detection methods during the intervention and rebound period and through activities to improve the quality of data collected. Overall, the lack of high-quality surveillance data (both inpatient and outpatient) highlights the critical need to strengthen surveillance systems for malaria and other infectious diseases.

Potential of modelling

Modelling may be a useful tool for exploring hypotheses of the immunological causes and epidemiological consequences of rebound, and for evaluating the cumulative impact in programmatic contexts, using a counterfactual model for comparison purposes. Several malaria simulation models exist, with some important differences and assumptions, and a consensus modelling approach is preferred wherever possible. Models will need to include considerations of the mechanism of protection of the tool or strategy, as well as the transmission context. Modelling may also help to identify areas or situations where withdrawing the intervention carries a greater risk of rebound, and where special ameliorative measures should be considered. Challenges with models include that different models are based on different assumptions; data to inform and improve them are often incomplete; and they use somewhat simplified abstractions of complex real-world interactions.

6 PUBLIC HEALTH CONSIDERATIONS

6.1 Current interventions

Based on available evidence, there is little concern that rebound is a public health concern for currently deployed interventions. There is thus no need to go back and re-evaluate these strategies or tools. In addition, current interventions for malaria are modestly effective – that is, they do not perfectly protect against infection and clinical disease, even in clinical trials. The deployment of such "leaky" interventions enables the development of NAI, albeit more slowly than in those who survive despite the lack of intervention. In the usual situation where programme coverage is lower than that achieved in trials, this leakiness may be more marked, further mitigating concern over rebound.

6.2 Future interventions

Although there is confidence that current interventions deliver an overall positive cumulative impact, this may not be the case with more effective future interventions or combinations of current interventions. The magnitude and duration of protection may be considerably higher (less leaky), and thus development of NAI may be more impaired than with less effective interventions. In these scenarios, the overall impact of rebound may need to be considered and carefully evaluated during the research and development phase. Examples of such tools might be a next-generation vaccine or monoclonal antibody, mosquitoes with gene drive technology, or strategies that co-deploy combinations that provide much better protection (e.g. ITNs + SMC + RTS,S) and for a longer period.

6.3 Modification of current interventions

Some existing interventions or strategies may be modified, raising the question of whether a review of their cumulative impact might be warranted. For example, is the expansion of SMC from the current target age group (3–59 months of age) to older children (5–10 years of age), or delivery of additional doses of chemoprevention in the first year of life sufficient to warrant a re-evaluation of the cumulative effect of the intervention?

At this stage, it is not possible to provide a definitive answer as to what constitutes a sufficiently different use case from the one in which rebound was originally evaluated that would merit a new evaluation. Investigators may need to consider how the modification affects both the duration and efficacy of protection. With greater efficacy and duration of protection (greater "area under the curve"), reassessment of rebound may become increasingly important. It may also be important to consider the modification of an intervention with respect to transmission and epidemiological setting. For example, the risk of rebound may be different when applying an intervention like SMC with amodiaquine plus sulfadoxine-pyrimethamine, which is currently used only in highly seasonal settings in West and Central Africa, to more perennial settings in that region.

6.4 Evaluation and management of rebound within the public health system

Once an intervention has been implemented and scaled up, it becomes difficult to rigorously evaluate rebound (see section on programmatic considerations). This highlights the need to obtain the best possible information on the characteristics of a new intervention, including rebound, during the research and development phase and before programmatic deployment. Quality surveillance systems that can reliably detect changes in disease incidence following the withdrawal of a time-limited intervention would be useful, but are currently not commonly found. It is a priority, therefore, to strengthen programme evaluation capacity, including surveillance and adverse event monitoring.

If a time-limited period of increased risk is identified during the research and development phase, it will be useful to consider what programme measures should be taken to ameliorate this risk. Response measures will need to be tailored to the local programmatic context and could include a variety of activities, such as enhancing awareness of new vulnerabilities arising from a rebound effect, improving access to and delivery of case management, targeting vector control measures, improving coverage with other interventions, e.g. ensuring provision of an effective ITN to those known to be at risk prior to the period of risk, and heightening surveillance in groups at greatest risk.

6.5 Rebound evaluations and timing of policy recommendations

The proper evaluation of a new intervention requires careful assessment of rebound, including an appropriate follow-up time, ideally long enough to show stabilized incidence rates and demonstrate that the overall cumulative impact is positive. The timeframe may vary depending on the mechanism of the intervention. In some cases, the evaluation may be achieved in the first year following the end of the efficacy trial, while in other cases longer follow-up may be appropriate.

In the case of an intervention that has been shown to be highly efficacious, there is legitimate concern that waiting for rebound data would delay implementation of a tool or approach that could save many lives. However, any new tool or approach requires a review of safety and efficacy data, and often the process of data review, subsequent policy consideration and roll-out of the intervention takes more than a year. This is enough time for initial rebound information to be generated and considered. During the scale-up period, additional longer term information on rebound (if needed) would become available. There is some risk to this approach: plans to roll out a promising intervention may need to be paused and/or modified in order to implement measures to ameliorate risk of rebound based on newly available data. The approach taken will need to be considered on a case-by-case basis, taking into account the characteristics of the intervention and the evidence generated during the evaluation. Product developers are encouraged to engage with the WHO Coordinated Scientific Advice procedure to ensure alignment of expectations for evaluation data *(9)*.

7 WITHDRAWAL OF INTERVENTIONS

There may be interest in withdrawing some interventions as transmission decreases to very low levels. Examples that have been considered include ITNs, IRS, and intermittent preventive treatment of malaria in pregnancy (IPTp) *(10–11)*. It may be helpful to consider the withdrawal of interventions and the potential for rebound in the context of the cumulative impact achieved by the intervention. This will reflect not only the biological aspects of the intervention or combination of interventions, but also many other components, including changes in transmission, health system characteristics, and human behaviour. Withdrawal/cessation of a time-limited intervention may result in an increase in clinical malaria, but it may be more relevant to assess how withdrawal affects the incidence of severe outcomes.

Currently, there is limited evidence to inform if, when and how interventions should be stopped. It would be useful to develop a package of tools, including modelling approaches, to help programmes evaluate when and how to withdraw interventions, as well as where rebound may be a risk, and to identify potential options for amelioration, if needed.

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ANNEX 2. AGENDA

MONDAY, 21 MARCH 2022		
	Agenda	**Session Lead**
13:00 – 13:10	Welcome and introductions	Kevin Marsh
13:10 – 13:20	Background	David Schellenberg
13:20 – 14:20	**Literature review** (30 mins) Summary of malaria rebound evaluations to inform understanding of the determinants of the extent of rebound, pros and cons of different study designs and analytical approaches *Discussion (30 mins)*	Caterina Guinovart / Maria Tusell
14:40 – 15:50	**Study design issues** (20 mins) Key design features, analytical approaches, and managing bias *Discussion (50 mins)*	John Aponte
15:50 – 16:00	**Wrap up**	Kevin Marsh
TUESDAY, 22 MARCH 2022		
13:00 – 13:10	Welcome & summary from day 1	Kevin Marsh
13:10 – 14:10	**Public health relevance of the rebound phenomenon** When is it a problem and how can it be managed?	Salim Abdulla
14:10 – 15:00	**General discussion**	Gina Rabinovich
15:15 – 15:50	*Recommendations on:* *a) Evaluation of rebound – where, when, how?* *b) Public health considerations – when and how to ameliorate?*	Kevin Marsh
15:50 – 16:00	**Wrap up**	Kevin Marsh

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