Statistical report, Malaria Vaccine Pilot Evaluation (MVPE), analysis of data to month 46

Paul Milligan and Ari Fogelson on behalf of the MVPE investigators

Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine,

4 Feb 2024

Table of Contents

Background 3
Key messages 3
Vaccine introduction and evaluation design 7
Vaccine introduction, Ghana 9
Vaccine introduction, Kenya 12
Vaccine introduction, Malawi 14
Mortality surveillance 16
Ghana: 16
Kenya: 17
Malawi: 18
Age distribution of severe malaria admissions and of all-cause mortality, in children included in impact analyses (who would have been eligible to receive 3 doses of RTS,S), in comparison areas 20
Percentage of admissions 1-59m in comparison areas, which had a diagnosis of severe malaria, the % with each form of severe malaria, and the case fatality rates. 29
Seasonality in severe malaria admissions and all-cause mortality 30
Number of doses administered 31
Analysis populations 33
Impact on mortality 34
Primary analysis of mortality 34
Secondary analyses, mortality 34
Impact on admissions to hospital with severe malaria 35
Meningitis 36
Admissions to sentinel hospitals without malaria parasitaemia, anaemia, or meningitis 36
Comparison of associations for cerebral malaria, meningitis, and mortality by sex interaction, with the signals observed in the phase 3 trial. 51
Comparison with results reviewed in 2021 52
Coverage estimates 54
Annex 1: Age distributions of deaths and of hospital admissions with severe malaria 57

Annex 2: Profile of deaths reported and included in analyses 71
Annex 2: Profile of admissions reported and included in analyses 75
Annex 3: Statistical methods 78
Analysis approach 78
Power calculations 82
Comparison of rate ratios for safety outcomes with safety signals from the phase 3 trial: 83
References 85

Background

The MVPE was planned to assess the effectiveness of the RTS,S/AS01 malaria vaccine when introduced through national immunization programmes. Specific questions were the whether the protection observed in the phase 3 trial could be replicated, in view of the perceived need for a 4-dose schedule with new immunization contacts; the impact on mortality in boys and girls; and whether the excess cases of meningitis and cerebral malaria observed during the Phase 3 trial were causally related to RTS,S/AS01 vaccination. The functioning of the immunisation programme and use of currently recommended malaria control measures by vaccine-eligible age groups of children were to be monitored including any adverse (or beneficial) effects on these of malaria vaccine introduction.

The vaccine was introduced in pilot areas in Malawi, Ghana, and Kenya in 2019 (on April 23rd, April 30th, and September 13th respectively), with evaluation in each country planned over 46 months. In July 2019 WHO proposed a framework for policy decisions on the vaccine, which was endorsed by SAGE/MPAG, whereby a WHO policy recommendation on the use of RTS,S/AS01 beyond the pilot countries could be made if and when concerns regarding the safety signals observed in the Phase 3 trial (related to meningitis, cerebral malaria and sex-specific mortality) were satisfactorily resolved and the data on severe malaria and mortality were assessed as consistent with a beneficial impact of the vaccine. Adjustments or refinements to the policy recommendation for broader use of RTS,S/AS01 could be made based on the final MVIP data set, with particular focus on the value of the fourth dose.

A statistical analysis plan defined the number of events required to determine whether MVIP data on meningitis, cerebral malaria, and sex-specific mortality, were consistent with the associations observed in the phase 3 trial (90% power to detect or exclude effects of the magnitude observed in the phase 3 trial if they occurred, after allowing for dilution due to incomplete vaccine coverage, and contamination), and the number of severe malaria cases to detect an impact if effectiveness was similar to that observed in the trial (similarly allowing for dilution of the effect in the MVIP). By April 2021 sufficient events of each type had accrued in the three countries combined, for a pooled analysis, and primary analysis of the safety outcomes, and impact on severe malaria, were undertaken and reviewed by WHO. These results formed the basis of the Oct 6 2021 policy recommendation on the vaccine. It was estimated that the projected number of deaths by the end of the 46-month evaluation would allow 90% power to detect a reduction of 10% in a pooled analysis, and primary analysis of mortality, pooled across countries, was planned at this time. The sample size in the MVPE protocol envisaged 90% power to detect a 10% reduction in mortality in each country, but in practice mortality rates have been lower than anticipated, thus there is power to detect this magnitude of effect only in pooled analysis of the data from the three countries.

Since the MVIP started, case control studies have been initiated in each country to measure vaccine effects in vaccinated children, to complement the population-level impact measured by the cluster-randomized evaluation. Results are expected to be available in late 2024.

This reports is based on final data received up to Jan 8, 2024.

Key messages

The RTS,S/AS01 malaria vaccine was introduced in Ghana, Malawi and Kenya in 2019, as part of routine childhood immunization, in a large-scale pilot scheme, with doses at 6,7, 9 and 24 months of age in Ghana and Kenya, and at 5,6,7 and 22 months in Malawi.

Delivery, which required addition of new visits for immunisation, was undertaken and monitored by the national immunisation programmes. Uptake of the vaccine in children, and its safety and impact, were carefully evaluated over a 46-month period by investigators in each country.

The evaluation, coordinated by WHO, employed robust methods, including the use of randomization to choose early-implementing and comparison areas, large-scale community surveillance for mortality, hospital-based surveillance with strengthened diagnostic procedures, and careful monitoring of contextual factors including uptake of other vaccines and other malaria control measures.

The MVPE protocol was approved by ethics committees at WHO and in each country. Oversight was provided by the MVIP Data Safety Monitoring Board and MVIP Programme Advisory Group (later the SAGE/MPAG working group), reporting regularly to MPAG and SAGE, and with additional technical guidance from ad-hoc expert groups.

By 2021 there was sufficient evidence about feasibility of delivery, safety, and the vaccine's impact on hospital admissions with severe malaria, for WHO to recommend wider use of the vaccine. The evaluation continued until 2023, including information on the uptake of the fourth dose of the vaccine and final data on the impact of vaccine introduction on overall mortality in young children.

Key outcomes for assessing impact were mortality of any cause except injury in boys and girls, and admission to hospital with a diagnosis of severe malaria. Malaria remains a leading cause of death in young children but it is not possible to measure malaria-specific mortality reliably, because many deaths occur at home, and even in hospital it can be difficult to establish if malaria was a direct or contributory cause of death, or was only an incidental infection. We could however confidently exclude deaths due to injury. It was anticipated that as malaria is a leading cause of death, the impact on *all cause deaths* might be about 10% and that pooled analysis combining the data for the three countries would have 90% power.

Key safety outcomes were admission to hospital with a diagnosis of meningitis, and with a diagnosis of cerebral malaria. Hospital surveillance was strengthened and standardised case definitions were employed.

Uptake of primary doses and of fourth dose, coverage of other vaccines, use of other antimalarial measures, and of care-seeking for fever, was monitored through large-scale household surveys at baseline, after 18months, and after about 30 months.

Primary analysis of safety and impact on severe malaria was undertaken after 24 months (19 months in Kenya), pooled across countries. The primary analysis of impact on mortality was planned after 46 months, also pooled across countries.

A randomized design was used, whereby areas with total population of about 100,000 (districts in Ghana, subcounties in Kenya, and catchment of groups of immunization clinics in Malawi) were randomized for immediate or delayed introduction of RTS,S. Randomization was constrained so that intervention and comparator areas would be comparable for population size, malaria burden, access to health facilities and to immunisation services.

Estimation of incidence rate ratios: Surveillance was maintained in children 1-59 months, this includes children who were eligible to receive the RTS,S vaccine, as well as children who were not eligible because they were too young, or were too old when the vaccine was introduced. The ratio of incidence (of mortality, or admission with severe malaria or meningitis) in eligible to non-eligible children is expected to be the same in both RTS,S and comparator areas, if the vaccine has no effect.

By comparing these ratios in the two areas, we can estimate the incidence rate ratio associated with vaccine introduction. This method helps to control for imbalance between areas, can improve efficiency, and does not require hospital catchment population sizes, which can be challenging to define and measure.

Vaccine delivery: In total, by the end of the evaluation period, 1.29 million children in early-implementing areas received their first dose of RTS,S/AS01, 1.07million had received their third dose, and 0.44million their fourth dose.

During the nearly 4 years of evaluation, introduction of the malaria vaccine was associated with reductions in all-cause mortality in young children, and in the number of children admitted to hospital with severe malaria (Figure 1):

Among children old enough to be eligible to have had a third dose of vaccine: there was a 13% reduction in total deaths (counting deaths of all causes apart from those due to injury), 95% confidence interval 2.7%-22%.

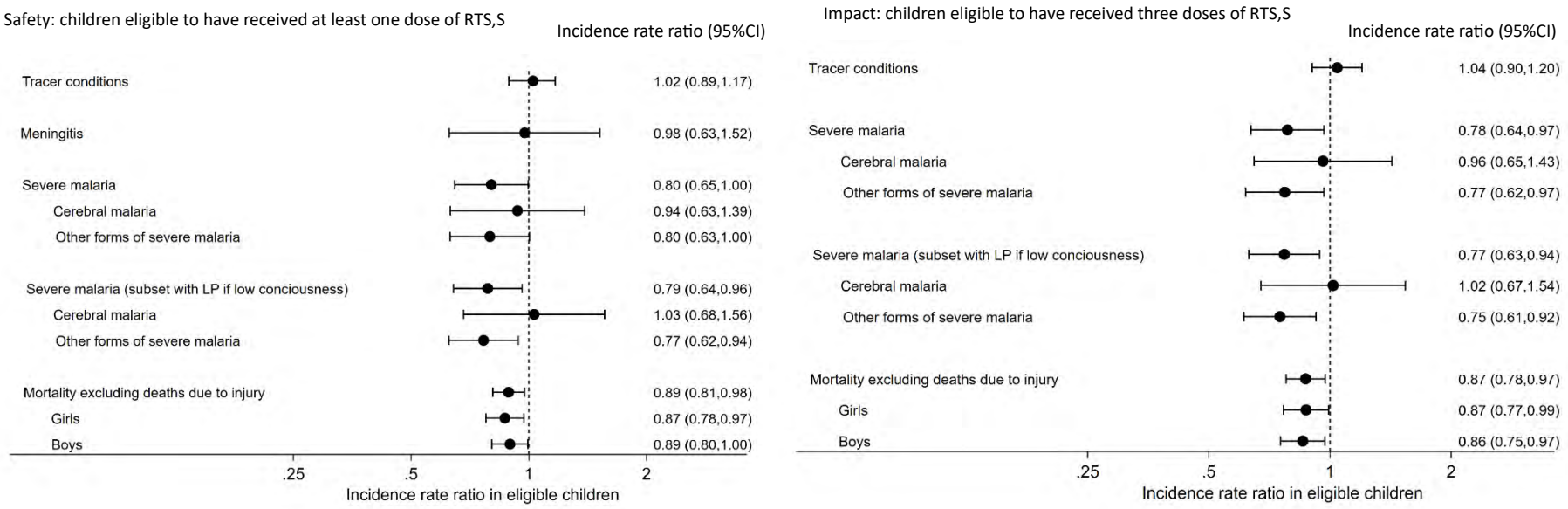
This impact of a malaria-specific intervention on all-cause mortality reflects the importance of malaria as a leading cause of death in young children in these populations. This impact was achieved in the context of moderate levels of coverage of the three primary doses (75% in Ghana, 69% in Kenya, and 63% in Malawi, in 1-year-old children surveyed in 2022) and relatively low uptake of the fourth dose (54%, 34% and 33% in children aged 30+ months (Ghana, Kenya) and 28+ months (Malawi) also surveyed in 2022). Impact could be increased further if vaccine coverage could be increased.

During the first 24 months of implementation (19 months in Kenya), there was a 32% reduction in the number of children admitted to hospital with severe malaria (95% confidence interval 5%,51%). Overall, over 46 months the reduction was 22% (3.4%,36%).

There was no statistical evidence that impact differed between the three countries.

The final data on safety further strengthen the evidence on safety reviewed by WHO in 2021.

Figure 1: Incidence rate ratios for safety and impact outcomes

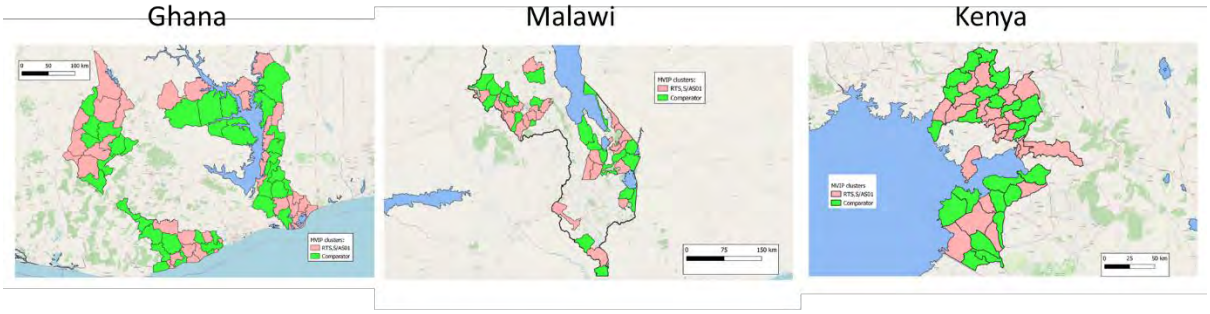


Vaccine introduction and evaluation design

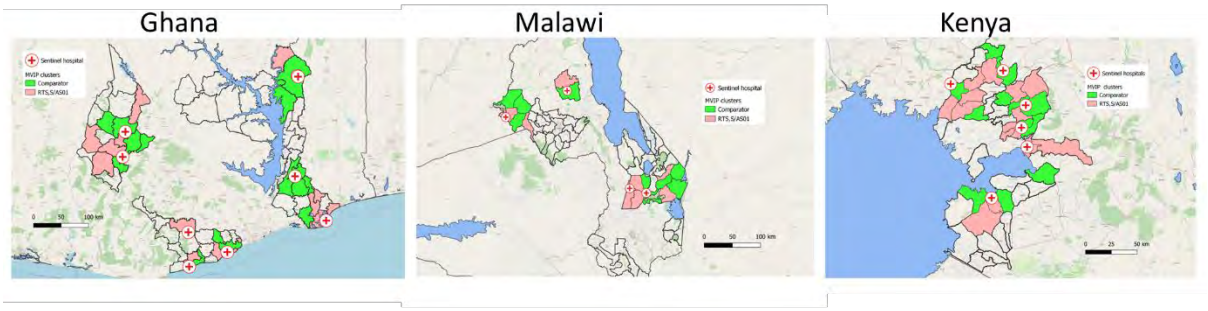
A total of 158 clusters, 66 in Ghana, 46 in Malawi and 46 in western Kenya, each cluster with a total population of about 100,000 on average, were randomized to either introduce RTS,S/AS01 vaccine in 2019 or to delay introduction until a decision was reached about safety and effectiveness. Throughout the evaluation areas, surveillance was maintained to record all deaths in children aged 1-59 months. Reporters recorded date of death, date of birth, age at death, gender, and residence location, and notified project staff who visited the home to complete a verbal autopsy (VA). The main purpose of assigning causes of death was to be to be able to exclude deaths due to injury from the analysis of effects of the malaria vaccine on overall mortality. Vaccination status was also recorded, copying details from the home-based record and completing a questionnaire to ask caregivers about vaccinations. In some circumstances, a limited VA was performed instead of a full VA, collecting only the key details, without determining cause of death, other than determining if death was due to accident or injury. Surveillance for severe illness, with a focus on meningitis and severe malaria, was maintained in part of the evaluation area in each country, through 18 sentinel hospitals, 8 in Ghana, 4 in Malawi and 6 in Kenya. These hospitals draw patients from a subset of clusters. The combined catchment areas include 32 of the clusters in Ghana, 17 clusters in Malawi, and 28 clusters in Kenya. Details of all inpatients aged 1 to 59 months were captured, including cluster of residence at the time of admission and the normal place of residence if different, the date of admission, age at admission, date of birth, gender, final diagnosis, outcome (died or discharged alive), and clinical and laboratory details (for suspected cases of meningitis and severe malaria). Vaccination status was also recorded for all admissions, copying details from the home-based record (HBR) where available, or completing a questionnaire to elicit caregiver recall about vaccinations.

Administration of doses of RTS,S/AS01 and of other vaccines was recorded by the EPI programme in each country using their normal record keeping system. Vaccination coverage was measured independently though community surveys, at baseline to measure coverage of EPI vaccines and Vitamin A, deworming treatment, malnutrition by MUAC, and the prevalence of P.falciparum infection (using an HRP2 Rapid Diagnostic Test); after about 18 months and after 30 months, to measure coverage of EPI vaccines and coverage of RTS,S doses. Each survey also recorded ITN (insecticide-treated bednet) use, and asked about care-seeking for fever.

Figure 2: Maps of the implementation and comparison areas in each country and the clusters served by sentinel hospitals.

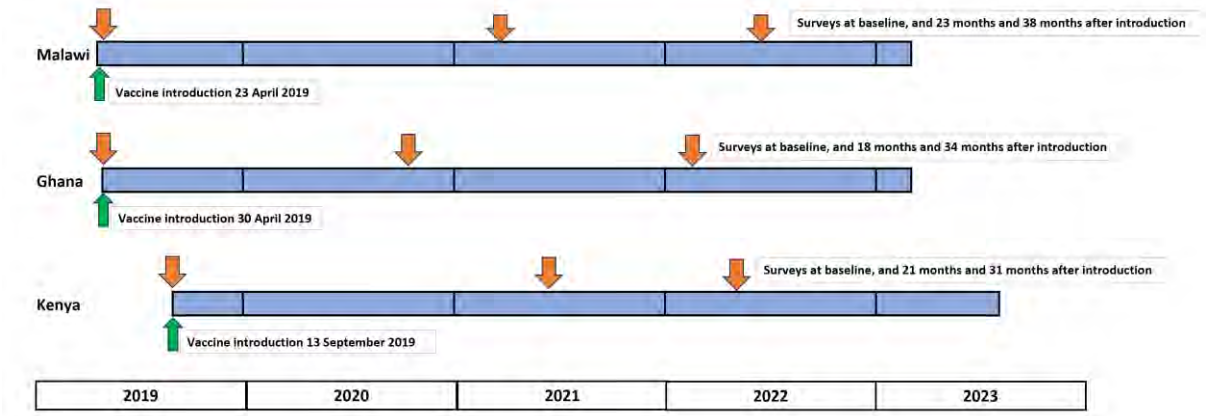


		Ghana	Malawi	Kenya	TOTAL
RTS,S/AS01	Clusters:	33	23	23	**79**
	Annual birth cohort surviving to 1 year:	128,624	126,698	107,728	**363,050**
Comparator	Clusters:	33	23	23	**79**
	Annual birth cohort surviving to 1 year:	133,702	125,747	113,997	**373,446**



	Ghana	Malawi	Kenya	TOTAL
Sentinel hospitals:	**8**	**4**	**6**	**18**
RTS,S/AS01				
Clusters in catchment of sentinel hospitals:	15	9	16	**40**
Annual birth cohort surviving to 1 year:	71992	49039	87824	**208,855**
Comparator				
Clusters in catchment of sentinel hospitals:	17	8	12	**37**
Annual birth cohort surviving to 1 year:	76097	37908	67836	**181,841**

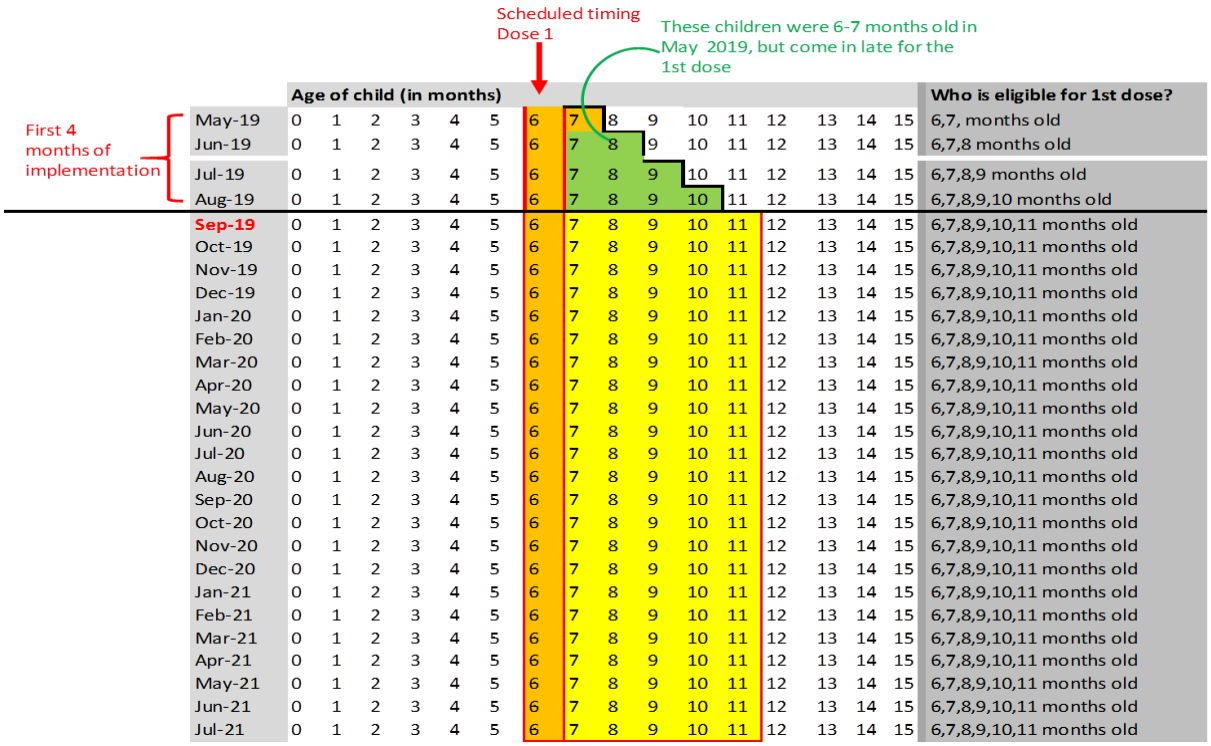
Figure 3: Timing of vaccine introduction and household surveys:



Vaccine introduction, Ghana

In Ghana, RTS,S/S vaccine was introduced on April 30, 2019. Children were eligible for their first dose from 6-11 months of age, but the vaccine was not offered to any child who was 8 months old or older at the start of introduction:

Figure 4: Diagram used by Ghana EPI to explain eligibility for RTS,S/AS01



	Age of child (in months)																Who is eligible for 1st dose?
May-19	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7, months old
Jun-19	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8 months old
Jul-19	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9 months old
Aug-19	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10 months old
Sep-19	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Oct-19	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Nov-19	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Dec-19	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Jan-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Feb-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Mar-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Apr-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
May-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Jun-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Jul-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Aug-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Sep-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Oct-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Nov-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Dec-20	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Jan-21	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Feb-21	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Mar-21	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Apr-21	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
May-21	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Jun-21	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old
Jul-21	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	6,7,8,9,10,11 months old

The second dose was recommended at 7 months and the third dose at 9 months, or one month after the preceding dose, and the fourth dose at 24 months. The upper age limits were that children 12 months and older were not eligible for the first dose and children 36 months and older not eligible for the fourth dose. RTS,S was introduced into comparison areas on Feb 20, 2023. Children in comparison areas aged 6-11 months were eligible to receive their first dose from that date, and a fourth dose at 18 months. Upper age limits were that children 12m and older were not eligible for the first dose and children 60m (5yrs) and older could not receive the fourth dose. In the original implementation areas, the age when dose 4 was offered was changed from 24m to 18m on the same date (Feb 20 2023), with same the upper limit of 5yrs.

Community surveillance for mortality and hospital surveillance for severe malaria and meningitis was maintained for all children aged 1-59 months from April 30 2019 to Feb 28 2023 (46 months). Three vaccine coverage surveys were undertaken, a baseline survey to establish EPI coverage before RTS,S was introduced, a 'midline' survey from 2 Nov 2020 to 26 Nov 2020, to record coverage of the primary three doses of RTS,S, and an 'endline' survey 28 Feb 2022-22 Mar 2022, to record coverage of primary doses and the fourth dose. Children aged 5 to 48 months were included in the surveys, which also measured uptake of ITNs, receipt of other EPI vaccines, and asked about care-seeking for fever, and tested for evidence of malaria infection by RDT. The layout of an implementation and comparison cluster is shown in Fig 2, showing ages of eligible cohorts and timing and age range of surveys. By the end of the evaluation, the first children to receive RTS,S were aged 52m. At the time of the 2021 analysis, the oldest child eligible to have received RTS,S was 30m.

Figure 5: Layout of implementation clusters, Ghana

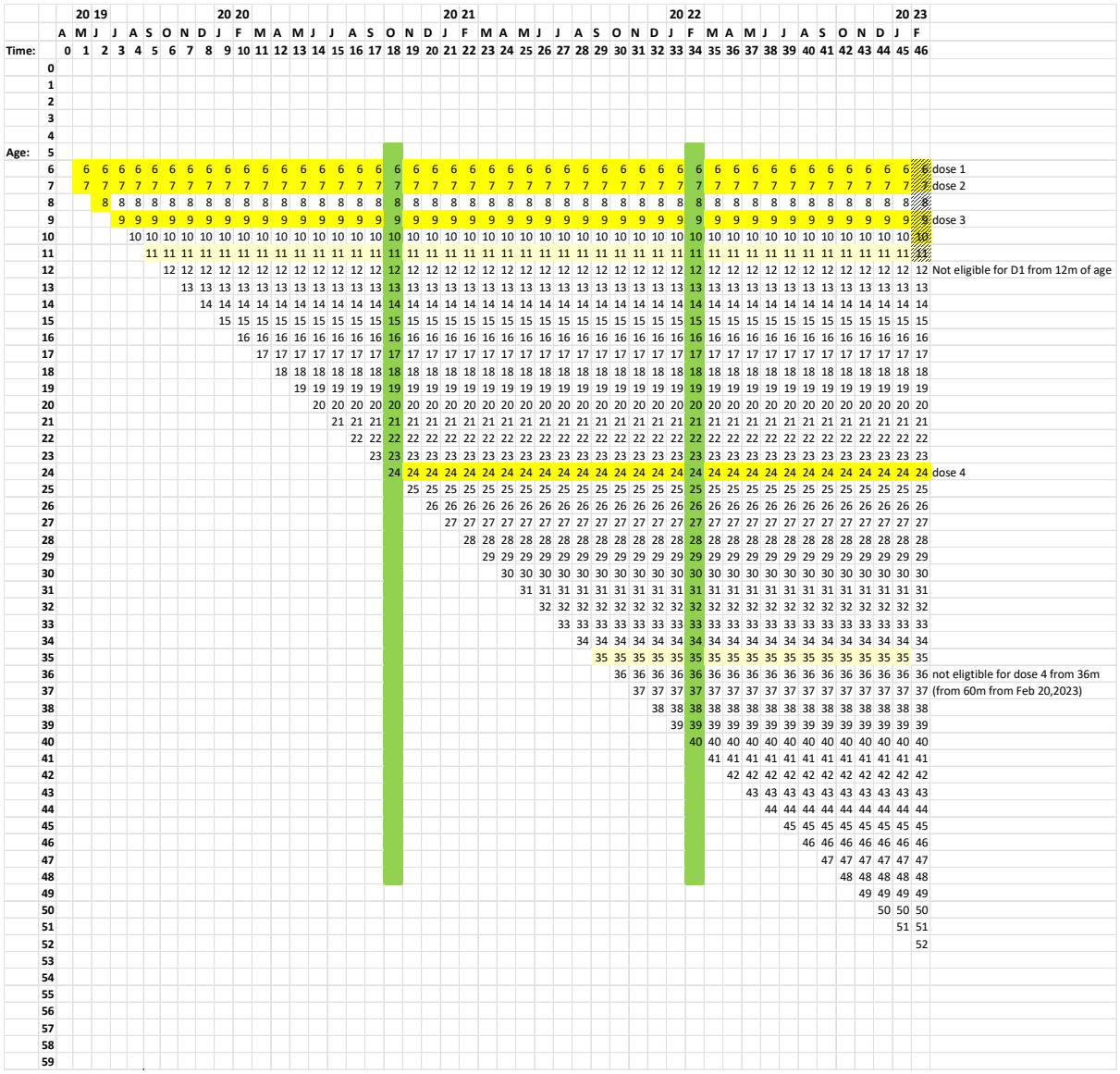
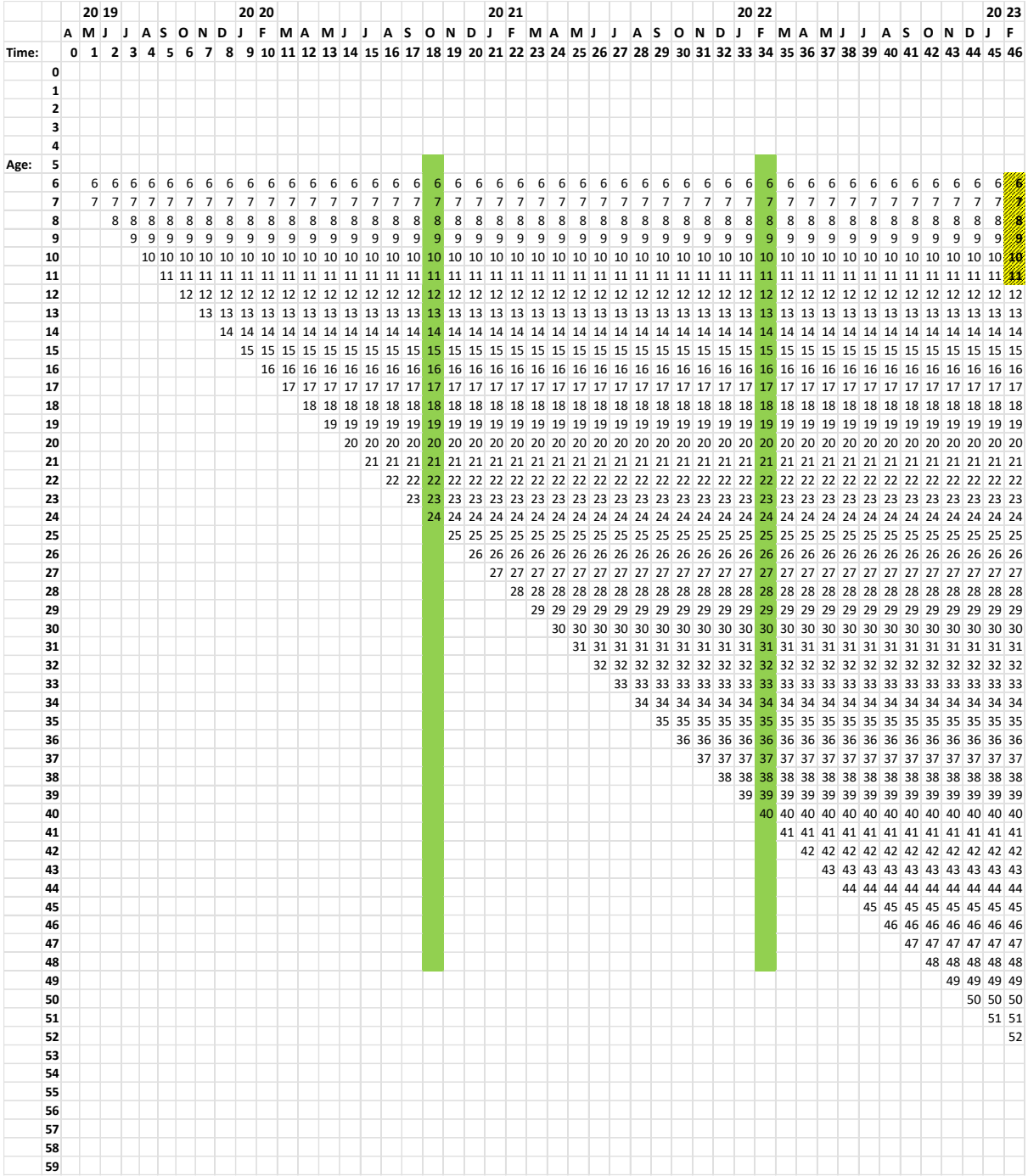


Figure 6: Layout of comparison clusters, Ghana



Vaccine introduction, Kenya

In Kenya, RTS,S was introduced on Sep 13 2019, children aged 6-11m were eligible for their first dose, and for a fourth dose at 24m. Upper age limits were that children 12m and older could not receive the first dose and the fourth dose could not be given to children 36m and older. RTS,S was introduced in comparison areas on 7 Mar 2023. In comparison areas, children aged 6-23m could receive their first dose from this date, and a 4th dose from the age of 24m. The extended range for the first dose in comparison areas was to be retained for a period of 2 years. Upper age limits in comparison areas were that the first dose could not be given in children 24m and older, and the 4th dose to children 36m (3yrs) and above. In implementation areas, the upper limit for the first dose remained at <12m.

Community surveillance for mortality and hospital surveillance for severe malaria and meningitis was maintained for all children aged 1-59 months from Sep 13 2019 to Jul 12 2023 inclusive (46 months).

The layout in implementation and comparison clusters in Kenya is shown in Figure 7 and Figure 8. The midline survey was done from 3 Apr 2021 to 13 Aug 2021 in children 12-23m of age and the endline survey from 4 Apr 2022 to 3 Jun 2022 in children 12-41m of age.

Figure 7: Layout of implementation cluster, Kenya

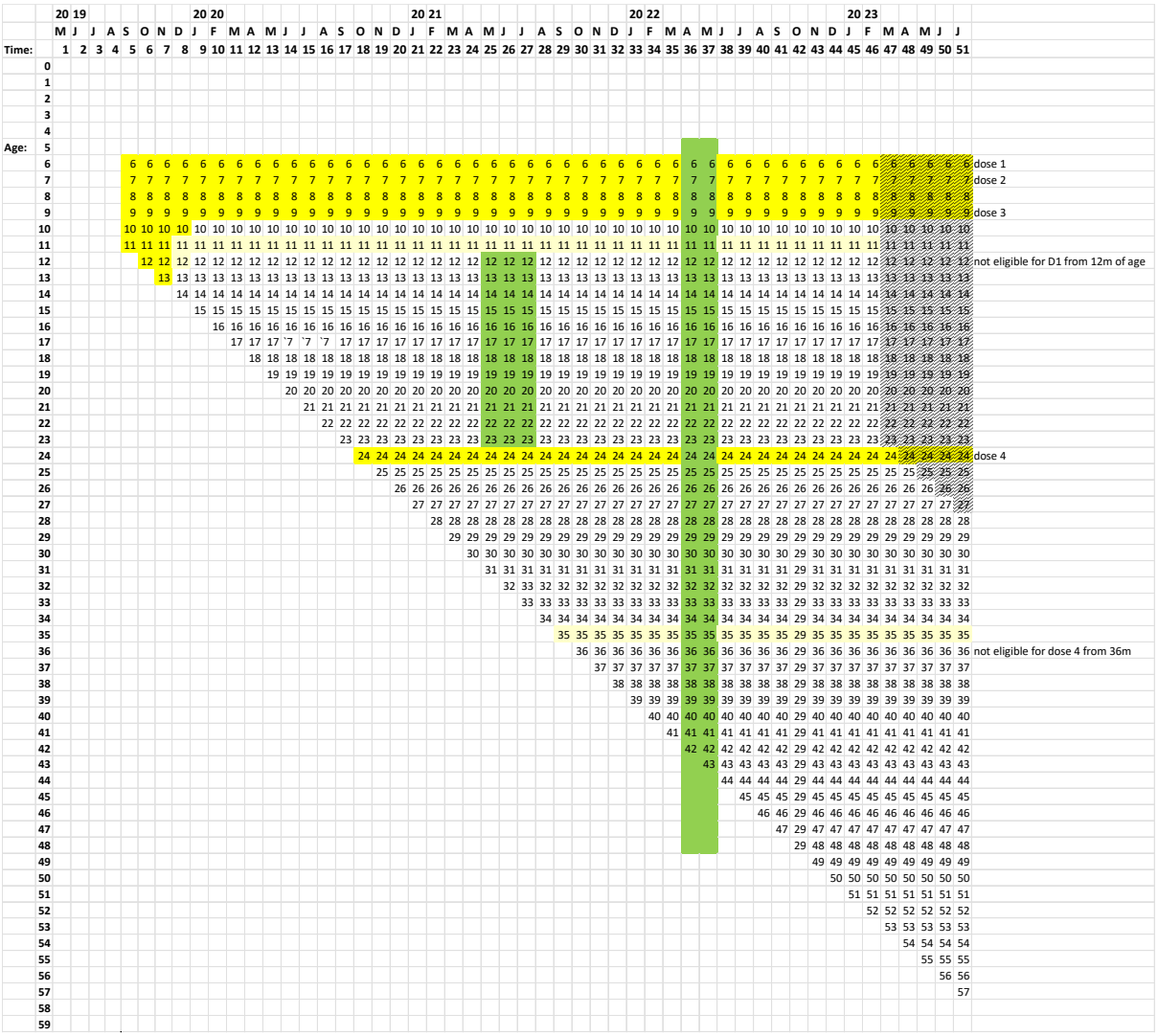
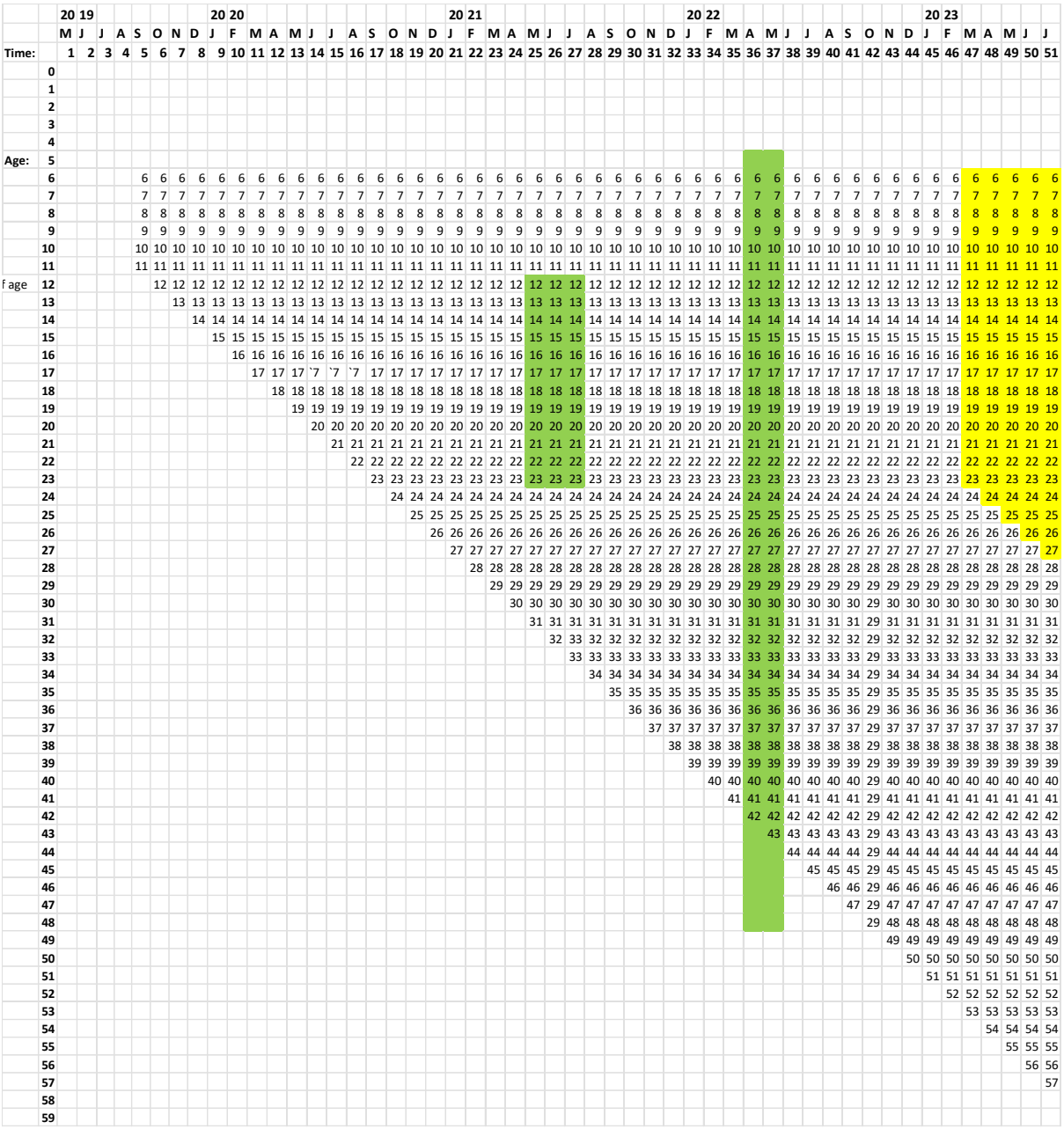


Figure 8: Layout of comparison cluster, Kenya



Vaccine introduction, Malawi

In Malawi, RTS,S was introduced on Apr23 2019, children were eligible for the first dose if aged 5-11m but children older than 5m when the vaccine was introduced were not eligible. The second and third doses were recommended at 6m and 7m (or 1 m after the preceding dose) and the fourth dose from 22m. Upper limits were that the first dose could not be given to children aged 12m and above and the 4th dose 36m and above. RTS,S was introduced in comparison areas on 29 Nov 2022, children aged 5-11m could receive the first dose from that date, and the fourth dose when they were 22m (with the same upper limit as in the original implementation areas).

Community surveillance for mortality and hospital surveillance for severe malaria and meningitis was maintained for all children aged 1-59 months from Apr 23 2019 to Feb 28 2023 inclusive (46 months).

Coverage surveys were undertaken from 22 Feb 2021-3 Apr 2021 and from 23 May 2022 to 30 Jun 2022, both in children aged 5-48m.

Layouts in implementation and comparison clusters are shown in Figure 9 and Figure 10.

Figure 9: Layout of implementation cluster, Malawi

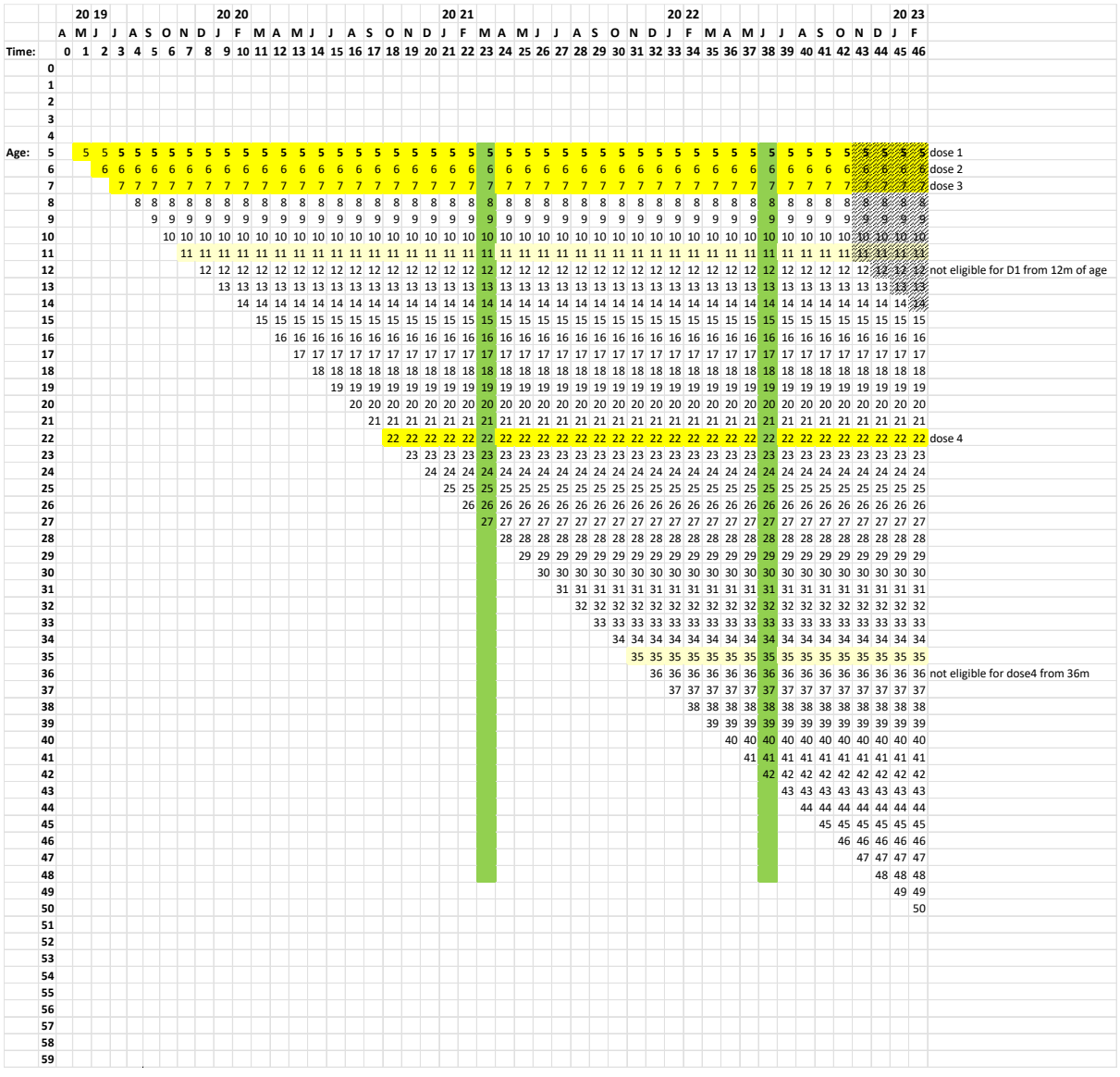
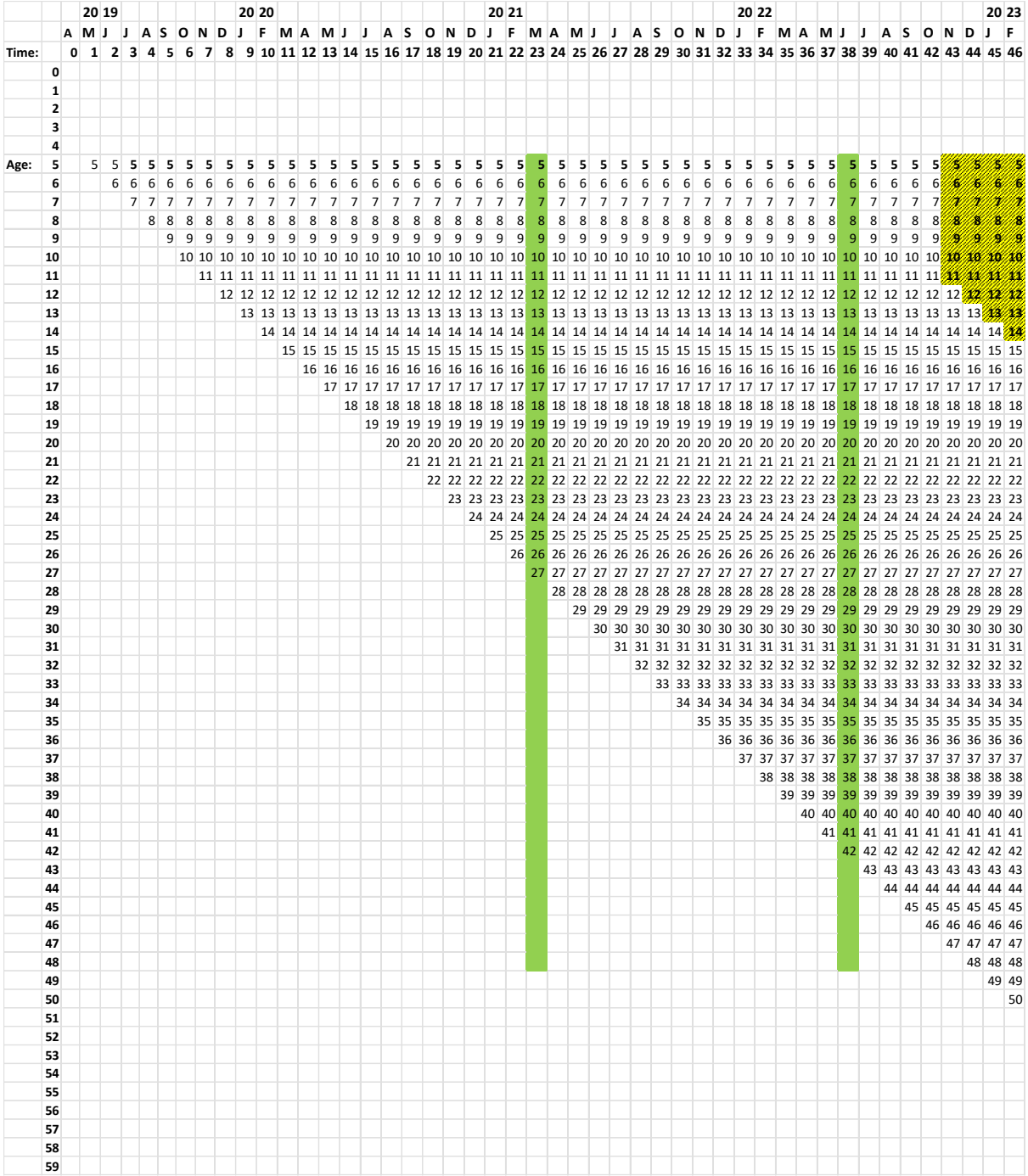


Figure 10: Layout of comparison cluster, Malawi

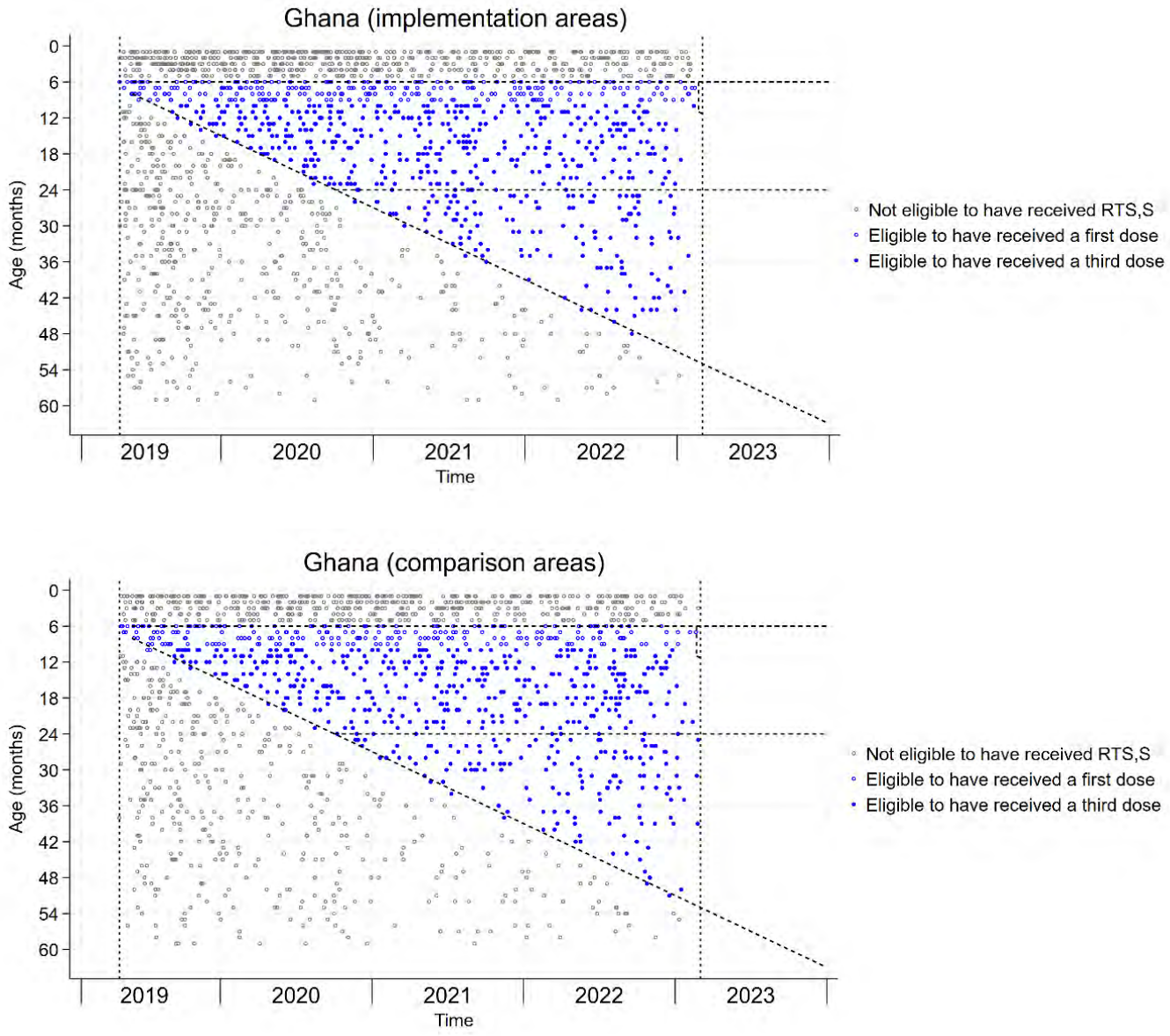


Mortality surveillance

Ghana:

In Ghana, 4178 deaths 1-59m during the evaluation period in implementation and comparison areas were reported. Of these, 36 without consent for VA were excluded. VAs were performed in all of the remaining 4113, 206 deaths due to injury were excluded, 415 with missing cause of death were retained with the assumption that death was not due to injury. Of the remaining 3907, 1593 were eligible, 2195 were not eligible and 119 excluded from analysis due to being just outside the eligible range (children too old to receive RTSS but within 2m of the cut-off date of birth were excluded from the non-eligible comparison group, as they might have received RTS,S), or in cohorts eligible to receive vaccine in comparison areas. Deaths included in analysis in implementation and comparison areas are shown in Figure 11.

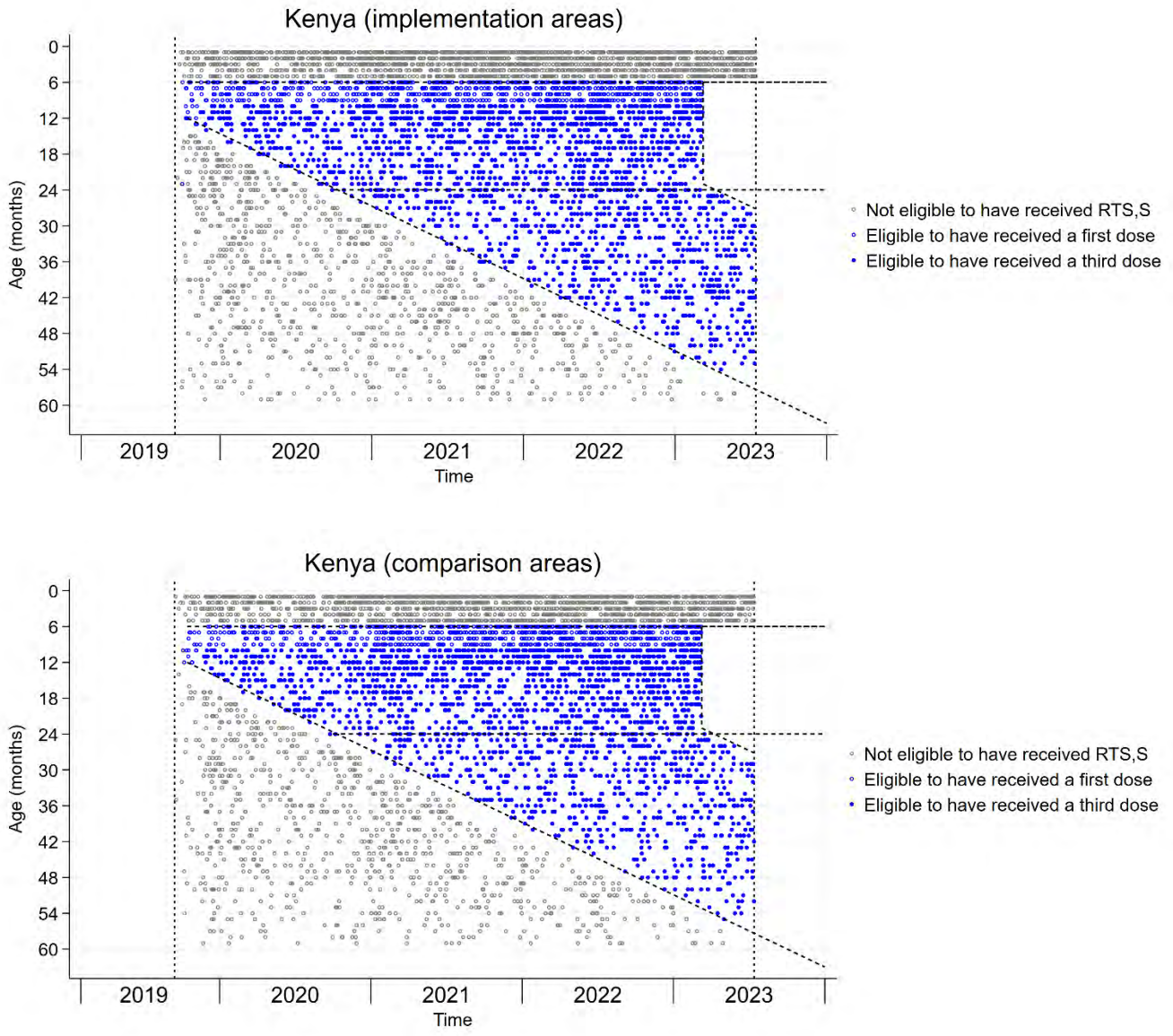
Figure 11: Distribution of deaths by age, time and eligibility, in implementation and comparison areas in Ghana



Kenya:

In Kenya, 13531 deaths were reported, 26 were excluded due to missing key information (age or sex), of the 13505 remaining, 5596 were noneligible, 1021 were excluded due to belonging to age cohorts that would be eligible in comparison areas, or were just too old to be eligible (<2m) , and 6888 were eligible for RTSS, of these VAs (or mini VAs) were performed in 6536 (94.9%). 337 deaths due to injury excluded, leaving 11795 included in analyses. In Kenya VAs were not performed in all non-eligible age groups, therefore in Kenya estimation of mortality rate ratios used total deaths of any cause in non-eligible age groups as the auxiliary variable.

Figure 12:Distribution of deaths by age, time and eligibility, in implementation and comparison areas in Kenya



Malawi:

In Malawi, 15984 1-59m from study area during evaluation period, 25 without consent for VA, 31 with missing key information (age, sex); of the remaining 15928, VAs or mini VAs were available for 15571 (97.8%). 837 whose death was due to injury were excluded. 897 community deaths with missing or unclear cause of death, and 351 facility deaths without VA, were included with the assumption that death was not due to injury. Of the 15085 remaining, 7652 were in RTSS-eligible age groups, 6787 were in non-eligible age groups, and the remaining 646 were excluded (because they were just outside the eligible age range by less than 2 months and thus might have been vaccinated, or because they were in age groups that, in comparison areas, had started to receive the vaccine).

Figure 13: Distribution of deaths by age, time and eligibility, in implementation and comparison areas in Malawi

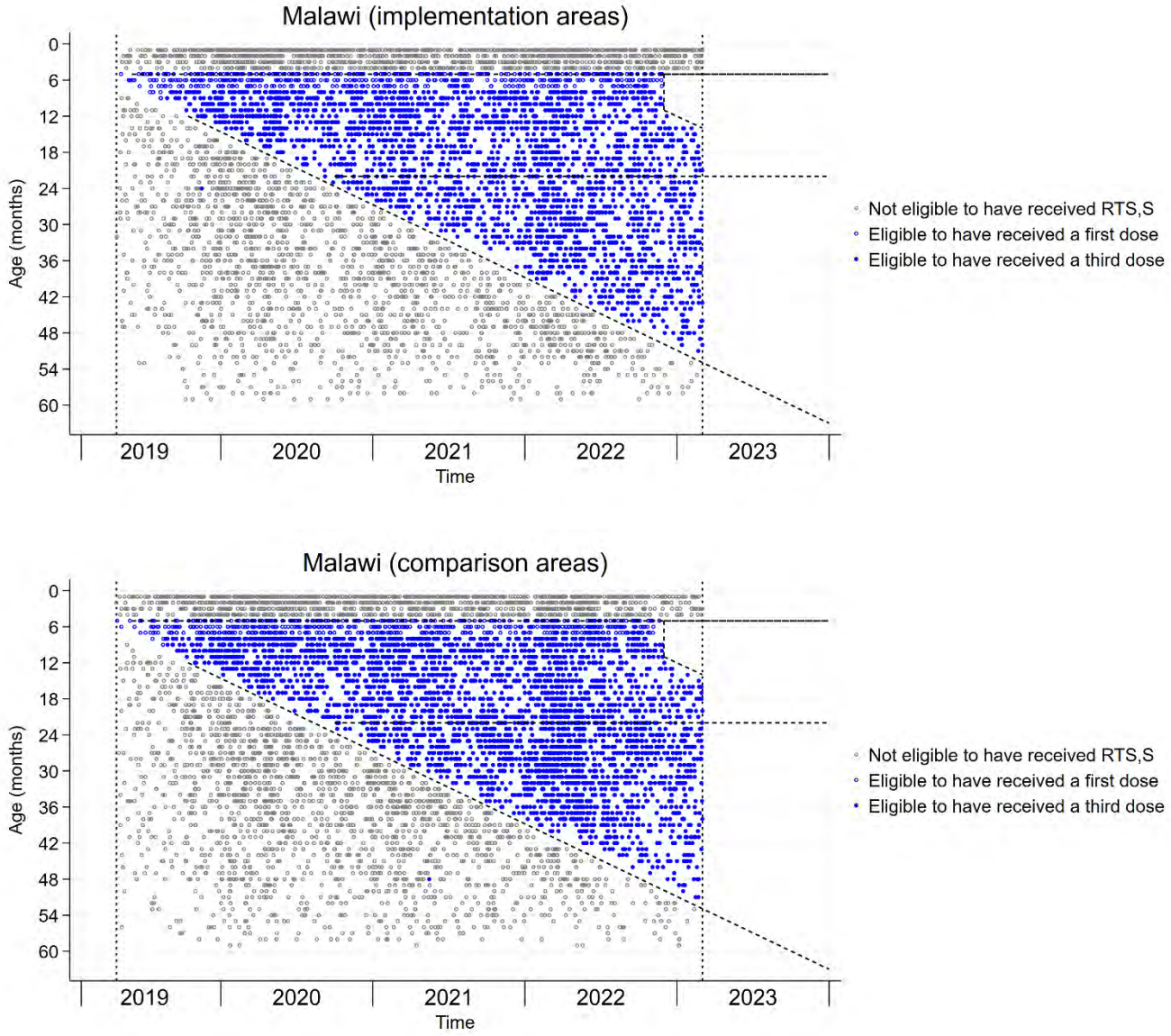
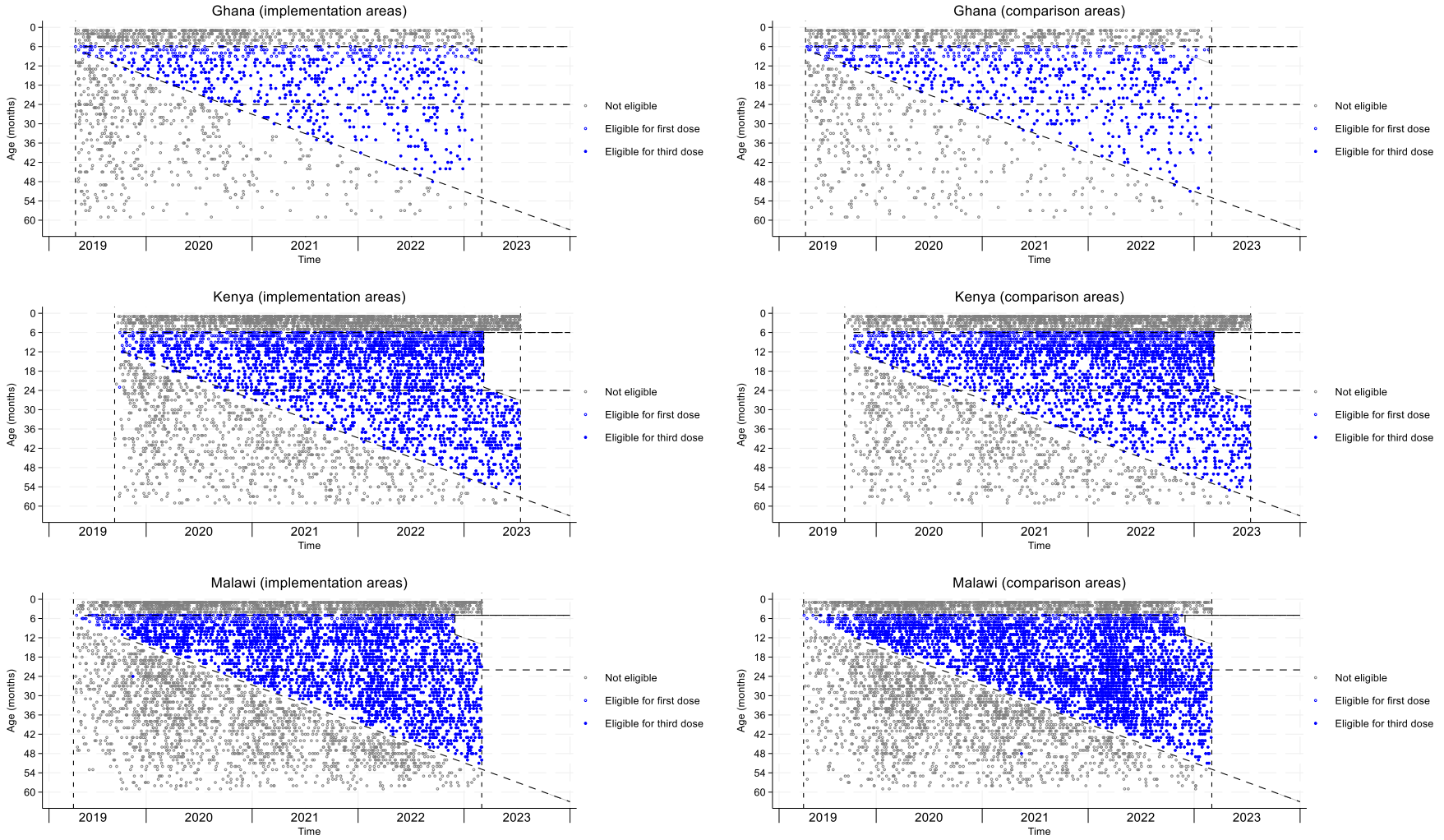


Figure 14 shows distribution of deaths in all implementation and comparison areas in the 3 countries.

Figure 14: Distribution of deaths in implementation and comparison areas in each country, that were included in analyses, by age, time and eligibility to have received RTS,S



Age distribution of severe malaria admissions and of all-cause mortality, in children included in impact analyses (who would have been eligible to receive 3 doses of RTS,S), in comparison areas

The impact observed on severe malaria admissions amongst the cohorts of children eligible to have received the vaccine will depend on how many are vaccinated, and the age they received their third and fourth dose, how long the protection lasted (protection is greatest in the few months after the third dose and after the fourth dose) and what proportion of the severe malaria burden falls in those more highly protected age ranges.

The third dose is recommended at 7 months of age in Malawi and 9 months in Ghana and Kenya. If the efficacy results from the phase 3 trial can be applied, we would expect to see the greatest impact on severe malaria admissions in the age ranges 8-13m in Malawi and 10-15m in Kenya and Ghana. Dose 4 was recommended at 22m in Malawi and 24m in Ghana and Kenya, we expect increased impact in the months after dose 4, but then little impact is expected from 12 months after dose 4. We therefore consider 4 age ranges: 8-13m, 14-21m, 22-33m, and 34 months and older, in Malawi, and 10-15m, 15m-23m, 24m-35m, and 36months and older, in Ghana and Kenya.

In comparison areas, of the severe malaria admissions in age ranges that would have been eligible to have received a 3rd dose of RTS,S, 29% were in the 'highly protected' range (within about 6m of dose 3), 30% in the 8m prior to the age recommended for dose 4, 29% within 12m of the age when dose 4 was recommended, and 12% more than 12-months post-dose 4.

This compares with the situation midway through the evaluation when WHO reviewed data on safety and impact in 2021. At that stage the first children to have been vaccinated were 30m old, whereas by the time of final analysis those children were over 4yrs old. The % of severe cases in comparison areas that fell in the highly protected age range was 45%, 41% in the 8m prior to dose 4, 14% within 12m of dose 4m, and none in the age range more than 12m after dose 4.

The impact on all cause mortality depends on the impact on malaria specific deaths (and therefore on the proportion of malaria deaths that falls in the highly protected age ranges), and on the proportion of all deaths that these represent. This cannot be observed directly due to the difficulty of determining cause of death (other than that the death was not caused by injury). Comparison of the impact on severe malaria and the impact on all cause mortality within specific age ranges gives an indication of the likely fraction of malaria attributable deaths in those age ranges.

Figure 15 and Table 1 show the % of deaths and of severe malaria admissions in the 4 age ranges in comparison areas, among children age-eligible for 3 doses of RTS,S.

Figure 16 and Table 2 show the % of admissions that had a diagnosis of severe malaria by age range, and the severe malaria case fatality rate, among children age-eligible for 3 doses of RTS,S.

Figure 17 to Figure 22 show density plots to illustrate the age distributions of deaths, severe malaria, and each of the forms of severe malaria, in comparison areas, restricted to children age-eligible to have received 3 doses of RTS,S, and for the whole age range 1-59months without limiting to eligible children.

Figure 15: Comparison of age distribution of deaths and of severe malaria admissions in the analysis of events to April 2021, and final analyses of events to Month 46. The percentage of events in each age group are shown for comparison areas, among children

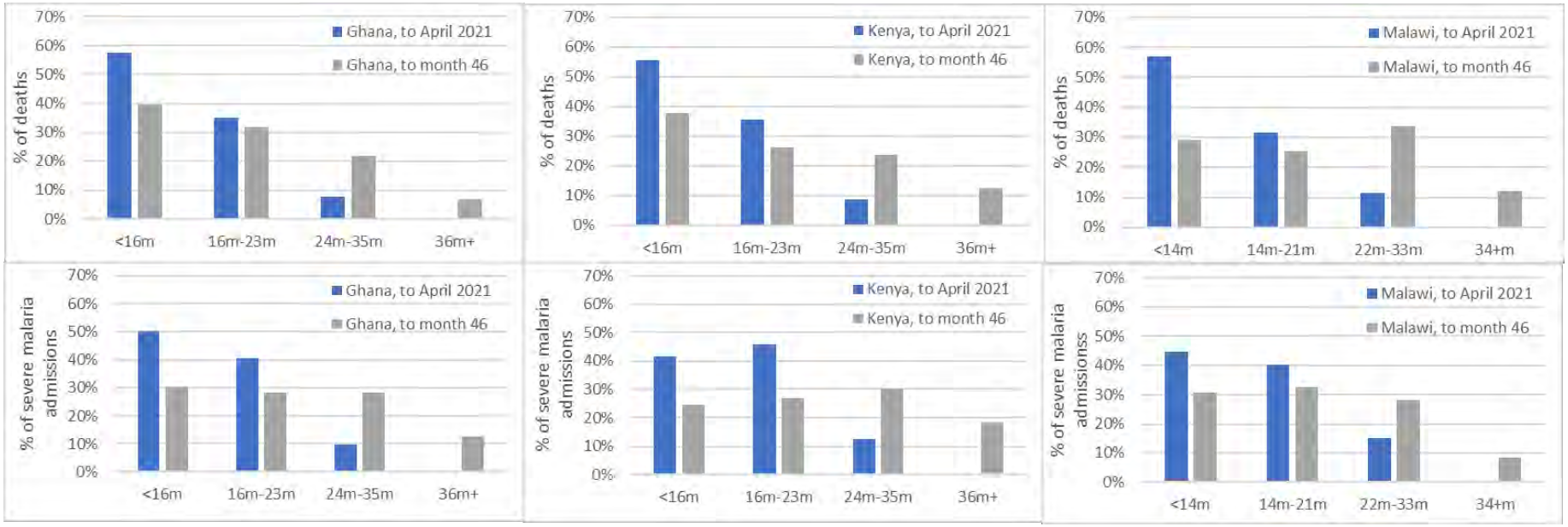


Table 1: Age distribution of deaths (all causes except injury) and of severe malaria admissions, to April 2021 and to month 46, comparison areas, children eligible for 3 doses of RTS,S

Mortality	Events to April 2021					Events to month 46			
	<16m	16m-23m	24m-35m	36m+		<16m	16m-23m	24m-35m	36m+
Ghana	112 (57.4%)	68 (34.9%)	15 (7.7%)	0 (0.0%)		217 (39.4%)	176 (31.9%)	121 (22.0%)	37 (6.7%)
Kenya	262 (55.6%)	168 (35.7%)	41 (8.7%)	0 (0.0%)		822 (37.8%)	569 (26.2%)	515 (23.7%)	267 (12.3%)
	<14m	14m-21m	22m-33m	34+m		<14m	14m-21m	22m-33m	34+m
Malawi	587 (57.0%)	324 (31.5%)	119 (11.6%)	0 (0.0%)		1032 (29.0%)	903 (25.4%)	1195 (33.5%)	432 (12.1%)
Total	961 (56.7%)	560 (33.0%)	175 (10.3%)	0 (0.0%)		2071 (32.9%)	1648 (26.2%)	1831 (29.1%)	736 (11.7%)
Severe malaria admissions									
	<16m	16m-23m	24m-35m	36m+		<16m	16m-23m	24m-35m	36m+
Ghana	52 (50.0%)	42 (40.4%)	10 (9.6%)	0 (0.0%)		92 (30.4%)	86 (28.4%)	86 (28.4%)	39 (12.9%)
Kenya	40 (41.7%)	44 (45.8%)	12 (12.5%)	0 (0.0%)		124 (24.6%)	136 (26.9%)	152 (30.1%)	93 (18.4%)
	<14m	14m-21m	22m-33m	34+m		<14m	14m-21m	22m-33m	34+m
Malawi	217 (44.7%)	195 (40.2%)	73 (15.1%)	0 (0.0%)		312 (30.8%)	331 (32.6%)	285 (28.1%)	86 (8.5%)
Total	309 (45.1%)	281 (41.0%)	95 (13.9%)	0 (0.0%)		528 (29.0%)	553 (30.4%)	523 (28.7%)	218 (12.0%)

Figure 16: The proportion of admissions in comparison areas with a diagnosis of severe malaria increased with age

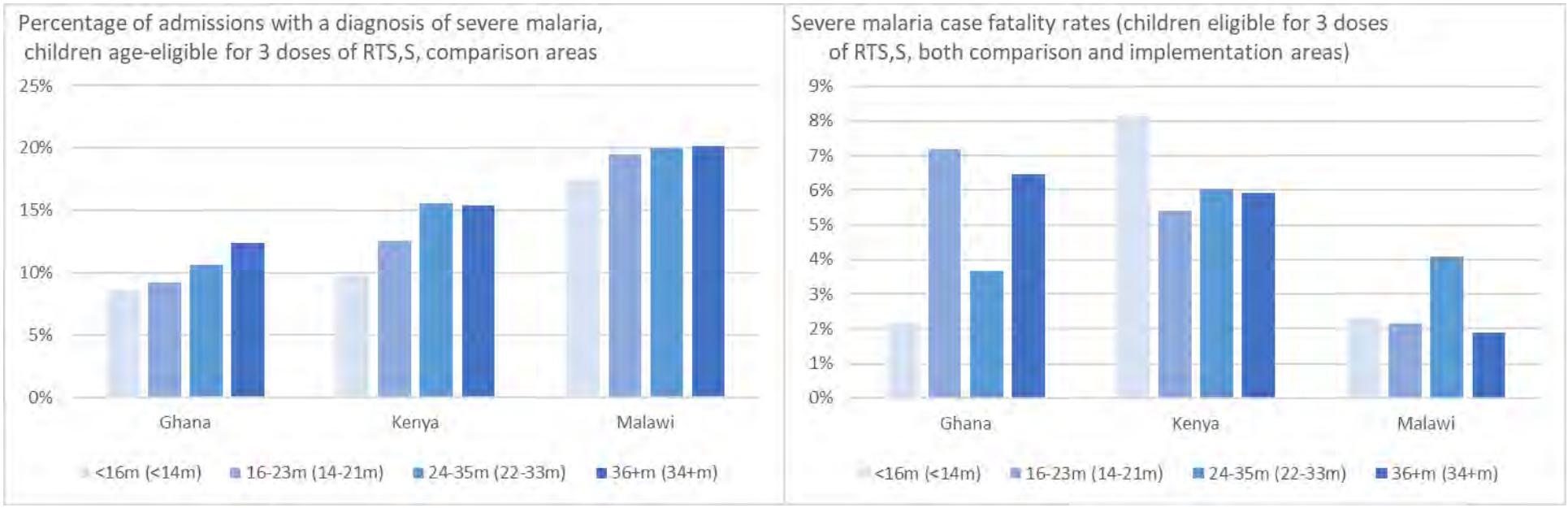


Table 2: Median age (no of cases) of forms of severe malaria, among children eligible for 3 doses of RTSS, comparison areas

Median age in months (number of cases):						
Country	Cerebral malaria	Other forms of severe malaria	Severe malaria anaemia	Respiratory distress	Convulsions	All severe malaria
Ghana	25 (67)	20 (236)	19 (121)	20 (57)	23 (88)	21 (303)
Kenya	26 (65)	23 (440)	25 (154)	18 (101)	23 (214)	23 (505)
Malawi	24 (64)	17 (950)	21.5 (226)	15 (355)	20 (423)	18 (1014)

Figure 17: Age distribution of deaths and of severe malaria admissions among children eligible for 3 doses of RTS,S, in comparison areas. The plots show the density with respect to age. The number of deaths was 551 (Ghana), 2173 (Kenya), 3562 (Malawi)

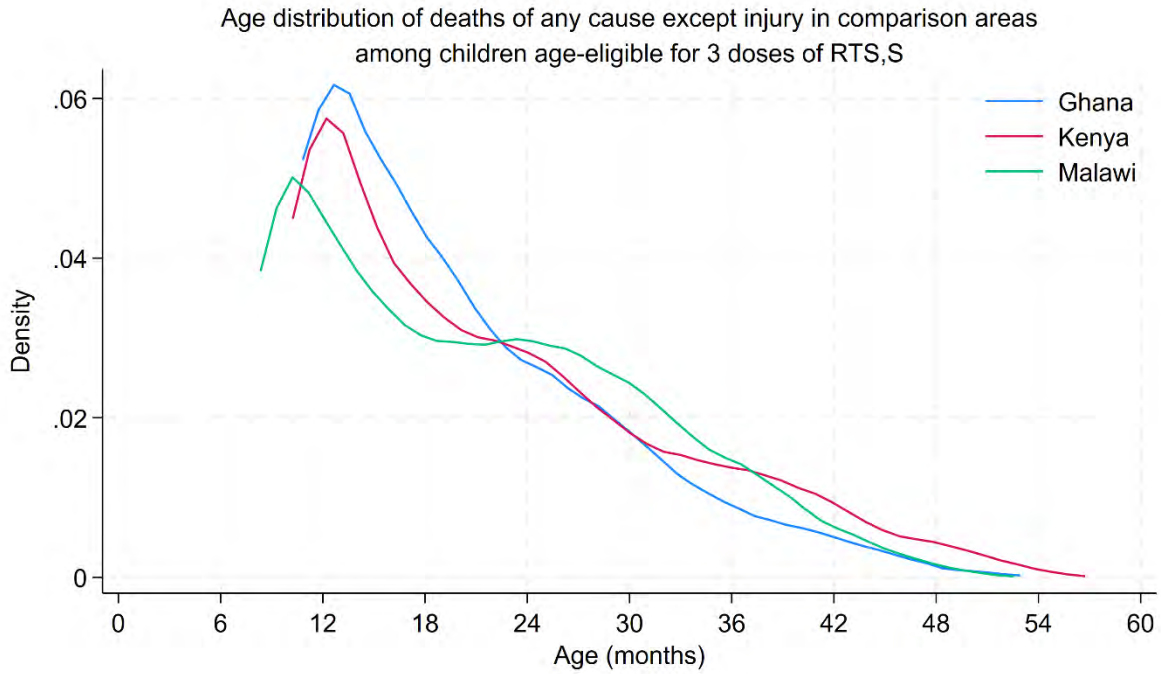


Figure 18: The corresponding plot including all deaths of any cause, throughout the age range 1-59months (not restricted to eligible children), in comparison areas, reflecting higher mortality in the 1-4yrs age range in Malawi.

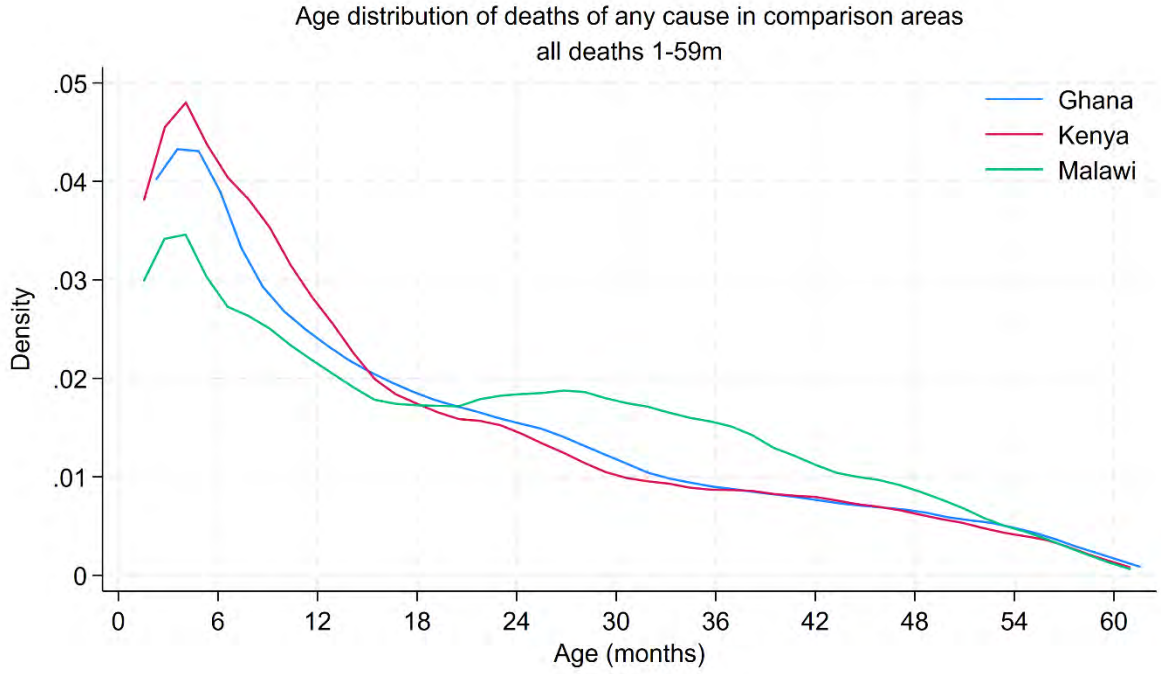


Figure 19: Age distribution of severe malaria admissions among children eligible for 3 doses of RTS,S, in comparison areas. The plots show the density with respect to age. The number of cases was 303 (Ghana), 536 (Kenya), 1014 (Malawi).

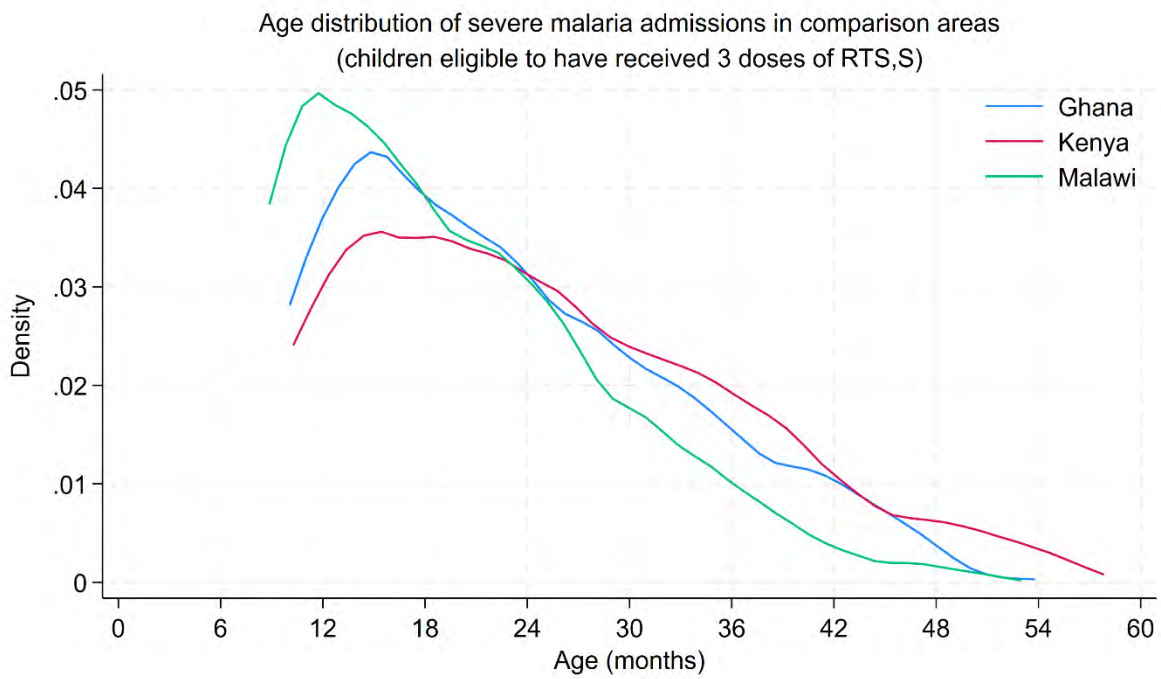


Figure 20: The corresponding distributions 1-59m (without excluding non-eligible children)

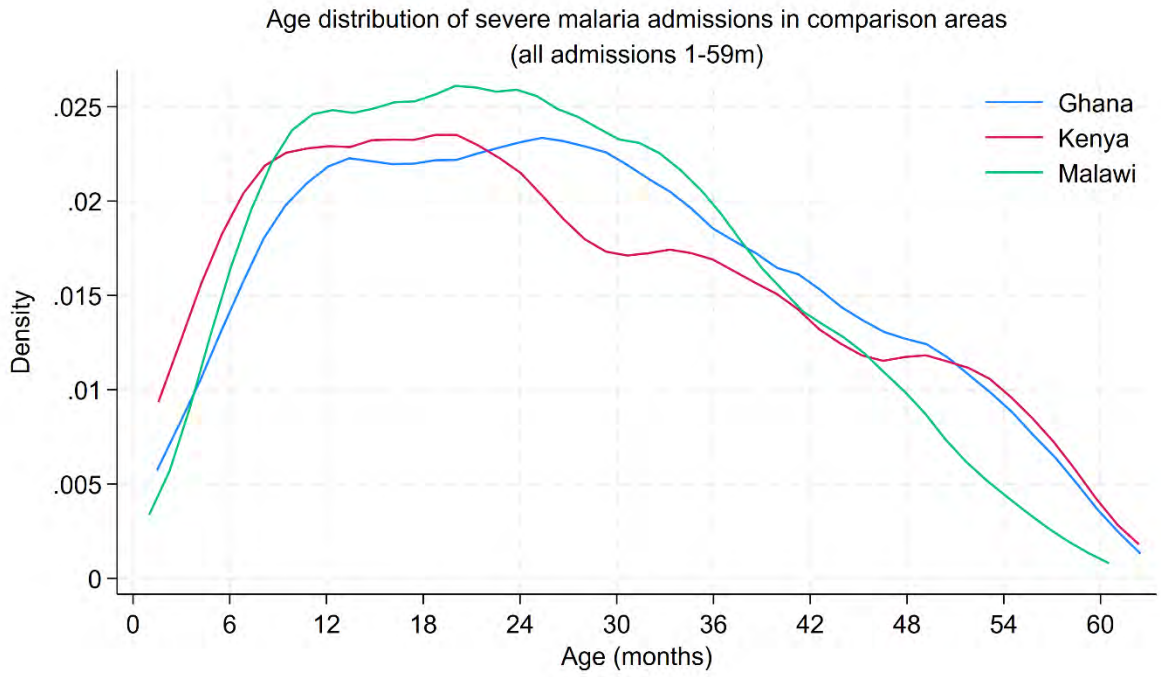


Figure 21: Fig: Age distribution of cerebral malaria and of other forms of severe malaria in comparison areas, among children eligible to have received 3 doses of RTS,S. The plots show the density for each outcome (area under each curve scaled to 1). Histograms of the data showing numbers of cases by age are shown in the Annex.

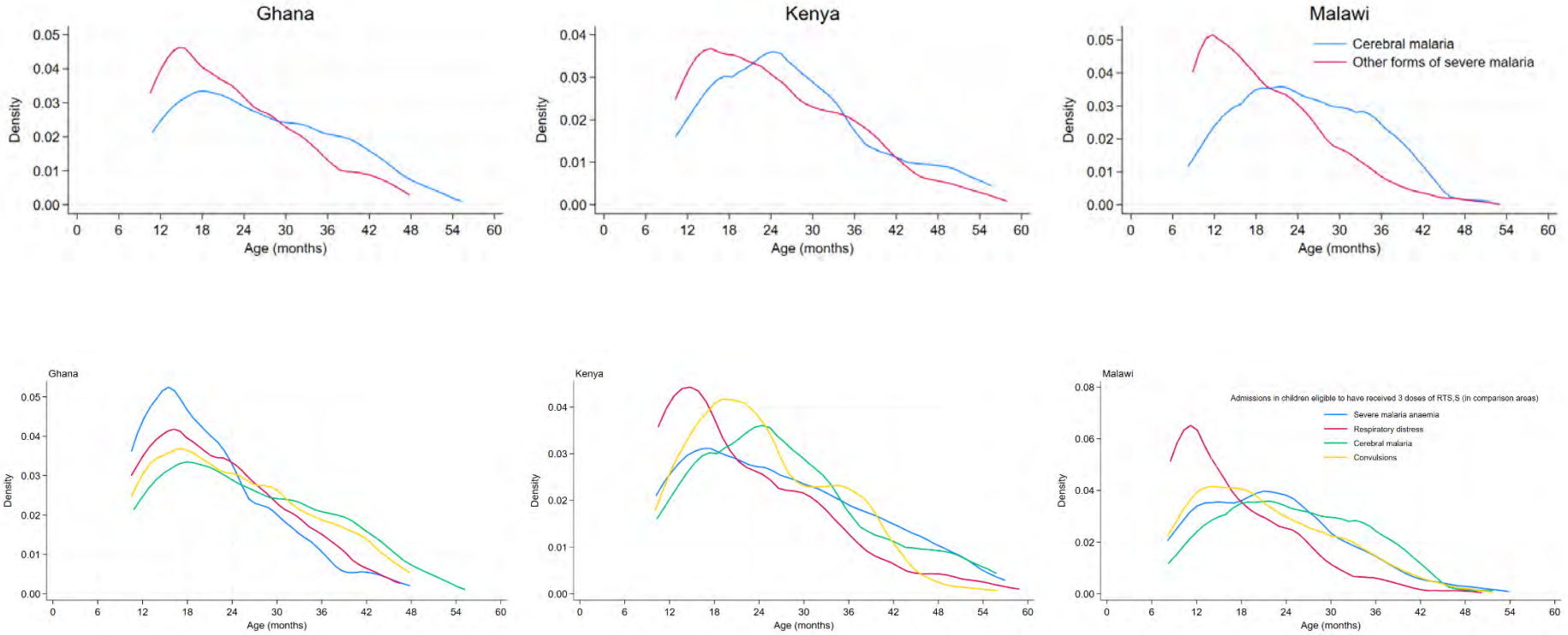
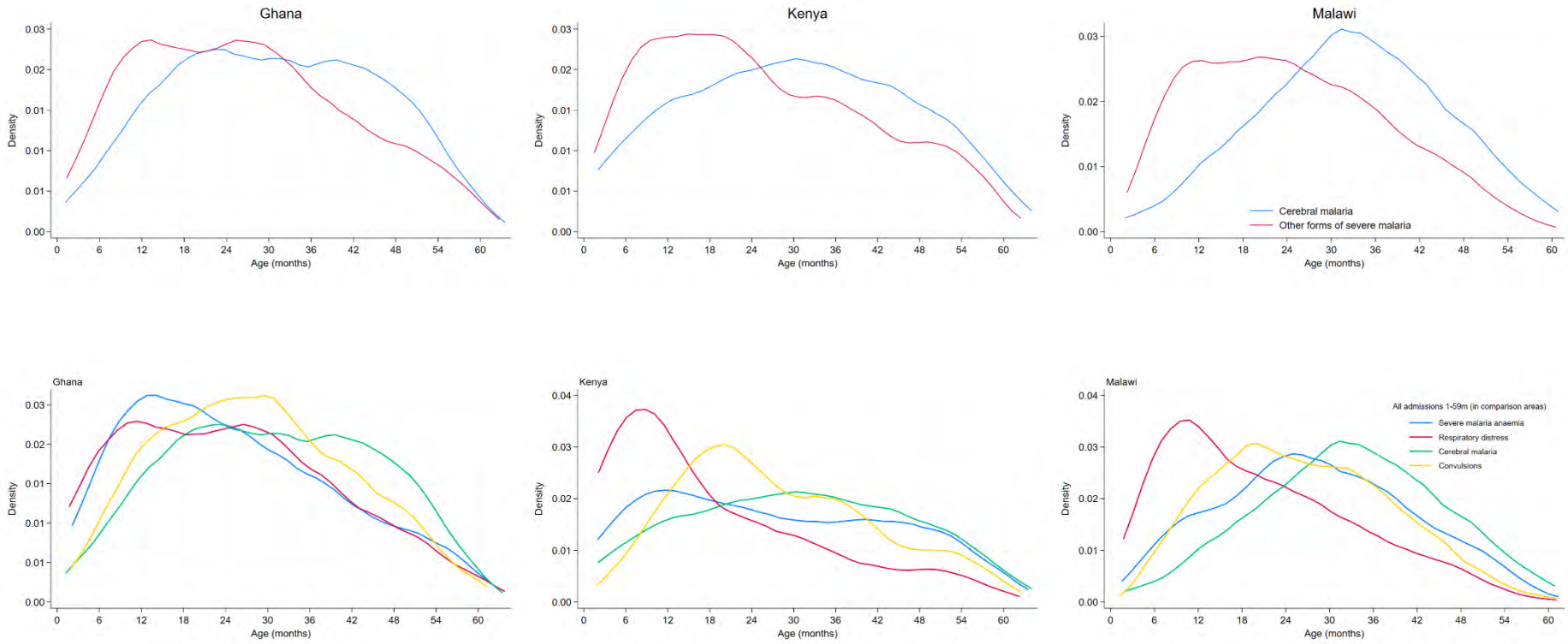


Figure 22: The corresponding distributions including all events in the 1-59month age range (not restricted to eligible children), in comparison areas.



Percentage of admissions 1-59m in comparison areas, which had a diagnosis of severe malaria, the % with each form of severe malaria, and the case fatality rates.

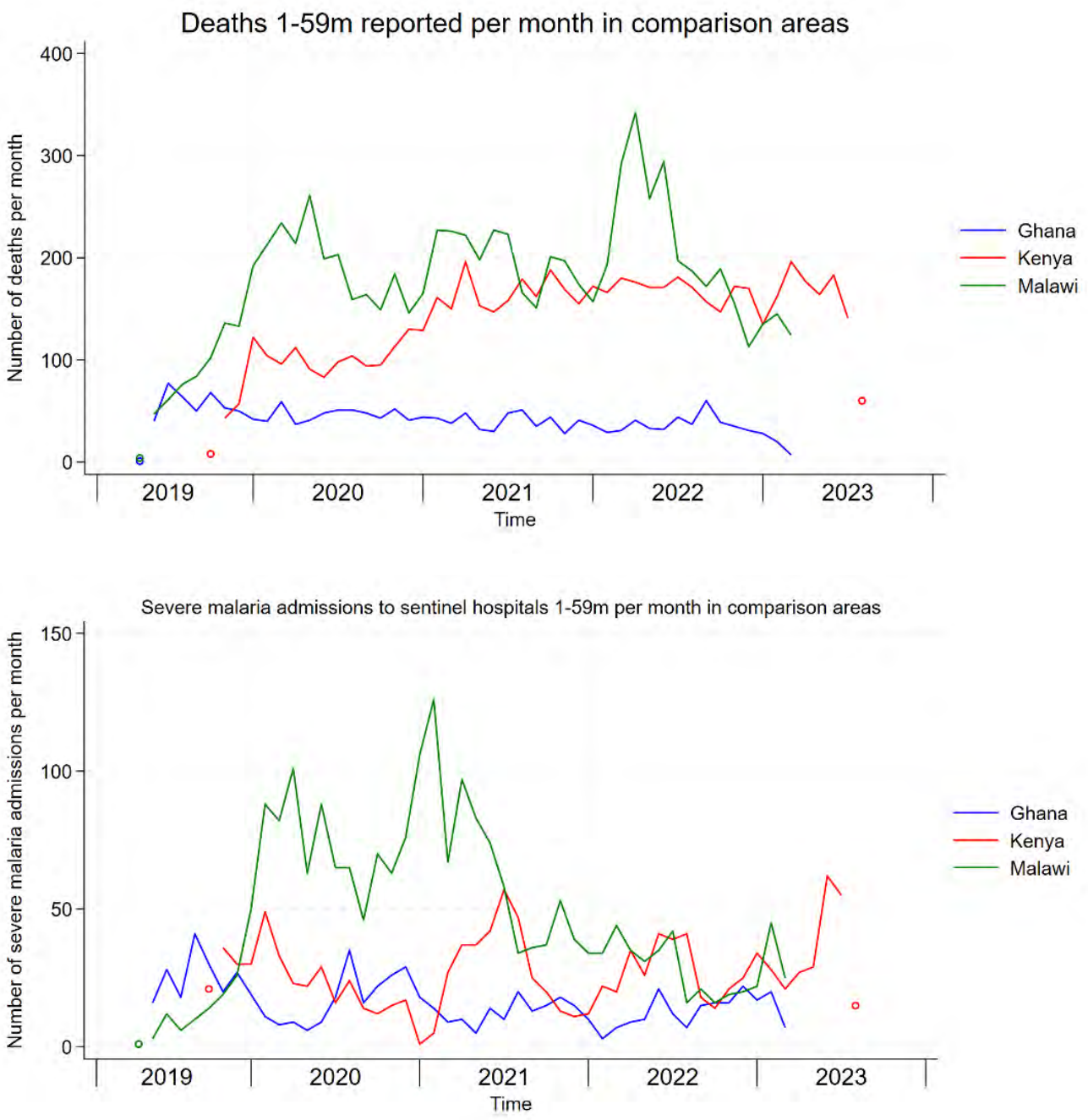
Severe malaria represents largest share of admissions in Malawi, considering all admissions 1-59m in comparison areas (not restricted to eligible children), 19% had a diagnosis of severe malaria in Malawi, compared to Ghana (10%), and Kenya (13%). Cerebral malaria was diagnosed in 25% of severe malaria cases in Ghana, 14% in Kenya, and 9% in Malawi.

Table 3:Percentage of admissions 1-59m in comparison areas, which had a diagnosis of severe malaria, the % with each form of severe malaria, and the case fatality rates.

	TOTAL	Ghana	Kenya	Malawi
% admissions with a diagnosis of severe malaria	4216/28979 (14.5%)	741/7156 (**10.4%)**	1278/10076 (**12.7%)**	2197/11747 (**18.7%**)
% cerebral malaria	555/4216 (13.2%)	186/741 (**25.1%)**	179/1278 (**14.0%)**	190/2197 (**8.6%)**
% severe malaria anaemia	1251/4216 (29.7%)	292/741 (39.4%)	442/1278 (34.6%)	517/2197 (23.5%)
% respiratory distress	1187/4216 (28.2%)	165/741 (22.3%)	289/1278 (22.6%)	733/2197 (33.4%)
% convulsions	1646/4216 (39.0%)	349/741 (47.1%)	161/1278 (12.6%)	1136/2197 (51.7%)
CFR, all admissions	961/28979 (3.3%)	134/7156 (1.9%)	584/10076 (5.8%)	243/11747 (2.1%)
CFR, severe malaria	182/4216 (4.3%)	41/741 (5.5%)	67/1278 (5.2%)	74/2197 (3.4%)
CFR, cerebral malaria	95/555 (17.1%)	29/186 (15.6%)	26/179 (14.5%)	40/190 (21.1%)
CFR, severe malaria anaemia	48/1251 (3.8%)	8/292 (2.7%)	24/442 (5.4%)	16/517 (3.1%)
CFR, respiratory distress	87/1187 (7.3%)	21/165 (12.7%)	29/289 (10.0%)	37/733 (5.0%)
CFR, convulsions	70/1646 (4.3%)	22/349 (6.3%)	11/161 (6.8%)	37/1136 (3.3%)

Seasonality in severe malaria admissions and all-cause mortality

Figure 23: The number of deaths, and number of admissions to sentinel hospitals with severe malaria, per month in each country (the numbers in incomplete months at the start or end of the evaluation period are shown as circle symbols).



The correlation between the monthly number of deaths and the monthly number of severe malaria admissions is 0.499 (p=0.004) in Malawi, 0.423 (p=0.0034) in Ghana, and 0.165 (p=0.269) in Kenya.

Number of doses administered

Up until vaccination started in comparison areas, a total of 1,289,504 children in implementation areas had received their first dose of RTS,S, 1,158,850 their second dose and 1,068,039 their third dose. Children receiving primary doses after this time did not contribute to the evaluation. A total of about 476,897 4th doses were administered up until the end of month 46, most of these contributing to the evaluation.

Table 4: Number of doses administered in implementation areas during the evaluation

	Malawi	**Ghana**	**Kenya**	**TOTAL**
Start of implementation	23 April 2019	30 April 2019	13 September 2019	
End of evaluation (month 46)	28 Feb 2023	28 Feb 2023	12 July 2023	
Doses administered during this period				
Dose 1	455,163	482,612	426,005	1,363,780
Dose 2	398,622	451,043	376,956	1,226,621
Dose 3	369,034	435,286	328,634	1,132,954
Dose 4	160,756	200,801	115,340	476,897
Total doses	1,383,575	1,569,742	1,246,934	4,200,251
Date RTSS introduced in comparison areas	29 Nov 2022	20 Feb 2023	7 Mar 2023	
Doses administered up to the date RTSS started in comparison areas:				
Dose 1	423,083	479,200	387,221	1,289,504
Dose 2	369,883	447,610	341,357	1,158,850
Dose 3	342,118	431,836	294,085	1,068,039
Dose 4	143,239	198,092	95,196	436,527
Total doses	**1,278,323**	**1,556,738**	**1,117,858**	**3,952,919**

Figure 24: Number of doses of RTS,S/AS01 administered per month. Arrows indicate the end of the evaluation period, showing high degree of consistency of delivery throughout the evaluation period.



Analysis populations

Cohorts eligible to have received the first dose of RTSS, from age they were first eligible for RTS,S-1 (5.0 months in Malawi, 6.0 months in Ghana and Kenya). This is the primary analysis population for safety. **(1)**

All cohorts eligible to have received the third dose of RTSS, from 1 month after the age they were first eligible for RTS,S-3 (i.e. from 8.0 months in Malawi, 10.0 months in Ghana and Kenya). This is the primary analysis population for impact. **(2)**

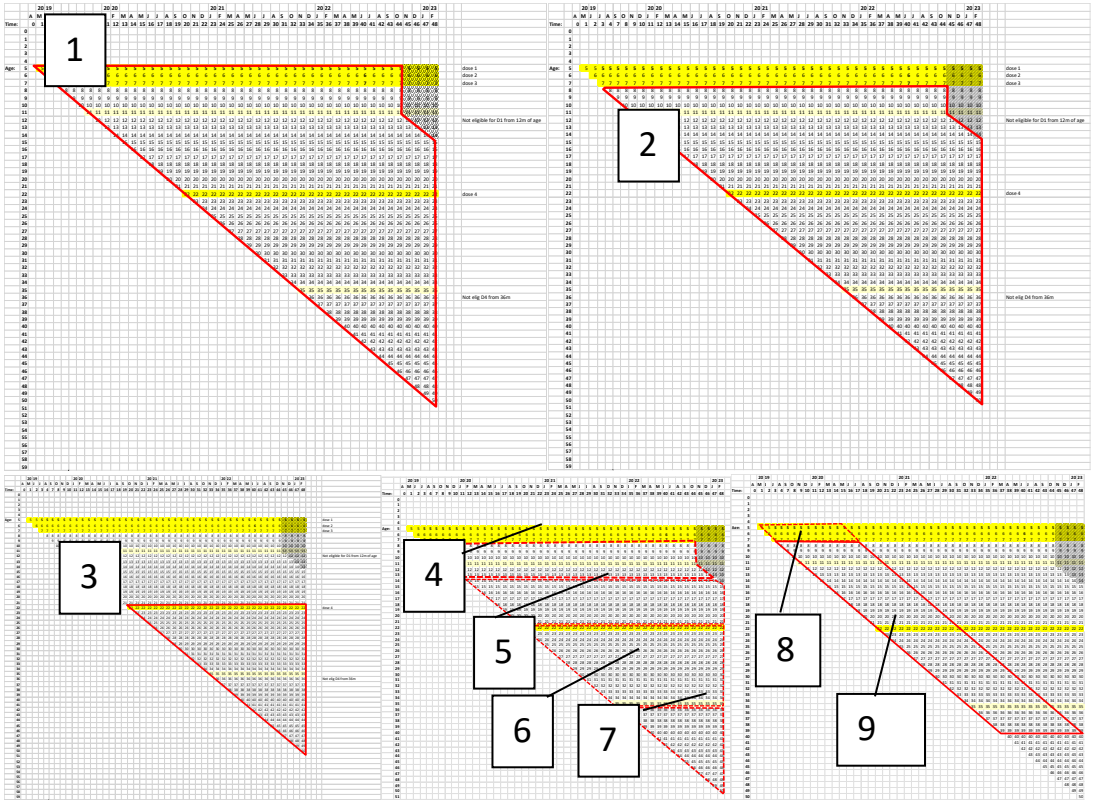
In addition the following analysis populations were defined:

All cohorts eligible to have received the 4th dose of RTSS, from the age they were eligible (22.0 months in Malawi, 24.0 months in Ghana and Kenya). **(3)**

Children eligible to have received the 3rd dose and aged under 14m (under 16m in Ghana and Kenya), i.e. within about 6m of dose 3 **(4)**; cohorts eligible to have received RTS,S who were aged 14m (16m in Kenya and Ghana) up to the age eligible for dose 4, i.e. the 8m prior to dose 4 **(5)**; children from the age eligible for dose 4 for the next 12m (up to 33m (Malawi) or 35m (Ghana and Kenya), **(6)**; children eligible to have received RTSS and who were aged more than 12m older than the age recommended for dose 4, i.e. more than 34m (Malawi), 36m (Ghana and Kenya). **(7)**

Cohorts eligible to have received the first dose **(8)**, or the third dose **(9)** of RTS,S, and followed up to 39 months of age, excluding children in the 'catch-up' cohorts at the start of vaccine introduction.

Figure 25: Definition of the analysis groups for estimating rate ratios illustrated for Malawi



Impact on mortality

Primary analysis of mortality

Analysis group (1). In total, 15444 deaths (any cause except injury) were reported among children eligible, based on age and date of birth, to have received at least one dose of RTS,S, 7433 from implementation areas (3515 girls and 3918 boys) and 8011 (3707 girls and 4304 boys) from comparison areas. This includes children eligible for their first dose at the start of vaccine introduction, the oldest of whom would have been aged over 4yrs (50m Malawi, 52m Ghana, 57m Kenya) by the end of the evaluation period, the youngest having only just turned 5m (Malawi) or 6m (Ghana, Kenya). The mortality rate ratio comparing mortality in implementation areas with that in comparison areas was 0.888 (95%CI 0.809,0.975), p=0.0133. The separate estimates for girls and boys were similar: 0.895 (0.804,0.995) (girls) and 0.879 (0.777,0.971) (boys), the interaction parameter (the ratio of the mortality ratio in girls to that in boys) was 1.037 (95%CI 0.934,1.152), p=0.4949.

Analysis group (2). Among children eligible to have received three doses of RTS,S, there were 11992 deaths, 5706 in implementation areas (2633 girls and 3073 boys) and 6286 in comparison areas (2891 girls and 3395 boys). The mortality rate ratio was 0.870 (95%CI 0.778,0.973), p=0.0152. The mortality rate ratio among girls was 0.856 (95%CI 0.754,0.971) and among boys, 0.872 (0.767,0.992), interaction parameter 1.001 (95%CI 0.894,1.122) p=0.9808.

Secondary analyses, mortality

Analysis group (3). Among children eligible to have received four doses of RTS,S, there were 4843 deaths, 2276 in implementation areas (1034 girls and 1242 boys) and 2567 in comparison areas (1148 girls and 1419 boys). The mortality rate ratio was 0.896 (95%CI 0.749,1.072). The mortality rate ratio among girls was 0.920 (95%CI 0.751,1.127) and among boys, 0.864 (0.703,1.062), interaction parameter 1.036 (95%CI 0.874,1.228) p=0.6825.

Analysis group (8). The cohorts of children who reached the age when they could receive the first dose of RTS,S during the first year of vaccine introduction, were all 'followed' up to at least 39m of age. The mortality rate ratios in these cohorts was 0.918 (95%CI 0.815,1.035).

Analysis group (9): and among those eligible to have received the 3rd dose, 0.887 (95%CI 0.775,1.015).

In the 4 successive age strata, estimates of impact (1-rate ratio) were 13.7% (95%CI 1.8%,24.1%), 12.4% (95%CI 2.7%,21.2%), 14.8% (-2.5%,21.4%), and 0.6% (95%CI -25.7%,21.4%) in the stratum about 34m or 36m of age when little impact of the vaccine would be expected.

Detailed results are in Table 5 to Table 15.

Impact on admissions to hospital with severe malaria

In Ghana, there were 19,483 admissions 1-59m, 1965 without consent (for most of these, consent not sought at the start of the evaluation), 1572 resided outside the defined sentinel surveillance areas, leaving 15946 included in analyses. RDT or blood film results were available for 15,218/15,946 (95.4%). There were 1407 cases of severe malaria, 66 were excluded (because they were just outside the eligible age range by less than 2 months and thus might have been vaccinated, or because they were in age groups that, in comparison areas, had started to receive the vaccine). There were 76 cases of meningitis, 2 of which were excluded.

In Kenya, there were 24,358 admissions 1-59m, 3248 resided outside the defined sentinel surveillance areas, leaving 21110 included in analyses. RDT or blood film results were available for 19,317/21,110 (91.5%). There were 2932 cases of severe malaria, 372 were excluded which belonged to age cohorts eligible to receive RTSS in comparison areas or being just outside the upper age limit of eligibility. There were 138 cases of meningitis, 10 of which were excluded.

In Malawi, there were 21,058 admissions 1-59m. RDT or blood film results were available for 18,373/21,058 (87.2%). There were 3587 cases of severe malaria, 207 were excluded which belonged to age cohorts eligible to receive RTSS in comparison areas or being just outside the upper age limit of eligibility. There were 101 cases of meningitis, 3 of which were excluded.

Detailed results are shown in Table 16 to Table 21.

Analysis group (1). In total, there were 3803 patients admitted to sentinel hospitals deaths met the criteria for severe malaria who were eligible, based on age and date of birth, to have received at least one dose of RTS,S, 1692 from implementation areas and 2011 from comparison areas. The incidence rate ratio comparing incidence in implementation areas with that in comparison areas was 0.802 (95%CI 0.646,0.996), p=0.0463. Of these severe malaria cases, 197 and 221 met criteria for cerebral malaria in implementation and comparison areas respectively. The rate ratio was 0.935 (95%CI 0.630,1.388). The rate ratio for other forms of severe malaria was 0.795 (95%CI 0.629,1.004). The interaction parameter for the difference in impact between cerebral and other forms of severe malaria was 1.086 (95%CI 0.723,1.631) p=0.6878. Thus there was no evidence of an increase in incidence of cerebral malaria in implementation areas and no evidence that impact differed from that for other forms of severe malaria, but the wide confidence intervals reflect the relatively small number of cases on which these estimates are based.

Analysis group (2). Among children eligible to have received three doses of RTS,S, there were 1457 cases in implementation areas and 1853 in comparison areas, the incidence rate ratio was 0.784 (95%CI 0.636,0.966), p=0.0228. Of these cases, 182 patients from implementation areas and 201 from comparison areas met the criteria for cerebral malaria. The rate ratio was 0.961 (95%CI 0.648,1.426). The interaction parameter comparing impact on cerebral malaria with that for other forms of severe malaria was 1.157 (0.787,1.703) p=0.4534.

Analysis group (3). Among children eligible to have received four doses of RTS,S, there were 714 cases in implementation areas and 772 in comparison areas, rate ratio 0.893 (95%CI 0.700,1.139).

Analysis group (8). The cohorts of children who reached the age when they could receive the first dose of RTS,S during the first year of vaccine introduction, were all 'followed' up to at least 39m of age. The rate ratio in these cohorts was 0.771 (95%CI 0.640,0.929).

Analysis group (9): and among those eligible to have received the 3rd dose, 0.761 (95%CI 0.626,0.926).

In the 4 successive age strata, estimates of impact (1-rate ratio) 39.6% (22.2%,53.1%), 20.4% (-2.0%,37.9%), 15.5% (-7.7%,33.7%), and 0.2% (-39.1%,28.4%) in the stratum about 34m or 36m of age when little impact of the vaccine would be expected.

Meningitis

Among children eligible to have received at least one dose of RTS,S, 87 patients from implementation areas and 78 from comparison areas met criteria for probable or confirmed meningitis. The incidence rate ratio was 0.976 (95%CI 0.626,1.519). See Table 16 and Table 17, Table 20 and Table 21.

Admissions to sentinel hospitals without malaria parasitaemia, anaemia, or meningitis

When incidence rate ratios were calculated for these 'tracer' conditions, expected to be uninfluenced by the malaria vaccine, the incidence rate ratio was among children eligible for at least one dose of RTS,S was 1.025 (95%CI 0.899,1.169), and among children eligible to have received for three doses, 1.042 (95%CI 0.903,1.201). See Table 16 and Table 17, Table 20 and Table 21.

Table 5: Pooled estimates of mortality rate ratios (deaths due to any cause except injury) in children eligible to have received at least one dose of RTS,S/AS01 (Analysis group 1)

Outcome:	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	t (df) p-value
Both sexes	79	79	7433/7534	8011/7044	0.888	0.0474	(0.809,0.975)	2.50 (152) p=0.0133
Boys	79	79	3918/3971	4304/3709	0.869	0.0562	(0.777,0.971)	2.51 (152) p=0.0133
Girls	79	79	3515/3563	3707/3335	0.895	0.0539	(0.804,0.995)	2.06 (152) p=0.0408
Interaction	79	79			1.037	0.0532	(0.934,1.152)	0.68 (152) p=0.4949

Table 6: Pooled estimates of mortality rate ratios (deaths due to any cause except injury) in children eligible to have received three doses of RTS,S/AS01 (Analysis group 2)

Outcome	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	t (df) p-value
Both sexes	79	79	5706/7534	6286/7044	0.870	0.0566	(0.778,0.973)	2.46 (152) p=0.0152
Boys	79	79	3073/3971	3395/3709	0.872	0.0651	(0.767,0.992)	2.11 (152) p=0.0368
Girls	79	79	2633/3563	2891/3335	0.856	0.0642	(0.754,0.971)	2.43 (152) p=0.0163
Interaction	79	79			1.001	0.0576	(0.894,1.122)	0.02 (152) p=0.9808

Table 7: Analysis group 4. Pooled estimates of mortality rate ratios (deaths due to any cause except injury) in children eligible to have received 3 doses of RTS,S/AS01 within 6m.

Outcome	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	t (df) p-value
Both sexes	79	79	1944/7534	2071/7044	0.876	0.0532	(0.788,0.973)	2.49 (152df) p=0.0139
Boys	79	79	1018/3971	1085/3709	0.878	0.0603	(0.779,0.989)	2.16 (152df) p=0.0322
Girls	79	79	926/3563	986/3335	0.865	0.0681	(0.756,0.989)	2.13 (152df) p=0.0347
Interaction	79	79			1.001	0.0693	(0.873,1.148)	0.02 (152df) p=0.9860

Table 8: Analysis group 5. Pooled estimates of mortality rate ratios (deaths due to any cause except injury) in children eligible to have received 3 doses of RS,S (8m prior to age when dose 4 is due)

Outcome	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	t (df) p-value
Both sexes	79	79	1486/7534	1648/7044	0.863	0.0653	(0.759,0.982)	2.25 (152df) p=0.0259
Boys	79	79	813/3971	891/3709	0.866	0.0731	(0.750,1.001)	1.96 (152df) p=0.0514
Girls	79	79	673/3563	757/3335	0.844	0.0820	(0.718,0.993)	2.06 (152df) p=0.0407
Interaction	79	79	0/0	0/0	0.979	0.0807	(0.834,1.148)	0.27 (152df) p=0.7910

Table 9: Analysis group 6. Pooled estimates of mortality rate ratios (deaths due to any cause except injury) in children eligible to have received four doses of RTS,S/AS01 and aged under 34m or 36m.

Outcome	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	t (df) p-value
Both sexes	79	79	1516/7534	1831/7044	0.852	0.0934	(0.709,1.025)	1.71 (152df) p=0.0895
Boys	79	79	820/3971	1005/3709	0.817	0.1101	(0.657,1.015)	1.84 (152df) p=0.0677
Girls	79	79	696/3563	826/3335	0.862	0.1039	(0.702,1.058)	1.43 (152df) p=0.1552
Interaction	79	79	0/0	0/0	1.032	0.0911	(0.862,1.236)	0.35 (152df) p=0.7272

Table 10: Analysis group 7. Pooled estimates of mortality rate ratios (deaths due to any cause except injury) in children eligible to have received RTS,S/AS01 and are aged 34m or 36m and above.

Outcome	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	t (df) p-value
Both sexes	79	79	760/7534	736/7044	0.994	0.1188	(0.786,1.257)	0.05 (152df) p=0.9570
Boys	79	79	422/3971	414/3709	0.969	0.1355	(0.741,1.266)	0.23 (152df) p=0.8151
Girls	79	79	338/3563	322/3335	1.047	0.1466	(0.784,1.399)	0.32 (152df) p=0.7531
Interaction	79	79	0/0	0/0	1.056	0.1295	(0.818,1.364)	0.42 (152df) p=0.6733

Table 11: Analysis group 3. Pooled estimates of mortality rate ratios (deaths due to any cause except injury) in children eligible to have received four doses of RTS,S/AS01.

Outcome	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	t (df) p-value
Both sexes	79	79	2276/7534	2567/7044	0.896	0.0910	(0.749,1.072)	1.21 (152df) p=0.2293
Boys	79	79	1242/3971	1419/3709	0.864	0.1045	(0.703,1.062)	1.40 (152df) p=0.1631
Girls	79	79	1034/3563	1148/3335	0.920	0.1027	(0.751,1.127)	0.81 (152df) p=0.4197
Interaction	79	79			1.036	0.0861	(0.874,1.228)	0.41 (152df) p=0.6825

Table 12: Analysis group 8. Pooled estimates of mortality rate ratios (deaths due to any cause except injury) in children eligible to have received at least one dose of RTS,S/AS01 during the first year of vaccine introduction and are aged under 39 m

Outcome	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	t (df) p-value
Both sexes	79	79	2576/7534	2842/7044	0.918	0.0606	(0.815,1.035)	1.41 (152df) p=0.1613
Boys	79	79	1360/3971	1527/3709	0.890	0.0800	(0.760,1.043)	1.46 (152df) p=0.1476
Girls	79	79	1216/3563	1315/3335	0.914	0.0684	(0.798,1.046)	1.32 (152df) p=0.1891
Interaction	79	79			1.020	0.0776	(0.875,1.189)	0.25 (152df) p=0.8004

Table 13: Analysis group 9. Pooled estimates of mortality rate ratios (deaths due to any cause except injury) in children eligible to have received 3 doses of RTS,S/AS01 during the first year of vaccine introduction and are aged under 39 m

Outcome	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	t (df) p-value
Both sexes	79	79	2154/7534	2469/7044	0.887	0.0682	(0.775,1.015)	1.76 (152df) p=0.0798
Boys	79	79	1152/3971	1326/3709	0.879	0.0866	(0.741,1.043)	1.49 (152df) p=0.1389
Girls	79	79	1002/3563	1143/3335	0.864	0.0785	(0.740,1.009)	1.86 (152df) p=0.0645
Interaction	79	79			0.988	0.0827	(0.839,1.163)	0.15 (152df) p=0.8828

Table 14: Mortality rate ratios (deaths due to any cause except injury) in children eligible to have received at least one dose of RTS,S/AS01, by country

Outcome	Country	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (uncorrected)	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	Test of homogeneity X^2 (p-value)
Both sexes	Ghana	33	33	818/1197	775/998	0.88	0.88	0.0920	(0.73,1.05)	1.82 p=0.4027
	Kenya	23	23	3161/2930	3038/2666	0.95	0.95	0.0704	(0.82,1.09)	
	Malawi	23	23	3454/3407	4198/3380	0.82	0.81	0.0893	(0.68,0.97)	
Boys	Ghana	33	33	410/604	413/551	0.91	0.90	0.1188	(0.71,1.14)	1.19 p=0.5506
	Kenya	23	23	1664/1564	1602/1370	0.91	0.91	0.0829	(0.77,1.07)	
	Malawi	23	23	1844/1803	2289/1788	0.80	0.79	0.0999	(0.65,0.97)	
Girls	Ghana	33	33	408/593	362/447	0.85	0.84	0.1053	(0.68,1.04)	2.25 p=0.3247
	Kenya	23	23	1497/1366	1436/1296	0.99	0.99	0.0852	(0.83,1.17)	
	Malawi	23	23	1610/1604	1909/1592	0.84	0.83	0.0927	(0.69,1.00)	
Interaction*	Ghana	33	33			0.94	0.93	0.1296	(0.71,1.20)	1.00 p=0.6058
	Kenya	23	23			1.09	1.08	0.0932	(0.90,1.31)	
	Malawi	23	23			1.05	1.05	0.0748	(0.90,1.22)	

Table 15: Mortality rate ratios (deaths due to any cause except injury) in children eligible to have received at three doses of RTS,S/AS01, by country

Outcome	Country	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (uncorrected)	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	Test of homogeneity X^2 (p-value)
Both sexes	Ghana	33	33	552/1197	551/998	0.84	0.83	0.1064	(0.67,1.03)	2.02 p=0.3641
	Kenya	23	23	2277/2930	2173/2666	0.95	0.95	0.0866	(0.80,1.13)	
	Malawi	23	23	2877/3407	3562/3380	0.80	0.80	0.1055	(0.64,0.98)	
Boys	Ghana	33	33	280/604	287/551	0.89	0.89	0.1347	(0.68,1.16)	1.21 p=0.5474
	Kenya	23	23	1235/1564	1163/1370	0.93	0.93	0.0968	(0.76,1.13)	
	Malawi	23	23	1558/1803	1945/1788	0.79	0.79	0.1163	(0.62,1.00)	
Girls	Ghana	33	33	272/593	264/447	0.78	0.77	0.1242	(0.60,0.98)	2.72 p=0.2564
	Kenya	23	23	1042/1366	1010/1296	0.98	0.98	0.1043	(0.79,1.21)	
	Malawi	23	23	1319/1604	1617/1592	0.81	0.80	0.1080	(0.65,1.00)	
Interaction*	Ghana	33	33			0.87	0.86	0.1480	(0.64,1.15)	1.36 p=0.5078
	Kenya	23	23			1.05	1.05	0.1023	(0.85,1.29)	
	Malawi	23	23			1.02	1.02	0.0791	(0.87,1.19)	

Table 16: Pooled estimates of incidence rate ratios for hospital outcomes in children eligible for at least one dose of RTS,S/AS01

Outcome	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio	Standard error of log rate ratio	95%CI, rate ratio	p-value
Tracer conditions	39	38	7347/4236	6979/4018	1.025	0.0657	(0.899,1.169)	0.7063
Meningitis	39	38	87/68	78/67	0.976	0.2222	(0.626,1.519)	0.9116
Severe malaria	39	38	1692/1705	2111/1773	0.802	0.1085	(0.646,0.996)	0.0463
Cerebral malaria	39	38	197/282	221/294	0.935	0.1982	(0.630,1.388)	0.7356
Other forms of severe malaria	39	38	1495/1423	1890/1479	0.795	0.1174	(0.629,1.004)	0.0541
Interaction	39	38			1.086	0.2040	(0.723,1.631)	0.6878
Severe malaria (subset)	39	38	1472/1341	1795/1369	0.785	0.1012	(0.642,0.961)	0.0197
Cerebral malaria (subset)	39	38	129/151	143/167	1.032	0.2083	(0.681,1.563)	0.8817
Other forms of severe malaria (subset)	39	38	1343/1190	1652/1202	0.766	0.1023	(0.625,0.940)	0.0113
Interaction (subset)	39	38			1.254	0.2037	(0.835,1.882)	0.2705
Severe malaria anaemia	39	38	695/659	601/548	0.879	0.1077	(0.709,1.089)	0.2339
Malaria admissions	39	38	4464/4933	5595/4914	0.846	0.0612	(0.749,0.956)	0.0078
Admissions due to any cause	39	38	14461/11752	15032/11149	0.918	0.0683	(0.801,1.052)	0.2158
Deaths in hospital	39	38	513/440	491/376	0.862	0.1127	(0.689,1.079)	0.1914

Table 17: Pooled estimates of incidence rate ratios for hospital outcomes in children eligible for three doses of RTS,S/AS01

Outcome	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio	Standard error of log rate ratio	95%CI, rate ratio	p-value
Tracer conditions	39	38	5831/4236	5490/4018	1.042	0.0715	(0.903,1.201)	0.5689
Meningitis	39	38	66/68	66/67	0.893	0.2561	(0.536,1.488)	0.6594
Severe malaria	39	38	1457/1705	1853/1773	0.784	0.1046	(0.636,0.966)	0.0228
Cerebral malaria	39	38	182/282	201/294	0.961	0.1979	(0.648,1.426)	0.8417
Other forms of severe malaria	39	38	1275/1423	1652/1479	0.772	0.1123	(0.617,0.966)	0.0242
Interaction	39	38			1.157	0.1936	(0.787,1.703)	0.4534
Severe malaria (subset)	39	38	1261/1341	1562/1369	0.770	0.1015	(0.629,0.942)	0.0120
Cerebral malaria (subset)	39	38	123/151	139/167	1.018	0.2071	(0.674,1.539)	0.9301
Other forms of severe malaria (subset)	39	38	1138/1190	1423/1202	0.751	0.1031	(0.611,0.923)	0.0070
Interaction (subset)	39	38			1.231	0.1990	(0.828,1.831)	0.3001
Severe malaria anaemia	39	38	588/659	518/548	0.857	0.1225	(0.671,1.094)	0.2107
Malaria admissions	39	38	3865/4933	4948/4914	0.834	0.0647	(0.733,0.949)	0.0065
Admissions due to any cause	39	38	11738/11752	12338/11149	0.922	0.0657	(0.808,1.051)	0.2184
Deaths in hospital	39	38	359/440	349/376	0.861	0.1235	(0.673,1.101)	0.2282

Table 18: Analysis groups 4-9. Pooled estimates of the rate ratio for severe malaria.

Analysis group	Clusters in implement-ation areas	Clusters in compar-ison areas	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI	t (df) p-value
Analysis group 3	39	38	714/1705	772/1773	0.893	0.1221	(0.700,1.139)	0.926 (71df) p=0.3573
Analysis group 4	39	38	299/1705	528/1773	0.604	0.1265	(0.469,0.778)	3.98(71df) p=0.0002
Analysis group 5	39	38	444/1705	553/1773	0.796	0.1244	(0.621,1.020)	1.84(71df) p=0.0703
Analysis group 6	39	38	439/1705	523/1773	0.845	0.1218	(0.663,1.077)	1.39(71df) p=0.1698
Analysis group 7	39	38	275/1705	249/1773	0.998	0.1665	(0.716,1.391)	0.01(71df) p=0.9922
Analysis group 8	39	38	636/1705	869/1773	0.771	0.0933	(0.640,0.929)	2.78(71df) p=0.0069
Analysis group 9	39	38	563/1705	793/1773	0.761	0.0982	(0.626,0.926)	2.78(71df) p=0.0069

Table 19: Summary of estimates of impact on severe malaria admissions and all-cause mortality by analysis group

Analysis group	Severe malaria		Mortality	
Analysis group 4	39.6%	22.2%,53.1%	13.7%	1.8%,24.1%
Analysis group 5	20.4%	-2.0%,37.9%	12.4%	2.7%,21.2%
Analysis group 6	15.5%	-7.7%,33.7%	14.8%	-2.5%,29.1%
Analysis group 7	0.2%	-39.1%,28.4%	0.6%	-25.7%,21.4%
Analysis group 8	22.9%	7.1%,36.0%	8.2%	-3.5%,18.5%
Analysis group 9	23.9%	7.4%,37.4%	11.3%	-1.5%,22.5%

Table 20: Incidence rate ratios for hospital outcomes in children eligible to have received at least one dose of RTS,S/AS01, by country

Outcome	Country	Imple-mentation clusters	Comp-arison clusters	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (uncorr-ected)	Rate rate (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI bias-corrected rate ratio	Test of homogeneity χ^2, p-value
Tracer conditions	Ghana	15	17	2749/1702	2013/1250	1.003	0.996	0.1227	(0.78,1.28)	1.16 p=0.5612
	Kenya	16	12	2446/1579	2322/1425	0.951	0.950	0.1148	(0.75,1.20)	
	Malawi	8	9	2152/955	2644/1343	1.145	1.117	0.1058	(0.89,1.40)	
Meningitis	Ghana	15	17	19/18	19/18	1.000	0.767	1.0298	(0.09,6.29)	0.34 p=0.8458
	Kenya	16	12	43/32	31/22	0.954	0.923	0.2605	(0.54,1.58)	
	Malawi	8	9	25/18	28/27	1.339	1.224	0.4671	(0.45,3.31)	
Severe malaria	Ghana	15	17	264/367	361/349	0.695	0.609	0.4261	(0.25,1.45)	1.40 p=0.4960
	Kenya	16	12	810/649	626/475	0.947	0.928	0.1710	(0.65,1.32)	
	Malawi	8	9	618/689	1124/949	0.757	0.744	0.1488	(0.54,1.02)	
Cerebral malaria	Ghana	15	17	41/106	76/104	0.529	0.440	0.5983	(0.13,1.49)	1.81 p=0.4050
	Kenya	16	12	106/98	78/79	1.096	1.065	0.3121	(0.56,2.02)	
	Malawi	8	9	50/78	67/111	1.062	0.995	0.2840	(0.54,1.82)	
Other forms of severe malaria	Ghana	15	17	223/261	285/245	0.734	0.632	0.4945	(0.23,1.74)	1.06 p=0.5899
	Kenya	16	12	704/551	548/396	0.923	0.902	0.1730	(0.63,1.29)	
	Malawi	8	9	568/611	1057/838	0.737	0.723	0.1688	(0.50,1.04)	
Interaction*	Ghana	15	17			0.721	0.678	0.4588	(0.27,1.73)	1.38 p=0.5009
	Kenya	16	12			1.187	1.173	0.2720	(0.67,2.05)	
	Malawi	8	9			1.441	1.336	0.4167	(0.55,3.25)	
Severe malaria (subset)	Ghana	15	17	234/262	308/269	0.780	0.710	0.2842	(0.40,1.27)	0.90 p=0.6365
	Kenya	16	12	752/604	579/429	0.922	0.899	0.1756	(0.63,1.29)	
	Malawi	8	9	486/475	908/671	0.756	0.740	0.1376	(0.55,0.99)	

Cerebral malaria (subset)	Ghana	15	17	26/39	44/48	0.727	0.521	0.9371	(0.08,3.53)	1.21 p=0.5465
	Kenya	16	12	73/76	58/55	0.911	0.896	0.3058	(0.48,1.68)	
	Malawi	8	9	30/36	41/64	1.301	1.264	0.2986	(0.67,2.39)	
Other forms of severe malaria (subset)	Ghana	15	17	208/223	264/221	0.781	0.725	0.2687	(0.42,1.26)	1.11 p=0.5750
	Kenya	16	12	679/528	521/374	0.923	0.896	0.1810	(0.62,1.30)	
	Malawi	8	9	456/439	867/607	0.727	0.709	0.1397	(0.53,0.95)	
Interaction (subset)*	Ghana	15	17			0.931	0.717	0.9316	(0.11,4.81)	2.29 p=0.3176
	Kenya	16	12			0.987	0.989	0.2834	(0.55,1.77)	
	Malawi	8	9			1.789	1.767	0.3087	(0.91,3.41)	
Severe malaria anaemia	Ghana	15	17	124/131	152/127	0.791	0.741	0.2255	(0.47,1.17)	1.26 p=0.5319
	Kenya	16	12	373/320	200/185	1.078	1.062	0.2277	(0.66,1.70)	
	Malawi	8	9	198/208	249/236	0.902	0.873	0.1454	(0.64,1.19)	
Malaria admissions	Ghana	15	17	1098/1854	1491/1375	0.546	0.491	0.4655	(0.19,1.27)	2.06 p=0.3576
	Kenya	16	12	1661/1257	1410/1079	1.011	0.999	0.2021	(0.66,1.51)	
	Malawi	8	9	1705/1822	2694/2460	0.855	0.840	0.0649	(0.73,0.96)	
Admissions due to any cause	Ghana	15	17	4234/3979	3812/2945	0.822	0.795	0.1860	(0.54,1.16)	0.74 p=0.6904
	Kenya	16	12	5621/4013	5207/3566	0.959	0.956	0.1133	(0.76,1.21)	
	Malawi	8	9	4606/3760	6013/4638	0.945	0.927	0.0964	(0.75,1.14)	
Death in hospital	Ghana	15	17	42/45	72/60	0.778	0.731	0.2756	(0.42,1.28)	0.99 p=0.6085
	Kenya	16	12	365/311	296/215	0.852	0.833	0.1527	(0.61,1.14)	
	Malawi	8	9	106/84	123/101	1.036	1.012	0.2098	(0.65,1.58)	

Table 21: Incidence rate ratios for hospital outcomes in children eligible to have received three doses of RTS,S/AS01, by country

Outcome	Country	Imple-mentation clusters	Comp-arison clusters	Number of events eligible/non-eligible, implemen-tation areas	Number of events eligible/non-eligible, comparison areas	Rate ratio (uncorr-ected)	Rate rate (bias-corrected)	Standard error of log rate ratio (bias-corrected)	95%CI bias-corrected rate ratio	Test of homogeneity χ^2, p-value
Tracer conditions	Ghana	15	17	2163/1702	1580/1250	1.005	0.997	0.1463	(0.74,1.34)	1.93 p=0.3809
	Kenya	16	12	1791/1579	1716/1425	0.942	0.942	0.1182	(0.74,1.20)	1.93 p=0.3809
	Malawi	8	9	1877/955	2194/1343	1.203	1.174	0.1137	(0.92,1.50)	1.93 p=0.3809
Meningitis	Ghana	15	17	13/18	17/18	0.765	0.612	0.7977	(0.12,3.12)	0.65 p=0.7210
	Kenya	16	12	32/32	25/22	0.880	0.835	0.3212	(0.43,1.62)	0.65 p=0.7210
	Malawi	8	9	21/18	24/27	1.313	1.219	0.5012	(0.42,3.55)	0.65 p=0.7210
Severe malaria	Ghana	15	17	214/367	303/349	0.672	0.589	0.4121	(0.25,1.37)	1.46 p=0.4809
	Kenya	16	12	689/649	536/475	0.941	0.921	0.1810	(0.63,1.34)	1.46 p=0.4809
	Malawi	8	9	554/689	1014/949	0.753	0.739	0.1348	(0.55,0.99)	1.46 p=0.4809
Cerebral malaria	Ghana	15	17	37/106	67/104	0.542	0.433	0.6566	(0.11,1.65)	1.64 p=0.4410
	Kenya	16	12	96/98	70/79	1.106	1.065	0.3000	(0.57,1.97)	1.64 p=0.4410
	Malawi	8	9	49/78	64/111	1.090	1.019	0.2873	(0.55,1.88)	1.64 p=0.4410
Other forms of severe malaria	Ghana	15	17	177/261	236/245	0.704	0.613	0.4658	(0.24,1.59)	1.15 p=0.5637
	Kenya	16	12	593/551	466/396	0.915	0.894	0.1823	(0.61,1.30)	1.15 p=0.5637
	Malawi	8	9	505/611	950/838	0.729	0.716	0.1496	(0.52,0.99)	1.15 p=0.5637
Interaction*	Ghana	15	17			0.770	0.684	0.5583	(0.22,2.14)	1.14 p=0.5658
	Kenya	16	12			1.209	1.183	0.2471	(0.71,1.97)	1.14 p=0.5658
	Malawi	8	9			1.494	1.394	0.3758	(0.63,3.11)	1.14 p=0.5658
Severe malaria (subset)	Ghana	15	17	192/262	256/269	0.770	0.703	0.2827	(0.39,1.25)	0.88 p=0.6453
	Kenya	16	12	640/604	495/429	0.918	0.892	0.1885	(0.61,1.31)	0.88 p=0.6453
	Malawi	8	9	429/475	811/671	0.747	0.730	0.1331	(0.55,0.97)	0.88 p=0.6453

Cerebral malaria (subset)	Ghana	15	17	26/39	44/48	0.727	0.521	0.9371	(0.08,3.53)	1.43 p=0.4888
	Kenya	16	12	67/76	55/55	0.882	0.864	0.2990	(0.47,1.60)	1.43 p=0.4888
	Malawi	8	9	30/36	40/64	1.333	1.291	0.3018	(0.68,2.46)	1.43 p=0.4888
Other forms of severe malaria (subset)	Ghana	15	17	166/223	212/221	0.776	0.725	0.2656	(0.42,1.25)	1.13 p=0.5681
	Kenya	16	12	573/528	440/374	0.922	0.893	0.1940	(0.60,1.33)	1.13 p=0.5681
	Malawi	8	9	399/439	771/607	0.716	0.695	0.1370	(0.52,0.93)	1.13 p=0.5681
Interaction (subset)*	Ghana	15	17			0.937	0.712	0.9698	(0.10,5.16)	2.85 p=0.2406
	Kenya	16	12			0.956	0.957	0.2677	(0.55,1.66)	2.85 p=0.2406
	Malawi	8	9			1.863	1.838	0.3128	(0.94,3.58)	2.85 p=0.2406
Severe malaria anaemia	Ghana	15	17	93/131	121/127	0.745	0.694	0.2472	(0.42,1.15)	1.44 p=0.4862
	Kenya	16	12	317/320	171/185	1.072	1.052	0.2432	(0.64,1.73)	1.44 p=0.4862
	Malawi	8	9	178/208	226/236	0.894	0.856	0.1731	(0.59,1.24)	1.44 p=0.4862
Malaria admissions	Ghana	15	17	892/1854	1243/1375	0.532	0.481	0.4376	(0.20,1.18)	2.32 p=0.3141
	Kenya	16	12	1406/1257	1202/1079	1.004	0.993	0.2040	(0.65,1.51)	2.32 p=0.3141
	Malawi	8	9	1567/1822	2503/2460	0.845	0.829	0.0690	(0.72,0.96)	2.32 p=0.3141
Admissions due to any cause	Ghana	15	17	3313/3979	3051/2945	0.804	0.777	0.1898	(0.53,1.14)	0.95 p=0.6230
	Kenya	16	12	4415/4013	4090/3566	0.959	0.956	0.1158	(0.75,1.21)	0.95 p=0.6230
	Malawi	8	9	4010/3760	5197/4638	0.952	0.936	0.0880	(0.78,1.13)	0.95 p=0.6230
Death in hospital	Ghana	15	17	26/45	52/60	0.667	0.583	0.4141	(0.25,1.36)	1.59 p=0.4523
	Kenya	16	12	243/311	196/215	0.857	0.836	0.1551	(0.61,1.15)	1.59 p=0.4523
	Malawi	8	9	90/84	101/101	1.071	1.042	0.2344	(0.63,1.72)	1.59 p=0.4523

Comparison of associations for cerebral malaria, meningitis, and mortality by sex interaction, with the signals observed in the phase 3 trial.

Primary analysis of safety outcomes was undertaken in 2021. Data on uptake of RTS,S/AS01 from the coverage surveys undertaken about 18 months after introduction of the vaccine were used to calculate estimates of dilution factors, these were then used to calculate modelled predictions of the rate ratios that would be expected if the safety signals observed in the phase 3 trial were to occur during the MVIP, as follows:

If the safety signals observed in the phase 3 trial occurred in the MVIP, the magnitude of the effect we would observe would be smaller than in the phase 3 trial, since not all children will have received the vaccine. Any effects would be further diluted if there was contamination due to some children in comparison areas, or children in non-eligible age groups, receiving the vaccine. We used estimates of coverage and timing of malaria vaccine doses from the household surveys in each country to estimate the person time in vaccinated children as a proportion of total person time, and the degree of contamination. These estimates were used to derive predictions of the expected effect in each country, if the safety signals in the phase 3 trial were to occur in the MVIP. The average of these effects for each outcome was compared with the observed rate ratio from the MVIP using a z-test.

For meningitis and for the interaction of vaccine impact on mortality by sex, the estimates obtained in the MVIP were inconsistent with the signal in the phase 3 trial, i.e. the hypothesis that the signal observed in the phase 3 trial occurred in the MVIP, given the degree of dilution that was estimated, was rejected ($p<0.05$). For the two definitions of cerebral malaria the corresponding p-values were 0.19 and 0.12.

Using the same approach and the same dilution factors, using the final data, the results were similar (Table 22). For meningitis and the sex interaction with respect to mortality, the MVIP data were clearly not consistent with the signals in the phase 3 trial after allowing for dilution. For cerebral malaria, although we found not evidence of an increased incidence associated with RTS,S introduction, we were not able to exclude the signals observed in the phase 3 trial.

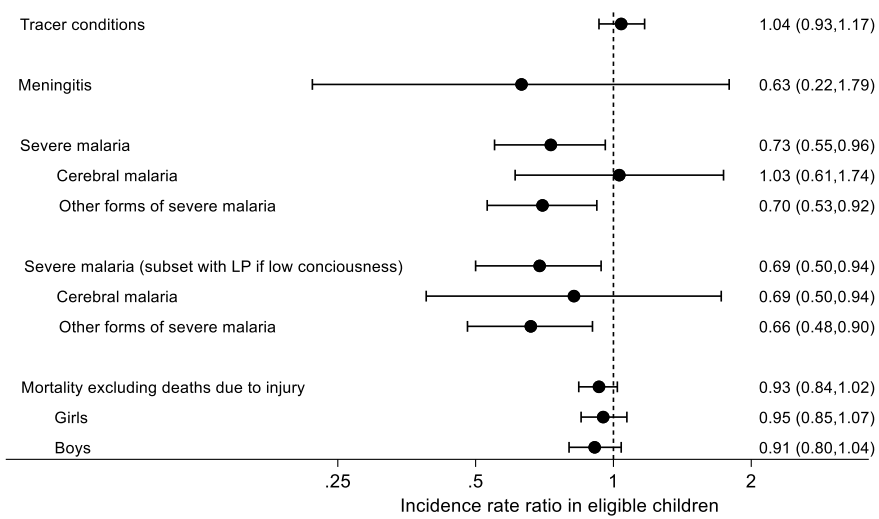
Table 22: Comparison of rate ratios for safety outcomes with the signals observed in the phase 3 trial

Outcome	Signal in the phase 3 trial (95%CI)	Diluted value	Rate ratio MVIP	z	p
Meningitis	10.5 (1.41,78.0)	4.09 (1.23,30.41)	0.98 (0.63,1.51)	2.20	0.0280
Cerebral malaria	2.15 (1.10,4.30)	1.62 (1.05,3.21)	0.94 (0.63,1.38)	1.86	0.0624
Cerebral malaria (subset)		1.62 (1.05,3.20)	1.03 (0.69,1.55)	1.49	0.1355
Mortality interaction	2.61 (1.29,5.26)	1.87 (1.18,3.77)	1.04 (0.93,1.15)	2.46	0.0140

Comparison with results reviewed in 2021

Figure 26:Comparison of rate ratios for safety outcomes up to April 2021 and including final data to month 46

Analysis of events up to April 2021



Final analyses including events up to month 46

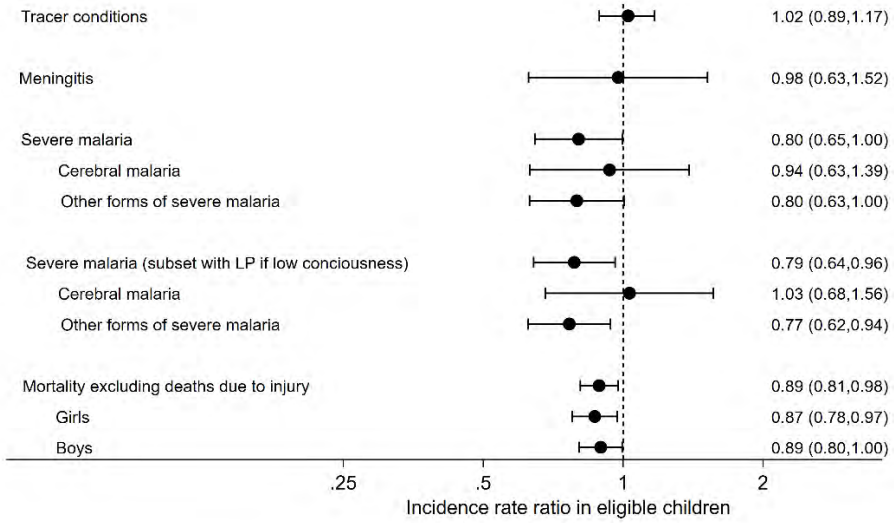
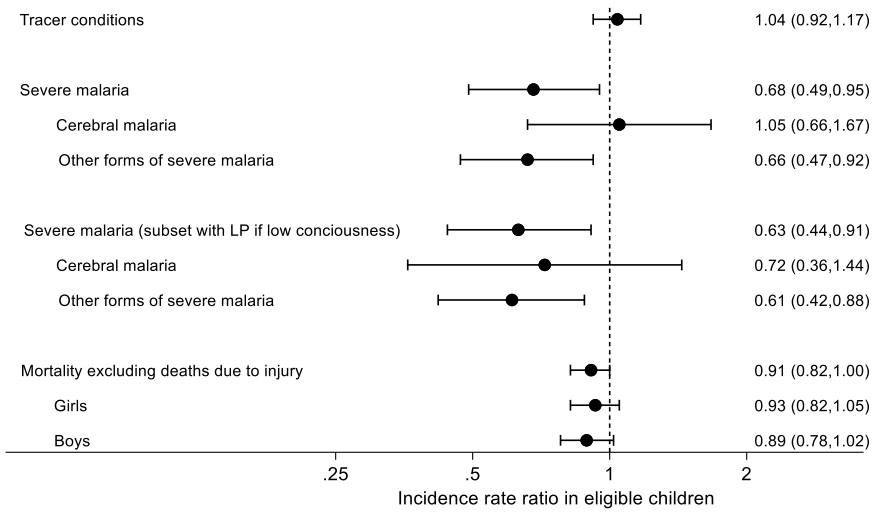
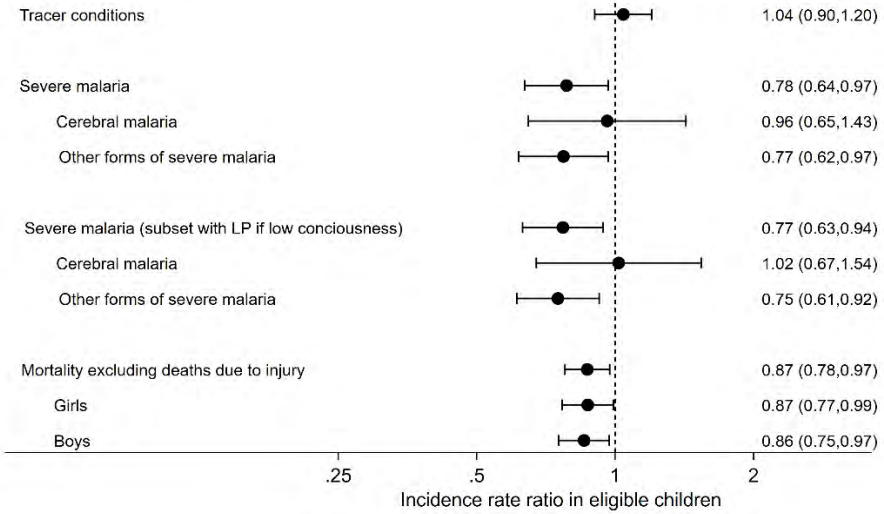


Figure 27: Comparison of rate ratios for impact outcomes up to April 2021 and including final data to month 46

Analysis of events up to April 2021



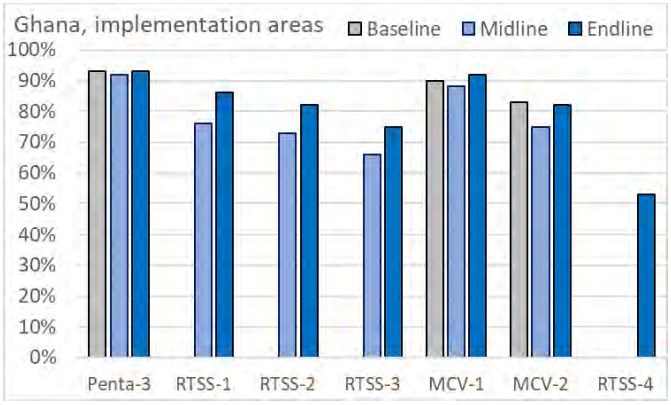
Final analyses including events up to month 46

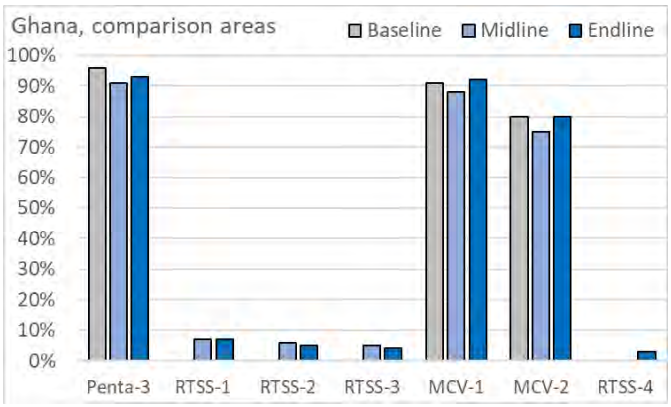


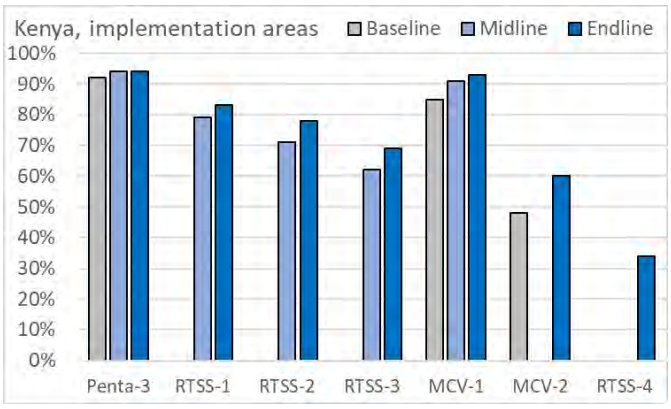
Coverage estimates

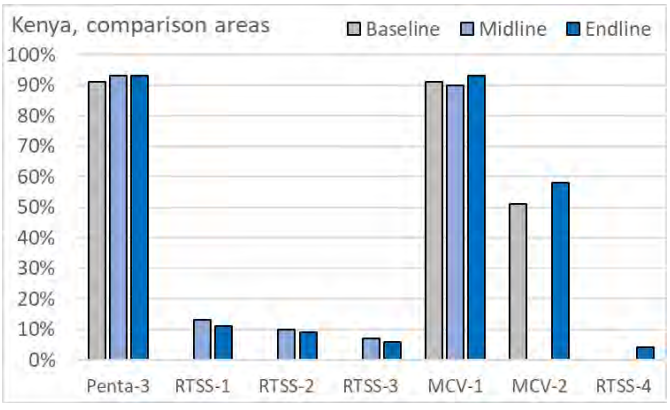
Details of vaccine coverage estimates will be presented in a separate annex. Briefly, relatively high levels of coverage of primary doses achieved soon after introduction in all countries. There was an improvement in coverage of the primary doses RTSS-1,2,3 between midline and endline surveys (an interval of about 16m). Coverage of the fourth dose was lower. Missed opportunities for RTS,S are evident from the higher coverage of the first dose of measles vaccine at 9m than of first dose of RTS,S. Coverage of Penta-3, MCV-1, MCV-2 were very similar in implementing and comparison areas, indicating no scope for confounding of RTS,S impact on mortality due to differences in uptake of these vaccines.

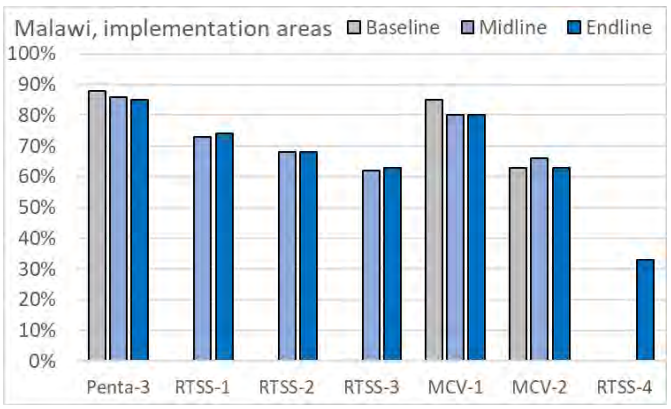
Table 23: Coverage of RTS,S doses 1-4, Penta-3, MCV1 and MCV2 in implementation and comparison areas in each country during the evaluation











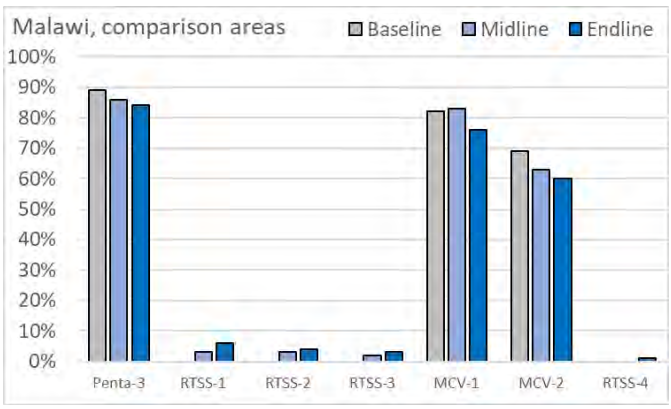
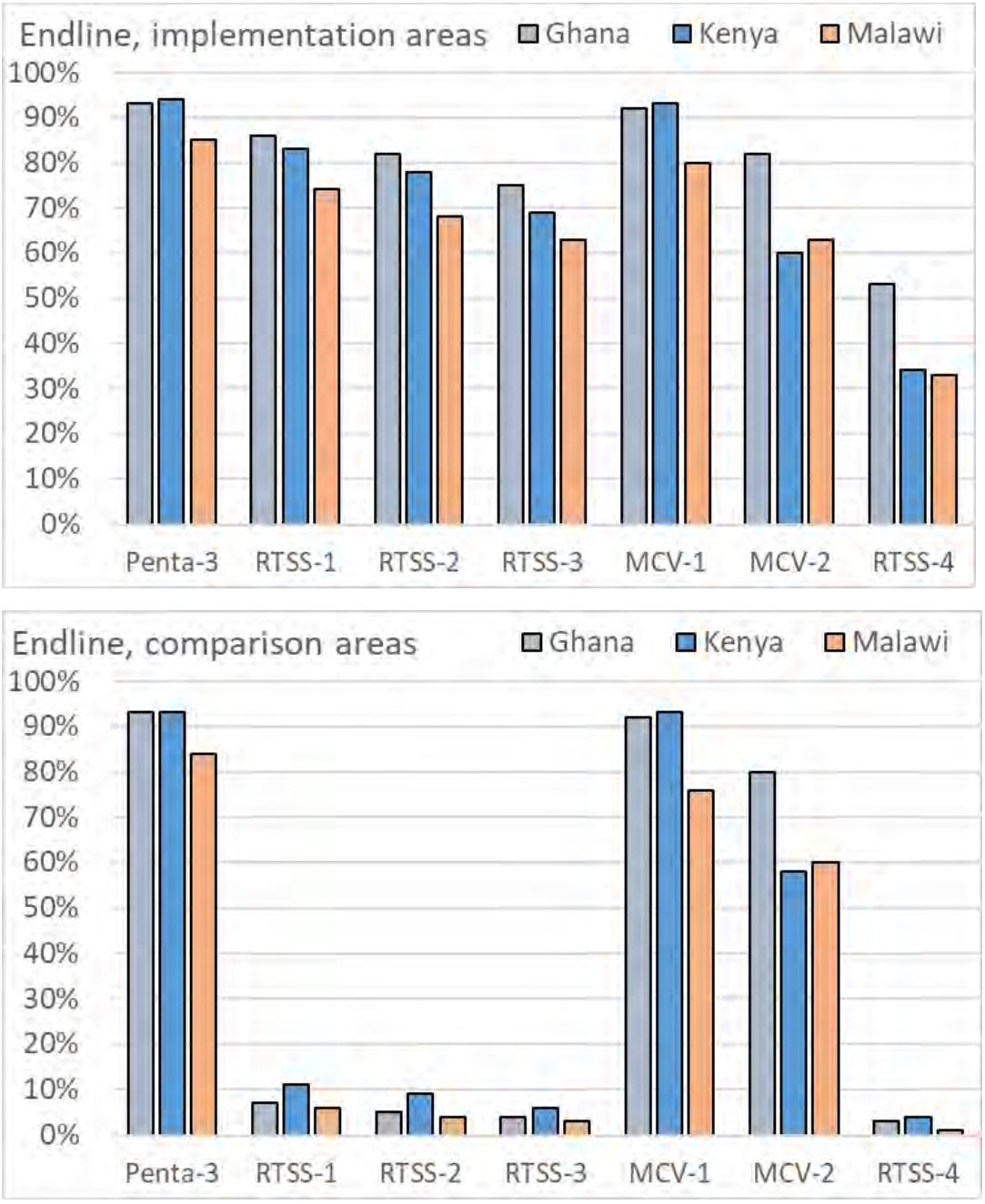


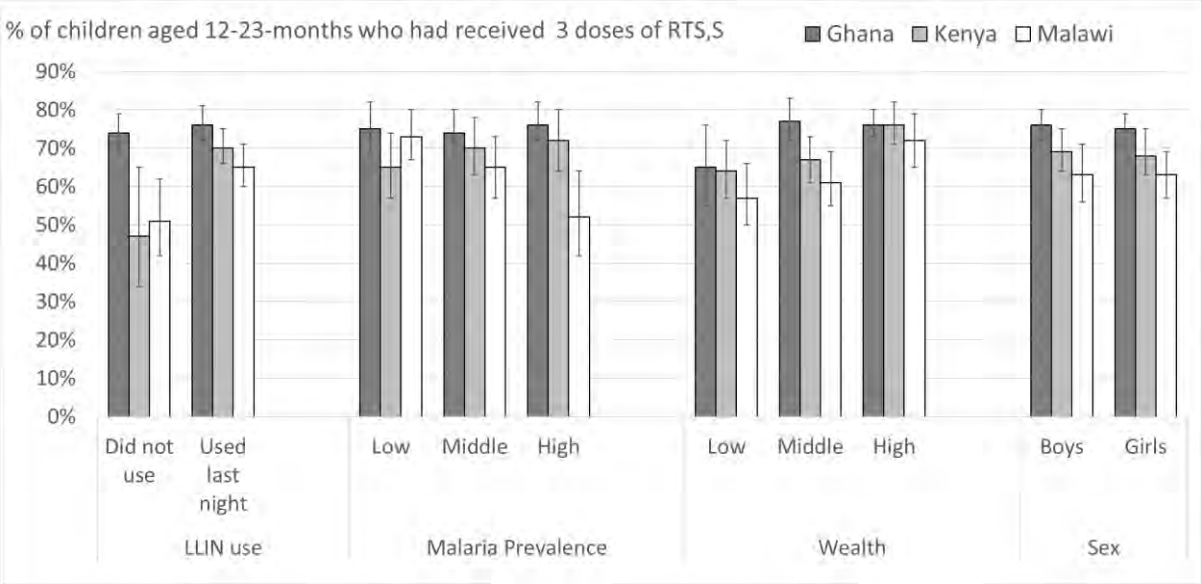
Figure 28 shows RTS,S coverage in each country in the endline surveys. There was similar coverage in each country in the first year of life, but with slightly lower uptake in Malawi. Coverage of MCV2 and RTSS-4 were higher in Ghana than in the other countries. Coverage of RTS,S in comparison areas (and hence contamination) was slightly higher in Kenya. In each country, coverage of other vaccines very similar in implementation and comparison areas.

Figure 28: Coverage of penta-3, MCV2 and RTS,S doses 1-4 in endline surveys in each country, in implementation and comparison areas



Shows uptake of RTS,S-3 in implementation areas in each country in relation to LLIN use, malaria prevalence strata as measured in baseline surveys, wealth ranking based on household assets, and sex. Although RTS,S uptake was lower in children who were not using an LLIN, nevertheless vaccine delivery was moderately effective in reaching those children, (74% of children not using an ITN received 3 doses of RTS,S in Ghana, 47% in Kenya, 51% in Malawi).

Figure 29: Equitability of uptake of RTS,S-3, in children 12-23months old surveyed in 2022

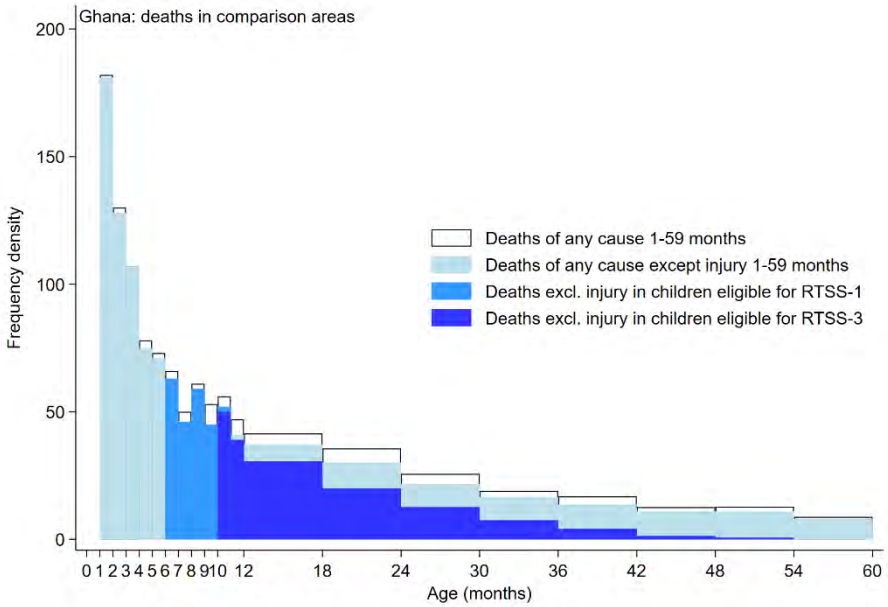


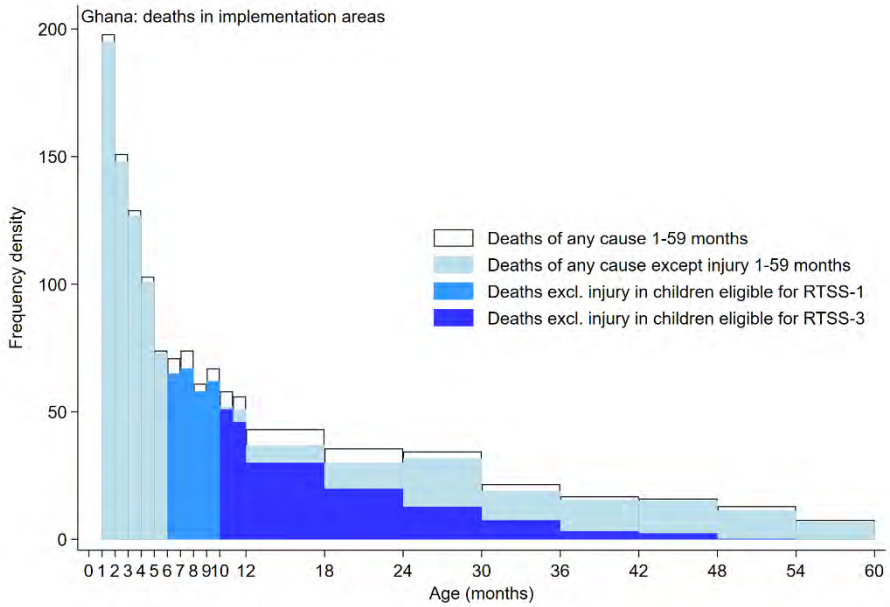
Annex 1: Age distributions of deaths and of hospital admissions with severe malaria

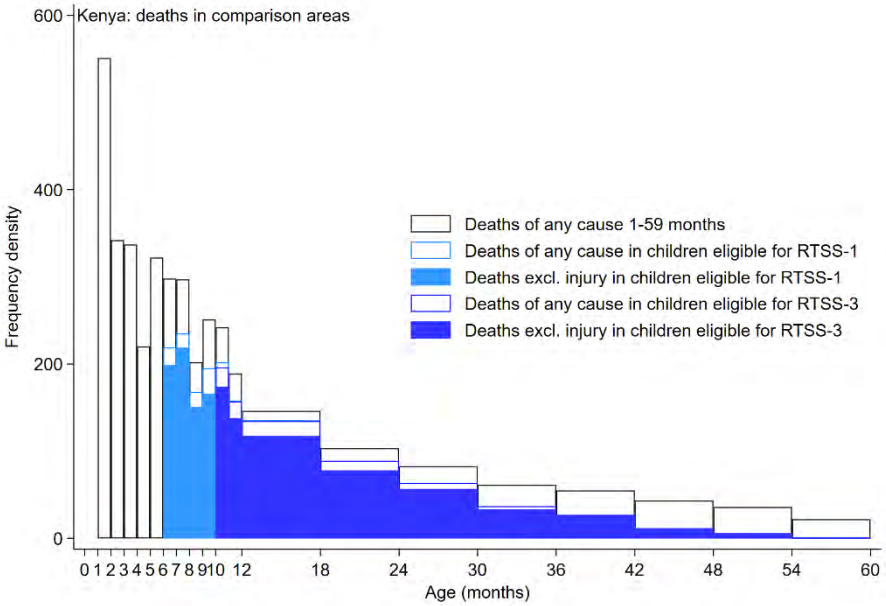
Age distributions

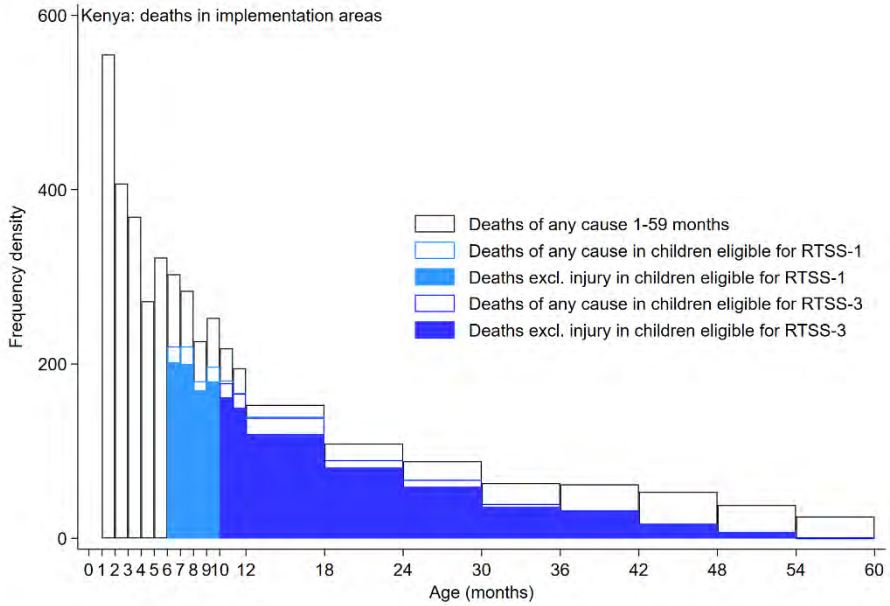
Age distribution of deaths in implementation and comparison areas in each country, showing:

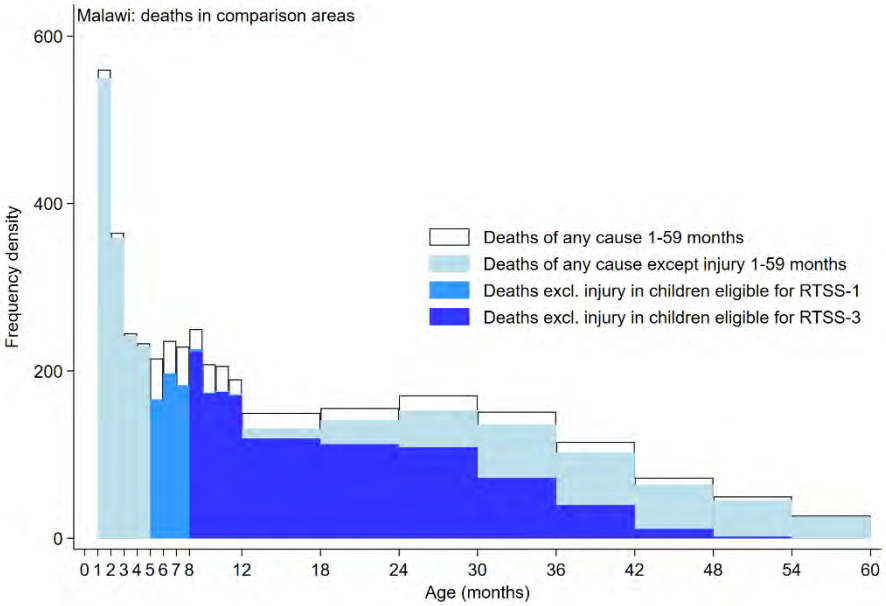
- deaths of any cause, 1-59 months
- deaths of any cause apart from injury, 1-59months
- deaths of any cause apart from injury, in children eligible for RTSS-1
- deaths of any cause apart from injury, in children eligible for RTSS-3 (the data used for impact assessment)

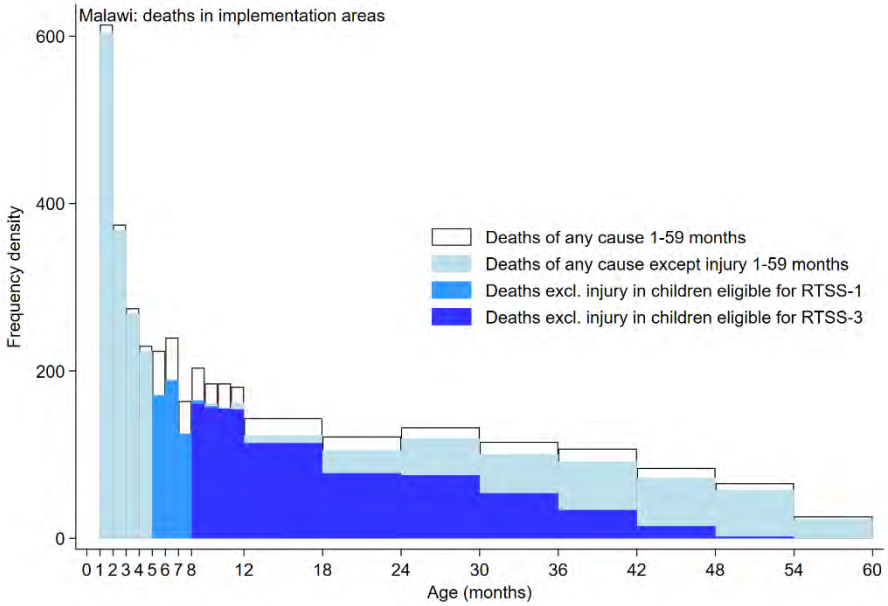

Ghana: deaths in comparison areas
Frequency density
200
150
100
50
0
Deaths of any cause 1-59 months
Deaths of any cause except injury 1-59 months
Deaths excl. injury in children eligible for RTSS-1
Deaths excl. injury in children eligible for RTSS-3
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)


Ghana: deaths in implementation areas
Frequency density
200
150
100
50
0
Deaths of any cause 1-59 months
Deaths of any cause except injury 1-59 months
Deaths excl. injury in children eligible for RTSS-1
Deaths excl. injury in children eligible for RTSS-3
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)


Kenya: deaths in comparison areas
Frequency density
600
400
200
0
Deaths of any cause 1-59 months
Deaths of any cause in children eligible for RTSS-1
Deaths excl. injury in children eligible for RTSS-1
Deaths of any cause in children eligible for RTSS-3
Deaths excl. injury in children eligible for RTSS-3
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)


Kenya: deaths in implementation areas
Frequency density
600
400
200
0
Deaths of any cause 1-59 months
Deaths of any cause in children eligible for RTSS-1
Deaths excl. injury in children eligible for RTSS-1
Deaths of any cause in children eligible for RTSS-3
Deaths excl. injury in children eligible for RTSS-3
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)


Malawi: deaths in comparison areas
Frequency density
600
400
200
0
Deaths of any cause 1-59 months
Deaths of any cause except injury 1-59 months
Deaths excl. injury in children eligible for RTSS-1
Deaths excl. injury in children eligible for RTSS-3
0 1 2 3 4 5 6 7 8 12 18 24 30 36 42 48 54 60
Age (months)


Malawi: deaths in implementation areas
Frequency density
600
400
200
0
Deaths of any cause 1-59 months
Deaths of any cause except injury 1-59 months
Deaths excl. injury in children eligible for RTSS-1
Deaths excl. injury in children eligible for RTSS-3
0 1 2 3 4 5 6 7 8 12 18 24 30 36 42 48 54 60
Age (months)

For each country:

Age distributions, in implementation and comparison areas, of:

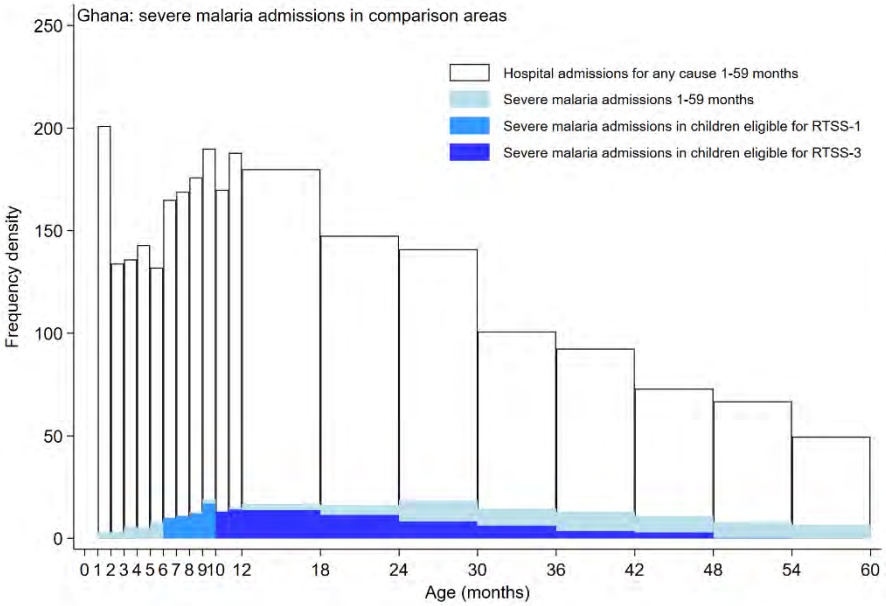
- all hospital admissions 1-59 months,
- severe malaria admissions 1-59 months, and
- severe malaria admissions in children eligible for RTSS-1
- severe malaria admissions in children eligible for RTSS-3

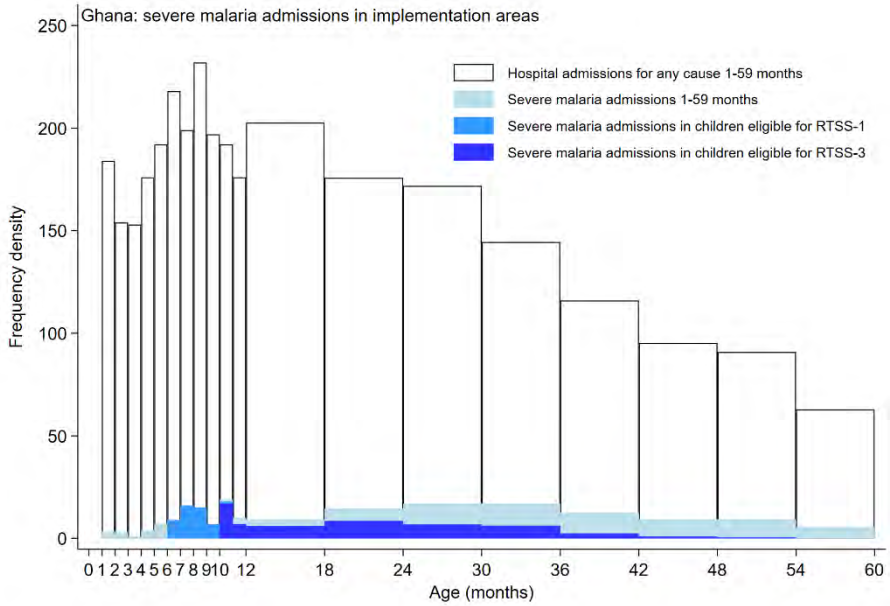
Age distributions, in implementation and comparison areas, of:

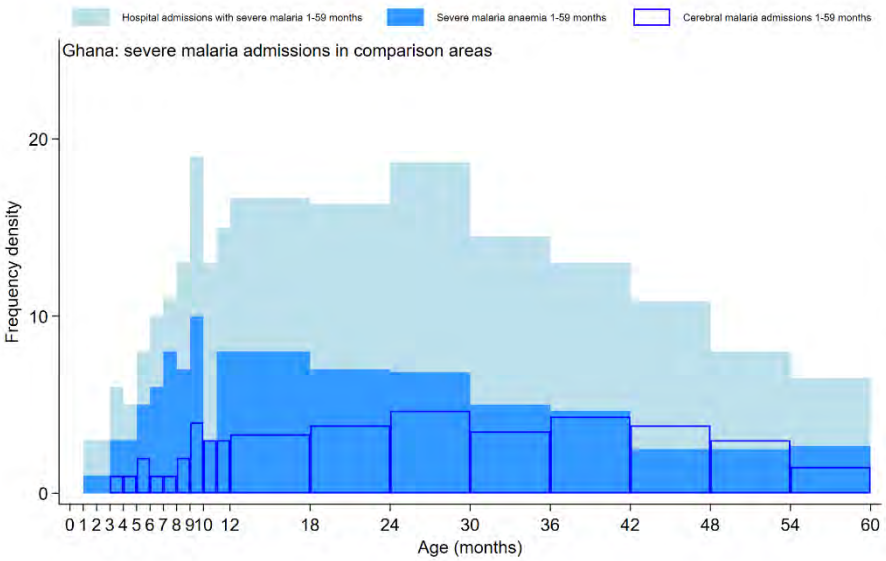
- severe malaria admissions 1-59 months, and
- severe malaria anaemia admissions 1-59 months
- cerebral malaria admissions in children 1-59 months

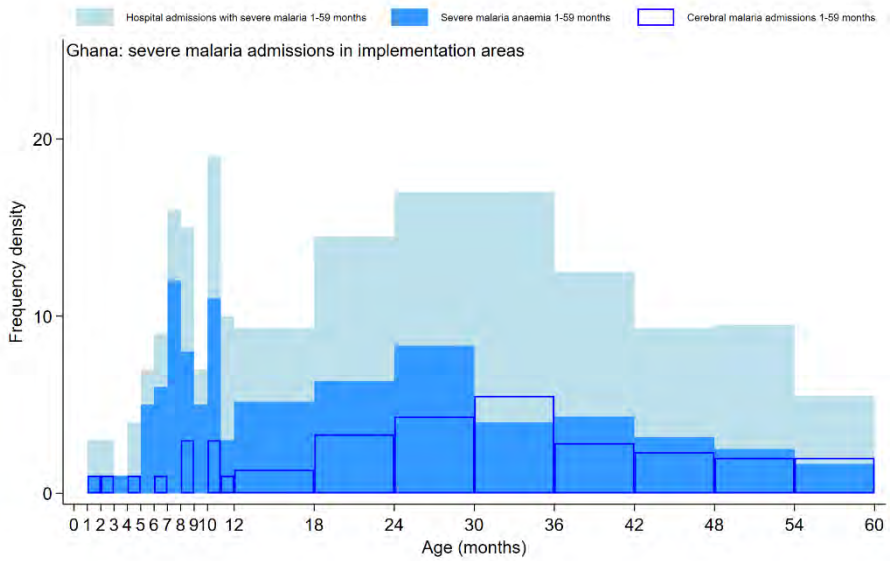
Age distributions, in implementation and comparison areas, of:

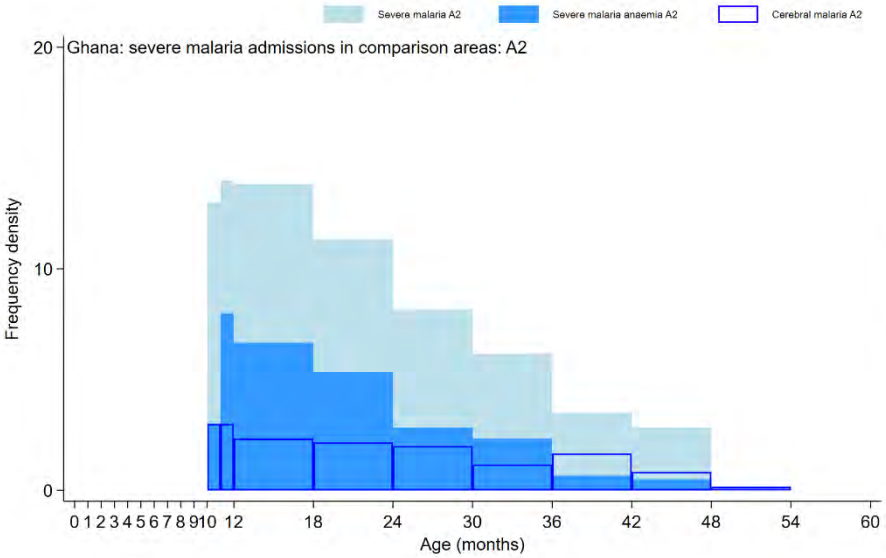
- severe malaria admissions in children eligible for RTSS-3
- severe malaria anaemia admissions in children eligible for RTSS-3
- cerebral malaria admissions in children eligible for RTSS-3

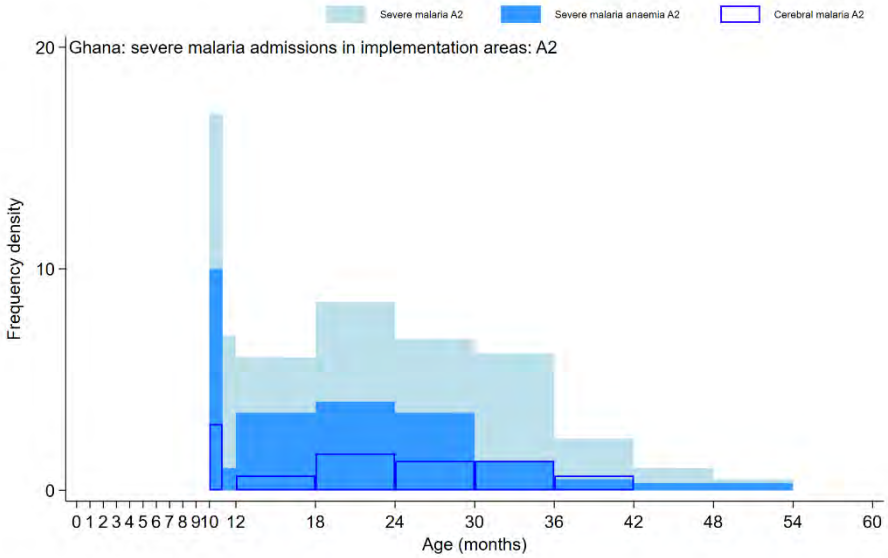

Ghana: severe malaria admissions in comparison areas
Hospital admissions for any cause 1-59 months
Severe malaria admissions 1-59 months
Severe malaria admissions in children eligible for RTSS-1
Severe malaria admissions in children eligible for RTSS-3
Frequency density
0
50
100
150
200
250
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

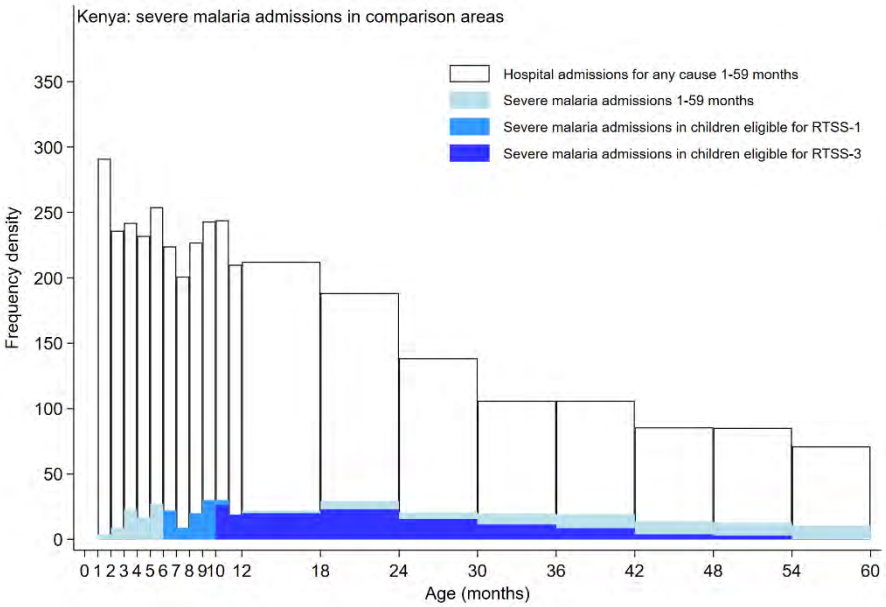

Ghana: severe malaria admissions in implementation areas
Hospital admissions for any cause 1-59 months
Severe malaria admissions 1-59 months
Severe malaria admissions in children eligible for RTSS-1
Severe malaria admissions in children eligible for RTSS-3
Frequency density
0
50
100
150
200
250
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

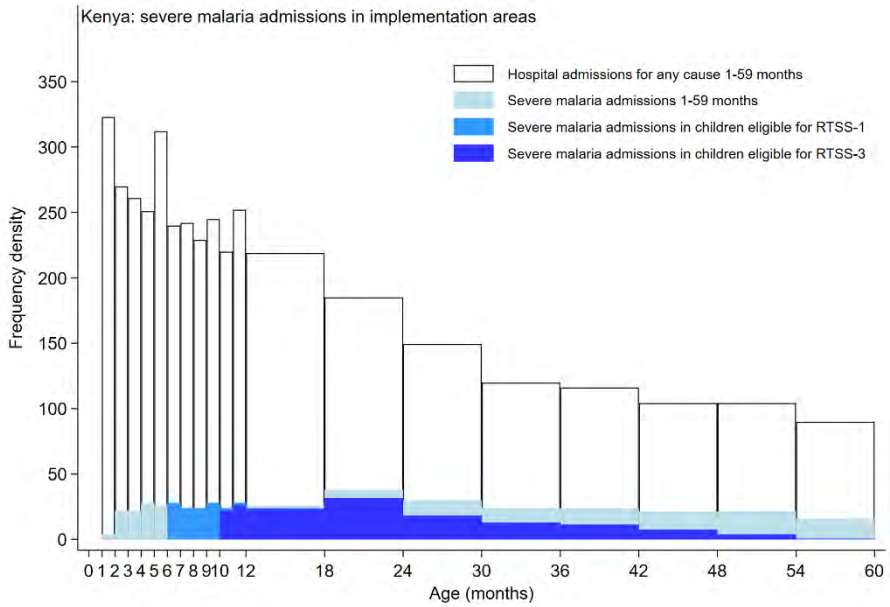

Hospital admissions with severe malaria 1-59 months
Severe malaria anaemia 1-59 months
Cerebral malaria admissions 1-59 months
Ghana: severe malaria admissions in comparison areas
Frequency density
0
10
20
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

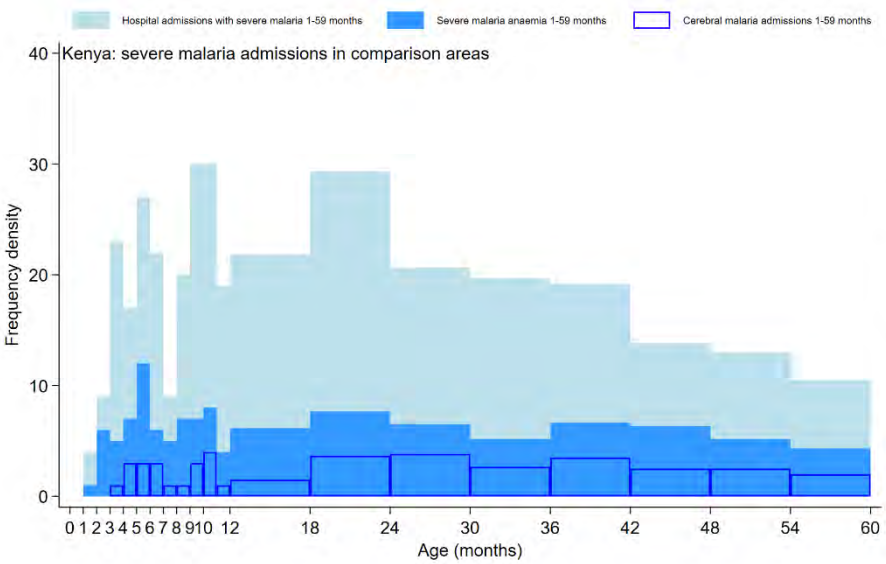

Hospital admissions with severe malaria 1-59 months
Severe malaria anaemia 1-59 months
Cerebral malaria admissions 1-59 months
Ghana: severe malaria admissions in implementation areas
Frequency density
0
10
20
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

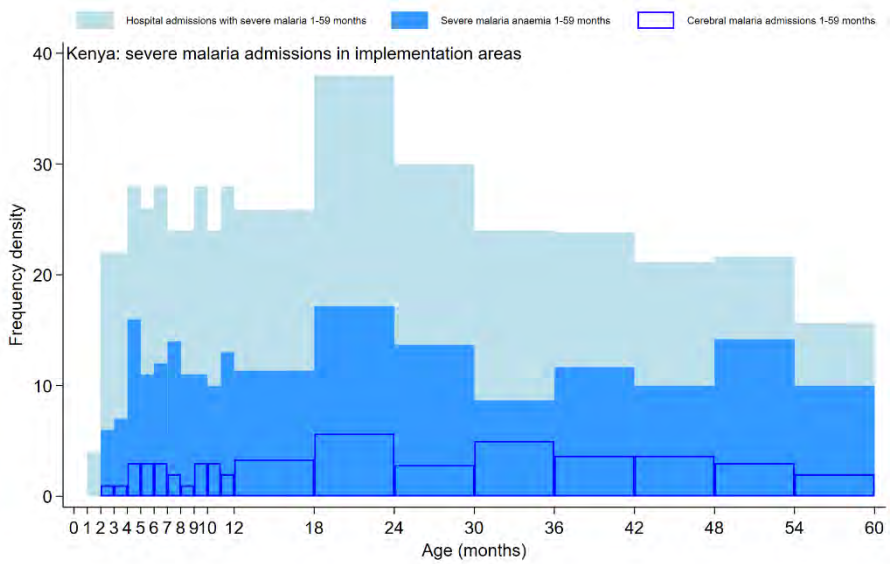

Severe malaria A2
Severe malaria anaemia A2
Cerebral malaria A2
Ghana: severe malaria admissions in comparison areas: A2
Frequency density
20
10
0
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

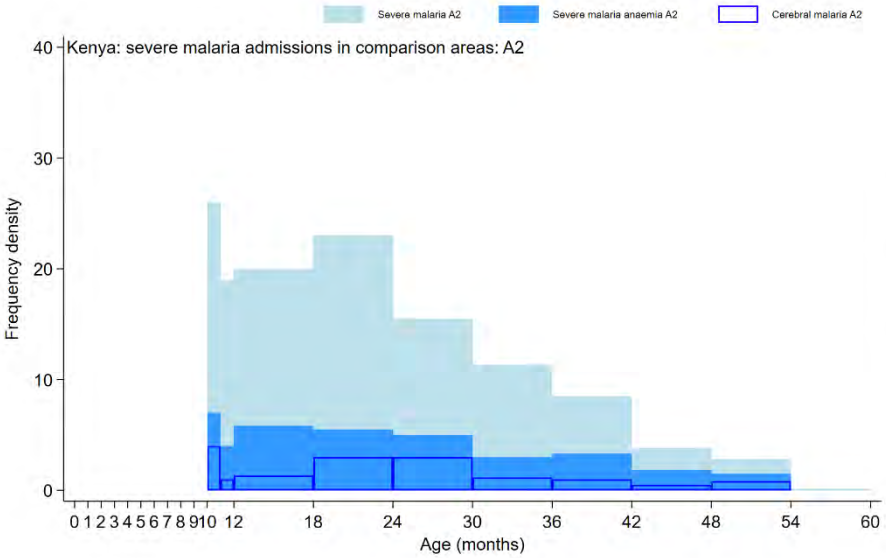

Severe malaria A2
Severe malaria anaemia A2
Cerebral malaria A2
Ghana: severe malaria admissions in implementation areas: A2
Frequency density
20
10
0
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

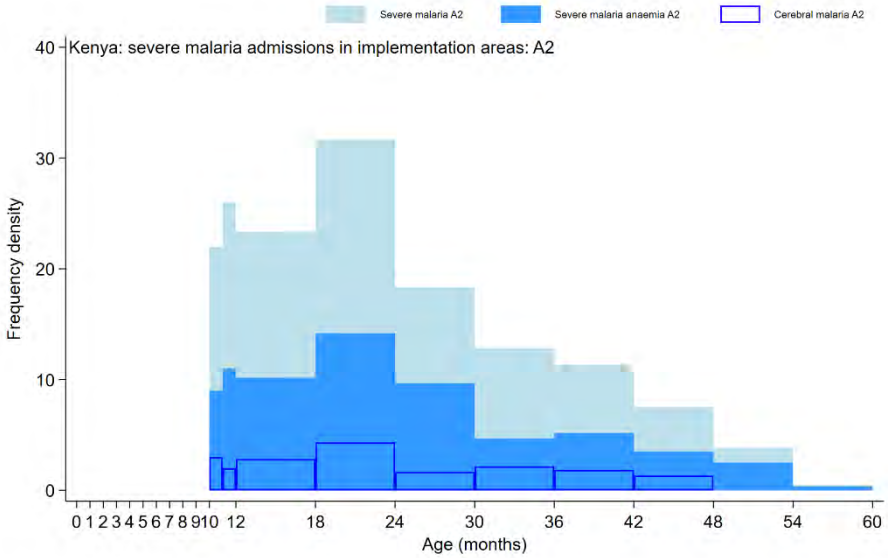

Kenya: severe malaria admissions in comparison areas
Hospital admissions for any cause 1-59 months
Severe malaria admissions 1-59 months
Severe malaria admissions in children eligible for RTSS-1
Severe malaria admissions in children eligible for RTSS-3
Frequency density
0
50
100
150
200
250
300
350
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

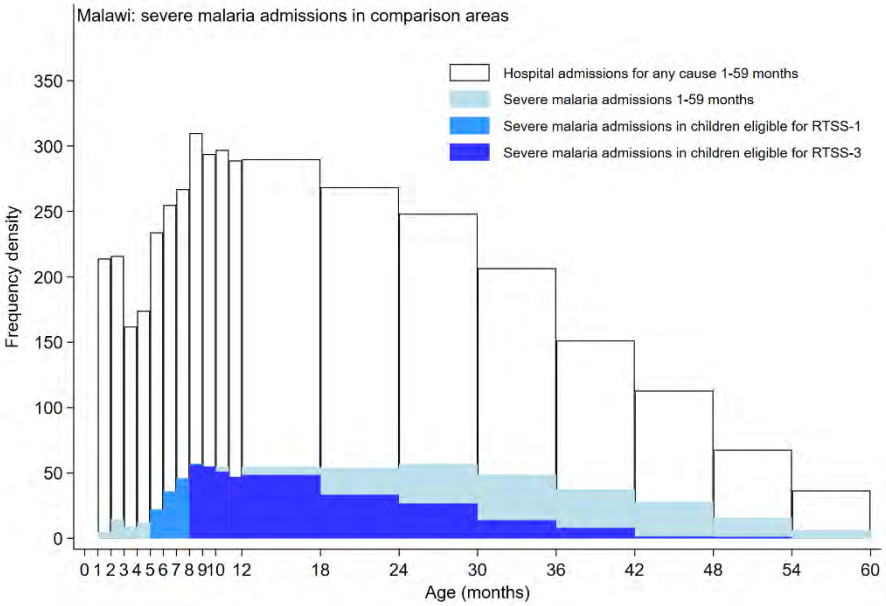

Kenya: severe malaria admissions in implementation areas
Hospital admissions for any cause 1-59 months
Severe malaria admissions 1-59 months
Severe malaria admissions in children eligible for RTSS-1
Severe malaria admissions in children eligible for RTSS-3
Frequency density
0
50
100
150
200
250
300
350
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

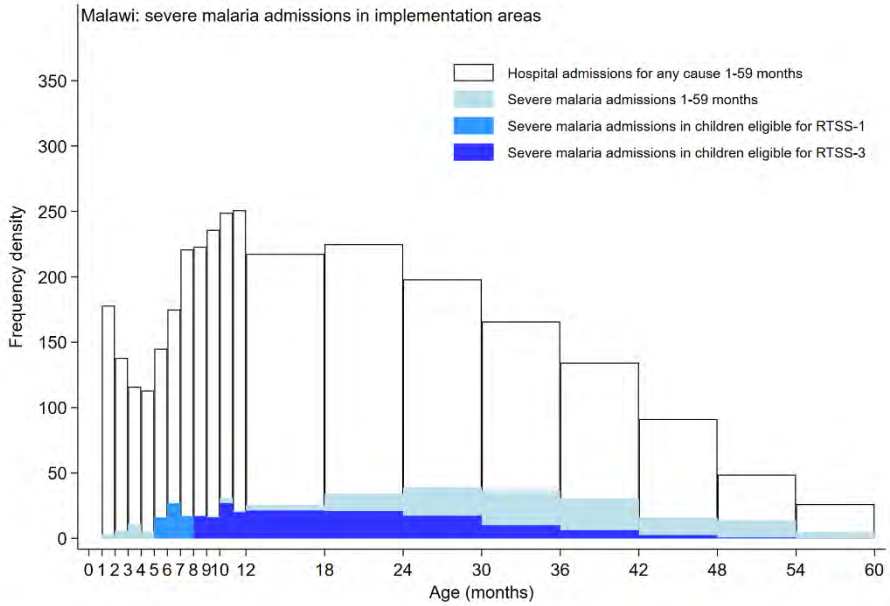

Hospital admissions with severe malaria 1-59 months
Severe malaria anaemia 1-59 months
Cerebral malaria admissions 1-59 months
Kenya: severe malaria admissions in comparison areas
Frequency density
0
10
20
30
40
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

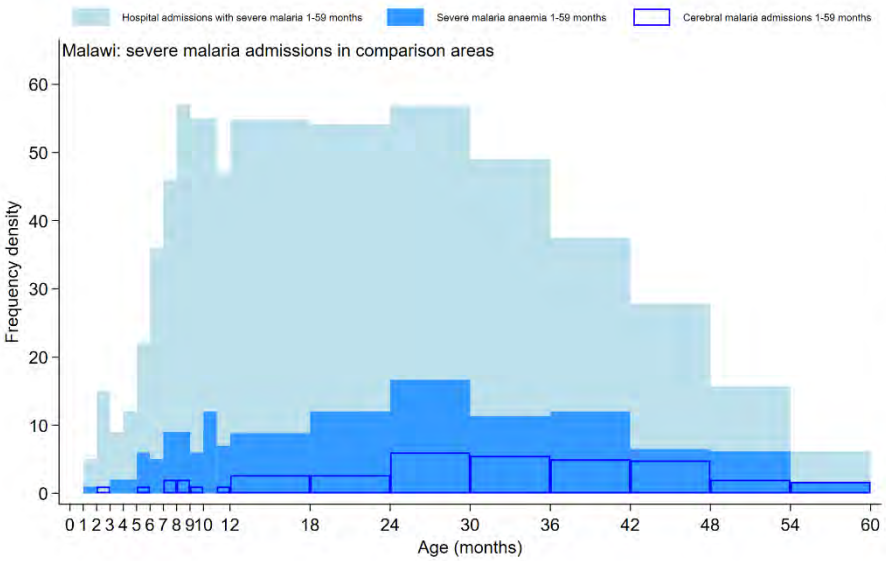

Hospital admissions with severe malaria 1-59 months
Severe malaria anaemia 1-59 months
Cerebral malaria admissions 1-59 months
Kenya: severe malaria admissions in implementation areas
Frequency density
0
10
20
30
40
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

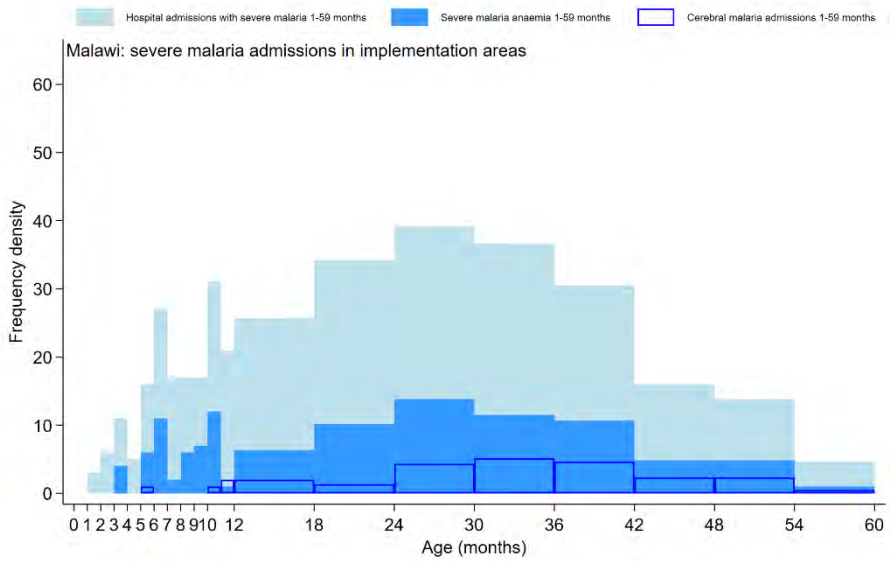

Severe malaria A2
Severe malaria anaemia A2
Cerebral malaria A2
Kenya: severe malaria admissions in comparison areas: A2
Frequency density
0
10
20
30
40
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

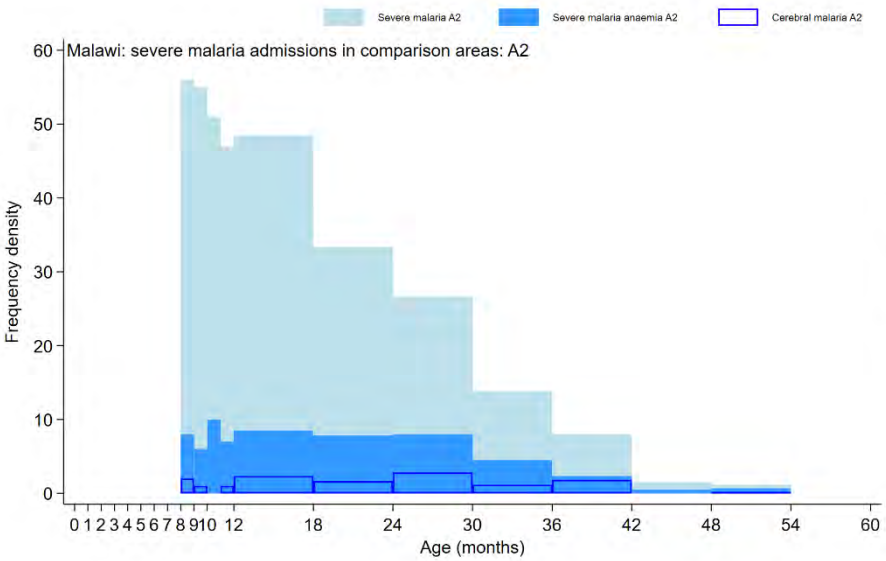

Severe malaria A2
Severe malaria anaemia A2
Cerebral malaria A2
Kenya: severe malaria admissions in implementation areas: A2
Frequency density
0
10
20
30
40
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

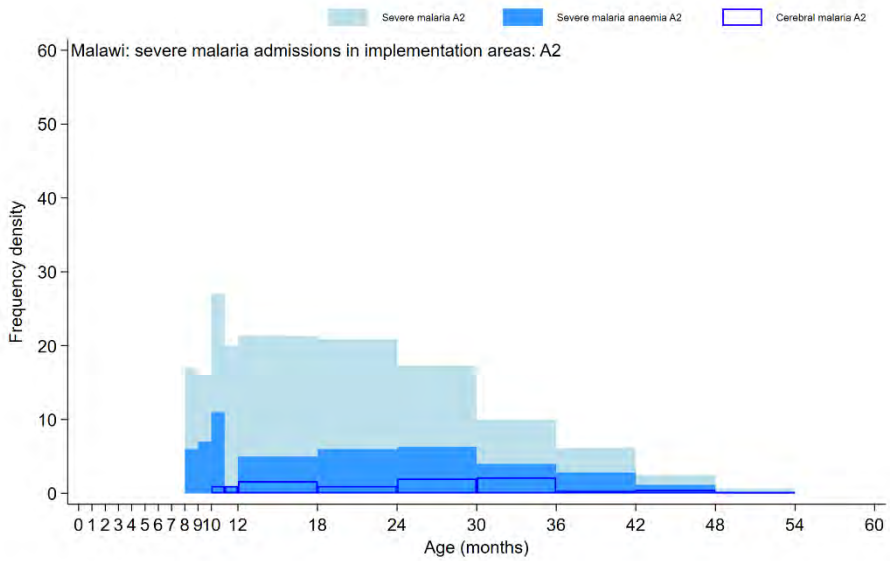

Malawi: severe malaria admissions in comparison areas
Hospital admissions for any cause 1-59 months
Severe malaria admissions 1-59 months
Severe malaria admissions in children eligible for RTSS-1
Severe malaria admissions in children eligible for RTSS-3
Frequency density
0
50
100
150
200
250
300
350
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)


Malawi: severe malaria admissions in implementation areas
Hospital admissions for any cause 1-59 months
Severe malaria admissions 1-59 months
Severe malaria admissions in children eligible for RTSS-1
Severe malaria admissions in children eligible for RTSS-3
Frequency density
0
50
100
150
200
250
300
350
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)


Hospital admissions with severe malaria 1-59 months
Severe malaria anaemia 1-59 months
Cerebral malaria admissions 1-59 months
Malawi: severe malaria admissions in comparison areas
Frequency density
0
10
20
30
40
50
60
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)


Hospital admissions with severe malaria 1-59 months
Severe malaria anaemia 1-59 months
Cerebral malaria admissions 1-59 months
Malawi: severe malaria admissions in implementation areas
Frequency density
0
10
20
30
40
50
60
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)


Severe malaria A2
Severe malaria anaemia A2
Cerebral malaria A2
Malawi: severe malaria admissions in comparison areas: A2
Frequency density
0
10
20
30
40
50
60
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)


Severe malaria A2
Severe malaria anaemia A2
Cerebral malaria A2
Malawi: severe malaria admissions in implementation areas: A2
Frequency density
0
10
20
30
40
50
60
0 1 2 3 4 5 6 7 8 9 10 12 18 24 30 36 42 48 54 60
Age (months)

Annex 2: Profile of deaths reported and included in analyses

Ghana			
	Notifications	8063	
Outside area		23	
		8,040	
	Implementation	Comparison	
	4,257	3,754	
Died before RTSS introduction	465	431	
Neonates	1,599	1,365	
>59m old	1	1	
No consent	20	16	
Missing key data			
	2,172	1,941	
VA done	2172	1941	
Death due to injury	102	104	
Cause of death missing (assumed not due to injury)	225	190	
Retained	2070	1837	
Buffer	54	64	
Expansion	16	9	
Eligible	818	775	
Not eligible	1197	998	
		TOTAL:	**3788**

In Ghana, 4178 deaths 1-59m from evaluation areas were reported, 36 without consent for VA were excluded. VAs were performed in all of the remaining 4113, 206 deaths due to injury were excluded, 415 with missing cause of death were retained with the assumption that death was not due to injury. Of the remaining 3907, 1593 were eligible, 2195 were not eligible and 119 excluded from analysis due to being just outside the eligible range or in cohorts eligible to receive vaccine in comparison areas.

Kenya			
	Notifications	15113	
Outside area		1573	
		13,540	
	Implementation	Comparison	
	6985	6555	
Died before RTSS introduction	5	4	
Neonates	0	0	
>59m old	0	0	
No consent	0	0	
Missing key data	24	2	
	6,956	6,549	13505
Excluded due to being just too old to be eligible (by <2m), or belonging to cohorts that would be eligible to receive vaccine in comparison areas	535	486	
Not eligible	2930	2666	
Eligible	3491	3397	
VA done	3341	3195	
Injury	180	157	
Eligible retained	3161	3038	
Not eligible	2930	2666	
		TOTAL:	**11795**

In Kenya, 13531 deaths were reported, 26 were excluded due to missing key information (age or sex), of the 13505 remaining, 5596 were noneligible, 1021 were excluded due to belonging to age cohorts that would be eligible in comparison areas, or were just too old to be eligible (<2m) , and 6888 were eligible for RTSS, of these VAs were performed in 6536 (94.9%). 337 deaths due to injury excluded, leaving 11795 included in analyses. In Kenya VAs were not performed in all non-eligible age groups, therefore in Kenya estimation of mortality rate ratios used total deaths of any cause in non-eligible age groups as the auxillary variable.

Malawi							
Facility notifications:		3047		Community notifications:		14474	
Outside MVIP area			418				0
		2,629				14474	
Implementation		Comparison		Implementation		Comparison	
	1343	1254			6889	7569	17055
Died before RTSS introduction	1	0			16	15	
Neonates	138	113			417	365	
>59m old	2	2			1	1	
No consent	0	0			8	17	
Missing key data	12	18			0	1	
	1190	1121			6447	7170	
VA done	993	967			6442	7169	
Death due to injury	24	27			407	379	
Cause of death missing(assumed not due to injury)	23	12			345	552	
Retained	1166	1094			6,035	6,790	
Buffer	47	39			293	267	
Eligible	581	537			2873	3661	
Noneligible	538	518			2869	2862	
		Eligible	3454	4198			
		Non-eligible	3407	3380			
				TOTAL:	**14439**		

In Malawi, 15984 1-59m from study area during evaluation period, 25 without consent for VA, 31 with missing key information (age, sex); of the remaining 15928, VAs or mini VAs were available for 15571 (97.8%). 837 whose death was due to injury were excluded. 897 community deaths with missing or unclear cause of death, and 351 facility deaths without VA, were included with the assumption that death was not due to injury. Of the 15085 remaining, 7652 were in RTSS-eligible age groups, 6787 were in non-eligible age groups, and the remaining 646 were excluded (because they were just outside the eligible age range by less than 2 months and thus might have been vaccinated, or because they were in age groups that, in comparison areas, had started to receive the vaccine).

Annex 2: Profile of admissions reported and included in analyses

Ghana			
	23824	admissions	
	2,407		Outside MVPE area
	Comparison	Implementation	
	11,451	12,373	
	0	0	Admitted before RTS,S introduction
	2,071	2,270	<1 month or >59 months of age
	983	982	Did not consent (or ineligible in Ghana)
	1,241	331	Outside MVPE sentinel area
	0	0	With missing age-eligibility or cluster
	7,156	8,790	Number of admissions that meet inclusion criteria
	15218/15946 (95.4%)		With RDT or blood film
	6,992	8,524	Strict definition of admission (overnight stay)
Severe malaria	741	666	
Eligible	361	264	
Non-eligible	349	367	
Buffer or belongs to age cohorts vaccinated in comparison areas	31	35	
Meningitis	38	38	
Eligible	19	19	
Non-eligible	18	18	
Buffer or belongs to age cohorts vaccinated in comparison areas	1	1	

Ghana: 19483 admissions 1-59m, 1965 without consent (most of these, consent not sought at the start of the evaluation), 1572 resided outside the defined sentinel surveillance areas, leaving 15946 included in analyses. RDT or blood film results were available for 15218/15946 (95.4%). There were 1407 cases of severe malaria, 66 were excluded (because they were just outside the eligible age range by less than 2 months and thus might have been vaccinated, or because they were in age groups that, in comparison areas, had started to receive the vaccine). There were 76 cases of meningitis, 2 of which were excluded.

Kenya			
	27272	admissions	
	1881		Outside MVPE area
	Comparison	Implementation	
	13367	12024	
	185	144	Admitted before RTS,S introduction
	331	373	<1 month or >59 months of age
	0	0	Did not consent (or ineligible in Ghana)
	2,772	476	Outside MVPE sentinel area
	0	0	With missing age-eligibility or cluster
	10,079	11,031	Number of admissions that meet inclusion criteria
	19317/21110 (91.5%)		With RDT or blood film
	9,979	10,929	Strict definition of admission (overnight stay)
Severe malaria	1276	1656	
Eligible	626	810	
Non-eligible	475	649	
Buffer or belongs to age cohorts vaccinated in comparison areas	175	197	
Meningitis	55	83	
Eligible	31	43	
Non-eligible	22	32	
Buffer or belongs to age cohorts vaccinated in comparison areas	2	8	

Kenya: 24358 admissions 1-59m, 3248 resided outside the defined sentinel surveillance areas, leaving 21110 included in analyses. RDT or blood film results were available for 19317/21110 (91.5%). There were 2932 cases of severe malaria, 372 were excluded which belonged to age cohorts eligible to receive RTSS in comparison areas or being just outside the upper age limit of eligibility. There were 138 cases of meningitis, 10 of which were excluded.

Malawi			
	21058	admissions	
		3,592	Outside MVPE area
	Comparison	Implementation	
	11750	9,308	
	0	0	Admitted before RTS,S introduction
	0	0	<1 month or >59 months of age
	1	0	Did not consent (or ineligible in Ghana)
	0	0	Outside MVPE sentinel area
	0	0	With missing age-eligibility or cluster
	11,750	9,308	Number of admissions that meet inclusion criteria
	18373/21058 (87.2%)		With RDT or blood film
	11,227	8,967	Strict definition of admission (overnight stay)
Severe malaria	2195	1392	
Eligible	1124	618	
Non-eligible	949	689	
Buffer or belongs to age cohorts vaccinated in comparison areas	122	85	
Meningitis	56	45	
Eligible	28	25	
Non-eligible	27	18	
Buffer or belongs to age cohorts vaccinated in comparison areas	1	2	

Malawi: 21058 admissions 1-59m. RDT or blood film results were available for 18373/21058 (87.2%). There were 3587 cases of severe malaria, 207 were excluded which belonged to age cohorts eligible to receive RTSS in comparison areas or being just outside the upper age limit of eligibility. There were 101 cases of meningitis, 3 of which were excluded.

Annex 3: Statistical methods

The statistical approach was defined in the Statistical Analysis plan [1], the Framework for Decision Making [2], and recommendations of the DSMB and PAG.

Analysis approach

Hospital and community mortality surveillance was maintained for children aged 1-59 months. This includes age groups eligible to receive RTS,S/AS01 vaccine, children who were too old to receive the vaccine, and children too young to have had their first dose. We take advantage of the data in non-eligible age groups to improve estimates of the incidence rate ratio in vaccine-eligible age groups. This adjusts for imbalance between the intervention and comparison areas, an important advantage when outcomes are detected in hospital and clusters are large relative to hospital catchments as constrained randomization may not be able to achieve good balance. A further advantage in our study is that reliance on person-time denominators, which can be challenging to estimate reliably, is avoided. The approach can also mitigate some of the loss of power arising from the clustered design. This is comparable to the use of paired data, for example the use of baseline data on the incidence of the outcome collected for a period prior to intervention in all clusters, for the same purpose of improving power and controlling confounding. A limitation of our approach is that indirect effects (i.e. intervention effects on the level of transmission) are not captured. However, this is not an issue for the safety outcomes, and for malaria outcomes any indirect effects of RTS,S/AS01 implementation in young children are likely to be negligible.

In each cluster, children aged 1-59 months who are admitted to hospital, and children reported to have died, can be classified into eligible or non-eligible groups. Classification into eligible (group A) and non-eligible (group B) is based on the age at admission or death and the date of RTS,S/AS01 introduction, not on whether they actually received RTS,S, so the classification can be applied in exactly the same way in comparison and implementation clusters.

The rate ratios can be estimated using the double ratio of counts estimator as follows. We denote the incidence rate in eligible age groups in implementation areas by n_{1A}/T_{1A}, where n_{1A} is the number of events and T_{1A} the person time. The rate in comparison areas is n_{0A}/T_{0A}. The corresponding rates in the non-eligible age groups are n_{1B}/T_{1B} and n_{0B}/T_{0B}. The rate ratio comparing the incidence in eligible age groups between implementation and comparison areas can be estimated by:

$$(n_{1A}/T_{1A})/(n_{0A}/T_{0A}) \times (n_{0B}/T_{0B})/(n_{1B}/T_{1B}),$$

where $(n_{0B}/T_{0B})/(n_{1B}/T_{1B})$ can be thought of as a correction term. This can be written: $(n_{1A}/n_{1B})x(n_{0B}/n_{0A}) \times (T_{0A}/T_{0B})x(T_{1B}/T_{1A})$. For practical purposes in this study, we assume that $(T_{0A}/T_{0B}) \approx (T_{1A}/T_{0A})$. (While it is possible to obtain approximate estimates of the population under 5yrs per cluster from census data, the proportion in each age group would be challenging to estimate separately in each area. If we apply the same national estimates of age structure to both areas, the person time term cancels out). The estimate of the rate ratio therefore becomes: $R=(n_{1A}/n_{1B}) / (n_{0A}/n_{0B})$, the ratio of the number of events in eligible to non-eligible age groups in implementation areas, divided by that in comparison areas. In this study we have used a bias-corrected version of the double ratio estimator, R'. Details of the bias correction are given in Ma *et al*. [3]

Ma *et al.* show that this estimator (R') of the incidence rate ratio is more efficient than the standard comparison of incidence rates per person time in the eligible age group, when there is a strong correlation between number of events in the eligible and non-eligible groups, and the coefficient of variation in the number of events per cluster is large. It is less efficient when the coefficient of

variation is small but importantly it provides a means of adjusting for randomization imbalance. By comparing the relative difference between eligible and non-eligible groups between implementation and comparison areas, we achieve some control for factors such as access to hospital, differences in diagnostic performance of hospitals, and differences in underlying disease burden, which may not be well balanced between intervention and comparison areas, but which are likely to be highly correlated between eligible and non-eligible age groups. With respect to mortality outcomes, the same approach can achieve some control for differences in completeness of mortality surveillance, and underlying mortality rates, between implementation and comparison areas, which are also likely to be highly correlated between eligible and non-eligible age groups.

The value of R' was calculated for each outcome in each country. The variance of log(R') is V(R)x(R/R')2, where V(R) is given by V(R1)+V(R0), where V(R1) and V(R0) are jackknife estimates of the ratios eligible to non-eligible events in implementation and comparison areas respectively. The estimates of log(R') for each country, were combined to give a pooled estimate, D= $\sum log\ R'_i$/V(log R'_i)/$\sum$1/V(log R'_i), i=1..3, with variance V(D)= 1/$\sum$[1/V(log R'_i)]. The pooled rate ratio was calculated as exp(D) and the 100(1-α)% confidence interval given by exp[D+/- $t_{\alpha/2,C-6}$√V(D)], with df equal to the total number of clusters C less 2x3=6. To test for interaction by country (Cochran's Q test), $\sum$[(D – $logR'_i)^2$/V($logR'_i$)] is referred to the χ^2 distribution with 2 degrees of freedom.

The female:male mortality ratio in eligible age groups in implementation areas was compared to the female:male mortality ratio in eligible age groups in comparison areas in a similar way. Denoting the total number of deaths in girls in group A in implementation (j=1) and comparison areas (j=0) by $g_{j,A}$, and in boys by $b_{j,A}$, and the corresponding number in group B by $g_{j,B}$ and $b_{j,B}$, the female:male mortality ratio in group A is $R_{j,A}$= $g_{j,A}/b_{j,A}$ and in group B, $R_{j,B}$=$g_{j,B}/b_{j,B}$, and the double ratio ($R_{j,A}/R_{j,B}$) is then compared between implementation and comparison areas. W=log($R_{1,A}/R_{1,B}$) - log($R_{0,A}/R_{0,B}$), is an estimate of the log of the ratio of the female:male mortality ratios in eligible age groups in implementation areas to that in comparison areas. This is the (log) of the 'r5' estimator of Ma et al. We have used the bias-corrected version of this estimator. For pooled analysis over the three countries, as before we will have a (bias-corrected) estimate of W for each country, W_1, W_2 and W_3, the combined estimate is then $\overline{W}$ = $\sum W_i/V(W_i)/\sum 1/V(W_i)$, i=1..3, and the variance is V($\overline{W}$)= 1/$\sum$[1/V(W_i)]. The final ratio of female:male mortality ratios is given by exp($\overline{W}$) and the 100(1-α)% confidence interval by exp[$\overline{W}$ +/- $t_{\alpha/2,C-6}$√V($\overline{W}$)], with df equal to the total number of clusters C less 2x3=6. Interaction by country is tested as described above.

We do not explicitly adjust for covariates in these analyses. Randomization was constrained to ensure balance with respect to measured cluster-level covariates, and as explained above the use of data for non-target age groups allows control for confounding with respect to measured and unmeasured cluster-level covariates. We have therefore taken steps to minimize imbalance but it is possible that some confounding remains.

Changes to data and methods since the 2021 WHO report: Preliminary results from this study were reviewed by WHO in 2021 [4]. The following changes to data and methods were made since the original statistical report: In Ghana the definition of eligibility in our analysis was changed to reflect that children were eligible for their first dose if aged 6 or 7 months (not just at 6 months as previously assumed); deaths occurring in April 2019 have been included (these data were incomplete at the time of the 2021 report); the definition of cerebral malaria was amended after review by an expert panel, to exclude patients with a clear alternative explanation for low conciousness (this resulted in 3 cases being excluded, all of them in non-eligible age groups, one with head injury, one with alcohol intoxication, one with seizure disorder). Two changes to the statistical methods were

made based on the findings of Ma *et al.*, a) we use the jackknife estimator of variances of ratios, in place of the standard linearised estimator which underestimates the variance, and b) we use bias-corrected estimators for incidence rate ratios. Despite these changes the analytic findings and conclusions remain consistent with those reported in the 2021 report [4].

	Oct 2021 results			**Updated estimates**		
	No. of events in eligible children			No. of events in eligible children		
	Imple-menting	Comp-arison	Rate ratio (95%CI)	Imple-menting	Comp-arison	Rate ratio (95%CI)
Children eligible for at least one dose of RTS,S (safety)						
Meningitis	27	24	0.81 (0.43,1.55)	28	25	0.63 (0.22,1.79)
Severe malaria broad	558	847	0.76 (0.61,0.95)	568	845	0.73 (0.55,0.96)
Cerebral malaria	49	54	0.96 (0.61,1.52)	52	56	1.03 (0.61,1.74)
Other forms of severe malaria	509	793	0.73 (0.58,0.92)	516	799	0.70 (0.53,0.92)
Interaction			1.16 (0.77,1.77)			1.34 (0.80,2.23)
Severe malaria strict	450	690	0.71 (0.56,0.91)	459	698	0.69 (0.50,0.94)
Cerebral malaria	25	30	0.77 (0.44,1.35)	27	32	0.82 (0.39,1.72)
Other forms of severe malaria	425	660	0.70 (0.54,0.89)	432	666	0.66 (0.48,0.90)
Interaction			0.94 (0.57,1.56)			1.01 (0.50,2.07)
Mortality (both sexes)						
Mortality, girls	1060	986	0.98 (0.87,1.09)	1166	1097	0.95 (0.85,1.07)
Mortality, boys	1091	1143	0.91 (0.80,1.04)	1220	1265	0.91 (0.80,1.04)
Interaction			1.08 (0.93,1.25)			1.03 (0.88,1.21)
Children eligible for three doses of RTS,S (impact)						
Severe malaria broad	418	689	0.70 (0.54,0.92)	427	697	0.68 (0.49,0.95)
Severe malaria strict	342	549	0.65 (0.49,0.86)	333	557	0.63 (0.44,0.91)
Mortality (both sexes)	1421	1443	0.93 (0.84,1.03)	1589	1631	0.91 (0.82,1.00)
Mortality, girls	691	662	0.98 (0.86,1.10)	766	754	0.93 (0.82,1.05)
Mortality, boys	730	781	0.90 (0.78,1.04)	823	877	0.89 (0.78,1.02)
Interaction			1.08 (0.92,1.28)			1.02 (0.86,1.21)

Analysis of household surveys: In each country, survey-weighted coverages of key indicators (pentavalent dose 3, measles dose 1, vitamin A within the last 6 months, LLIN use, and full basic vaccination coverage)were estimated amongst children aged 12 to 23 months (inclusive) in both vaccinating and comparison areas in the baseline and midline surveys. Coverage of RTS,S dose 3 was also estimated within both vaccinating and comparison areas in the midline surveys in all countries amongst children aged 12 to 23 months (inclusive). Vaccination status and receipt of vitamin A in the last six months was determined from home-based records where available, or through caregiver recall where the HBR was not available (recall responses were not collected in the Ghana baseline survey, and Vitamin A coverage was determined from HBR only in both surveys in Ghana, recall only in both surveys in Malawi, and by recall and HBR in both surveys in Kenya). Children were considered vaccinated if the HBR was available and dates were recorded (regardless of the validity of these dates with respect to the timing of doses in relation to the child's age and to other doses), or if the HBR was unavailable and the caregiver reported receipt of the vaccine dose. Children were considered unvaccinated if the HBR was available, but dates were not recorded, or if the HBR was unavailable and the caregiver reported that the child had not received the vaccine dose. Children were excluded from coverage estimates of specific vaccination indicators where the HBR was not available, and the recall response for ever having received a vaccination for the antigen was either missing or 'don't know', or 'Yes' but the response for the number of doses was missing. Children were excluded from coverage estimates of Vitamin A within the last 6 months where the HBR was not available, and the recall response was either missing or 'don't know'. Full vaccination coverage was defined as receiving all doses of the basic EPI vaccines by the time of the survey (BCG at birth, OPV x3 (excluding birth dose), Pentavalent x3, and one dose of measles. Children who received IPV at 14 weeks in place of OPV3 were considered fully vaccinated for Polio (IPV status was only available by recall in Malawi, and not available in Kenya). LLIN use was determined from caregiver recall, and children were excluded from coverage estimates if the response to sleeping under a net last night was either "don't know" or missing.

Vaccine recall questions were asked differently in each country. In Ghana, caregivers were asked if they had received each specific dose (dose 1? y/n; dose 2? y/n; dose 3? y/n). Where a caregiver reported that the child had received a later dose but not received an earlier dose for the same antigen, the later doses were shifted down and counted as if they were the earlier dose (e.g. a child reported to have received Pneumococcal conjugate vaccines (PCV) dose 2 but not dose 1 or 3 is considered to have only PCV dose 1). In Kenya, caregivers were asked if the child had ever been vaccinated against each antigen, and if yes, then asked how many doses they had received. In Malawi, caregivers were asked if the child had ever been vaccinated against each antigen, and then if yes, asked if they had received each specific dose (dose 1? y/n; dose 2? y/n; dose 3? y/n). Where a caregiver reported that the child had received a later dose but not received an earlier dose for the same antigen, the later doses were shifted down and counted as if they were the earlier dose (e.g. a child reported to have received PCV dose 2 but not dose 1 or 3 is considered to have only PCV dose 1).

For second year of life vaccines (MCV2 and RTSS4) it is useful to report the 'stepped-down' estimate (the % of children that had received 2 or 4 doses), and the % of children that received a dose after the first second year of life. Thus a child could receive RTSS at age 24m without having previously received all 3 primary doses.

Age ranges for reporting are 12-23m (first year of life vaccines; children surveyed who had received the dose (not necessarily by 12m); and for MCV" and RTS,S4, the reporting age range is a range of 12m starting from 6m after the recommended age for the dose:

Recommended age: 15m Evaluation range: 21m-32m

Recommended age: 18m Evaluation range: 24m-35m

Recommended age: 22m Evaluation range: 28m-39m

Recommended age: 24m Evaluation range: 30m-41m

If by the time of the survey, children at the upper end of the age range would not have been eligible to receive RTSS, the age range was truncated.

We accounted for the survey design using survey poisson regression, with sampling weights reflecting the probability of selection into the survey, and response rates, using the survey (svy) commands in Stata. Survey poisson regression was used to estimate coverage, and the relative difference in coverage between the midline and baseline surveys in the vaccination arm adjusting for the same difference in the comparison arm. Survey poisson regression was also used to estimate the association between LLIN use, malaria prevalence, wealth category (split at tertiles of the wealth index), gender, and coverage of dose 3 of RTS,S in the midline survey.

Power calculations

In the phase 3 trial, 21 cases of meningitis occurred in RTS,S/AS01 recipients, a rate of 1.05/1000, and one case in control children, a rate of 0.1/1000; the rate ratio was 10.5 (95%CI 1.41,78.0). There were 43 cases of cerebral malaria in RTS,S/AS01 recipients and 10 cases in control children, a rate ratio of 2.15 (1.1,4.3). There were 67 deaths in girls who received RTS,S/AS01 and 17 in girls in the control group, a mortality ratio of 2, while in boys there were 45 deaths in RTS,S/AS01 recipients and 29 in boys in the control group, mortality ratio 0.8. The relative mortality ratio (girls:boys) was 2.61 (95%CI 1.29,5.26). For safety outcomes, the research question was whether the excess of cases of meningitis and cerebral malaria, and the excess mortality in girls, which were unexplained, were causally related to the vaccine. We therefore estimated the number of events required for 90% power to detect rate ratios for these safety signals, if they were of the magnitude observed in vaccinated children the phase 3 trial, after allowing for dilution due to vaccine coverage being less than 100%, and allowing for effects of contamination. We also allowed for potential confounding whereby, in the case of meningitis, if RTS,S/AS01 recipients have also received Hib and pneumococcal vaccine, which protect against meningitis, this could to some extent mask a safety signal (in practice this was a small effect due to the fact that vaccine-preventable serotypes were relatively uncommon causes of meningitis). Assuming 5% vaccination coverage in comparison areas, we calculated that the meningitis signal in the phase 3 trial would equate to a rate ratio of 4 if vaccine coverage was 60% in implementation areas, or 5 if vaccine coverage was 70%. Equivalently, the cerebral malaria signal would equate to a rate ratio of 1.7 to 2, and the mortality signal in girls to a mortality ratio of 1.4 to 1.6. (These values were used in the power calculations. More accurate estimates were made later, when data on RTS,S/AS01 coverage from the household surveys was available). Power was estimated using simulations in which the number of events in cluster j and age group k, was a random value from a poisson distribution with mean equal to $r.k_{ij}y_{jkt}\theta_{jk}$, where r is the assumed underlying incidence rate, k_{ij} is an adjustment factor for the relative access to hospital *i* for cluster *j*, y_{jkt} is the person time in cluster *j* in age group *k* at time *t*, and θ_{jk} is the rate ratio for the outcome associated with vaccine introduction, for cluster *j* and age group *k*. $\theta_{jk}=\theta$ for vaccine-eligible age group in clusters in the intervention arm, $\theta_{jk}=1$ otherwise. *kij* represents the relative access to hospital *i* from cluster *j*, *kij*=1 for the cluster in which the hospital is located, 0<*kij*<1 for other clusters in the catchment area, and *kij*=0 for other clusters. *k* values were estimated for each hospital, using data on the number of admissions under 5 yrs from

each cluster in the catchment area, for a period before intervention started: *kij*=(*aij*/*nj*)/(*ai**/*n**), *aij* = admissions to hospital *i* from cluster *j*, *nj*=population in cluster *j*; *ai** is the number of admissions to hospital *i* from the cluster the hospital *i* is located in, and *n** is the population of that cluster. For each simulation, the ratio of the number of events between the two age groups was compared between arms using a ratio estimator. The simulation was repeated 10,000 times, to determine the distribution of the estimate of θ and of the 95% confidence limits. Simulations were done for null value (θ =1) for a range of assumed underlying incidence rates, and for various values of θ >1 (safety) and θ <1 (impact) to estimate power to detect or exclude effects of interest, using estimates of the cluster populations in each age group. Simulations were repeated for a range of values of the underlying incidence rate, for various time points, in order to determine the number of events that would be required to have adequate power, at each time point. We estimated that 90 cases of meningitis and 400 cases of cerebral malaria, in eligible and non-eligible age groups combined, would be required for 90% power, and that 2000 deaths in vaccine-eligible ages would allow 90% power to detect a gender interaction. For impact outcomes, we estimated that a total of 3000 severe malaria cases (eligible and non-eligible groups combined) would be required for 80% power to detect a reduction of 24%, and 4000 for 90% power. Based on event rates observed in the first year of the evaluation we anticipated that the required number of events for each outcome would have accrued by approximately the same time, at about 24 months after the first introduction of the vaccine (April 2021), if data for all three countries were combined.

Comparison of rate ratios for safety outcomes with safety signals from the phase 3 trial:

Data on uptake of RTS,S/AS01 from the coverage surveys undertaken about 18 months after introduction of the vaccine were used to recalculate estimates of dilution factors, these were then used to calculate modelled predictions of the rate ratios that would be expected if the safety signals observed in the phase 3 trial were to occur during the MVIP.

If the safety signals observed in the phase 3 trial occurred in the MVIP, the magnitude of the effect we would observe would be smaller than in the phase 3 trial, since not all children will have received the vaccine. Any effects would be further diluted if there was contamination due to some children in comparison areas, or children in non-eligible age groups, receiving the vaccine. We used estimates of coverage and timing of malaria vaccine doses from the midline household surveys in each country to estimate the person time in vaccinated children as a proportion of total person time, and the degree of contamination. These estimates were used to derive predictions of the expected effect in each country, if the safety signals in the phase 3 trial were to occur in the MVIP, using data up to April 2021, in Table 24 below. The average of these effects for each outcome is shown in column 3 of the table, and this is compared with the observed rate ratio from the MVIP (column 4) using a z-test. For meningitis and for the interaction of vaccine impact on mortality by sex, the estimates obtained in the MVIP were inconsistent with the signal in the phase 3 trial, i.e. the hypothesis that the signal observed in the phase 3 trial occurred in the MVIP, given the degree of dilution that was estimated, was rejected ($p<0.05$). For the two definitions of cerebral malaria the corresponding p-values were 0.19 and 0.12.

Table 24: Comparison with signals observed in the phase 3 trial, including events to April 2021

Outcome	Rate ratio in the phase 3 trial[4] (95%CI)	Modelled prediction of the rate ratio if the signal observed in the phase 3 trial were to occur during the MVIP (95%CI)[5]	Rate ratio observed in the MVIP (95%CI)	z	p-value
Meningitis	10.5 (1.41,78.0)	3.67 (1.21,11.1)	0.63 (0.22,1.79)	2.28	0.022
Cerebral malaria[1]	2.15 (1.1,4.3)	1.61 (1.05,2.4)	1.03 (0.61,1.74)	1.31	0.19
Cerebral malaria[2]		1.59 (1.05,2.4)	0.82 (0.39,1.72)	1.56	0.12
Relative mortality ratio[3]	2.61 (1.29,5.26)	1.83 (1.17,2.8)	1.03 (0.88, 1.21)	2.91	0.004

1: Cerebral malaria, using, for MVIP, a case definition including cases in which lumbar puncture had not been performed. 2: Cerebral malaria, MVIP cases in which lumbar puncture had been performed to exclude cases with probable meningitis. 3: The relative mortality ratio, in the phase 3 trial, was defined as the ratio of the mortality rate between vaccine recipients and controls, for girls, relative to that for boys. 4: Rate ratio in the phase 3 trial comparing the combined vaccine groups (R3R and R3R) with the control group, from month 0 to study end.

5: For any outcome, denote the log of the rate ratio comparing the RTS,S and comparator areas in country i by Di, with variance V(Di). The pooled estimate of the log rate ratio, combining the data from the three countries, is: $D_{pooled} = \sum w_i D_i$, i=1..3, where the countries are weighted by the inverse of the variance, weights are $w_i = [1/V(D_i)] \div \sum 1/V(D_i)$ and the variance of the pooled estimate is $V(D_{pooled}) = 1/\sum[1/V(D_i)]$. These are the pooled estimates in the main text. Denote the rate ratio for the same outcome from the phase 3 trial by R. From the phase 3 trial we have the estimates of R for each outcome and a confidence interval (provided by GSK, comparing the two vaccine groups of the trial (R3C and R3R combined) with the control group, over the whole trial period month 0 to study end), and hence can calculate the standard error of log(R). In each country, we calculated a modelled prediction of the rate ratio that would be expected if the safety signal in the phase 3 trial were to occur during the MVIP. The dilution effect is different in each country because coverage of RTSS varied and the degree of contamination (RTSS in comparison areas) also differed. Let the diluted effect in country *i* be R_i' (details of how this was obtained are given below). We can calculate a weighted average of the logged R_i' values, using the same country weights, w_i, that we used in (1): $\sum w_i \log R_i'$. Call this weighted value, F. We need the standard error of F. Noting that the factor by which the log rate ratio from the phase 3 has been diluted is equal to F/log(R), =k say, and noting that we have the s.e. of log(R) from the phase 3 data, then the s.e. of F is k x s.e. of log(R). To compare the observed pooled log rate ratio (Dpooled) with the (pooled) diluted phase 3 estimate, F, we calculated the difference (Dpooled – F). The standard error of this difference is: se(diff) = sqrt(s.e.(F)^2+ V(Dpooled)), and then we treated (Dpooled-F)/se(diff) as a z-value and obtained a p-value using the normal distribution.

To estimate the proportion of person time spent vaccinated in each country, we considered each month of the evaluation, and for the cohort of children reaching the eligible age (i.e. *s*=5 months in Malawi, *s*=6 months in the other countries) in that month, we summed the Kaplan-Meier estimates of the proportion of children vaccinated by age *a* months from , p(a), multiplied by the person time for that calendar month and age, t(a,m), from the starting age until the end of the evaluation period (up to M months in total, M=25 in Malawi and Ghana (April 2019 to April 2021), M=20 in Kenya Sep 2019 to April 2019), and then divide by the total person time:

$$\sum_{j=1}^{M} \sum_{a=s}^{s+M-j} p(a)t(a,j) \,/\, \sum_{j=1}^{M} \sum_{a=s}^{s+M-j} t(a,j).$$

In the absence of denominator data, the person time t(a,m) was set to 1 for each calendar month and age,xcept the first month which is a partial month depending on the date vaccination started (Apr 23 in Malawi, Apr 30 in Ghana, Sep 13 in Kenya). In Kenya and Ghana, children were eligible if they were aged 6 months or 7 months, and in Kenya if they were 6 months to 11 months old at the start, and the total doses administered, reported by the EPI, was higher in the initial months in these countries, reflecting this catch-up. We estimated the person time in the catch-up cohorts (children who were aged 7 months in the first month in Ghana, and children who were aged 7-11 months in the first month in Kenya) by estimating the average target population per month as the average number of doses administered per month, divided by the survey estimate of coverage, and then allocating the excess doses in the initial months, to the catch-up cohorts to estimate the proportion vaccinated. In Malawi, in practice children were vaccinated at the start only if they were strictly aged 5 months. The survey data included too few RTSS-vaccinated children to be able to estimate proportion vaccinated by

month of age in comparison areas of the MVIP, and in non-eligible age groups. We assumed that the proportion of vaccinated person time would be in the same proportion to the proportion eventually vaccinated, as in implementation areas, and applied this to the survey estimates of coverage in comparison areas and in older age groups, to obtain rough estimates of the proportion of vaccinated person time in comparison areas and in older age groups in implementation areas. We assumed no vaccination in older age groups in comparison areas (a conservative assumption in that this assumption results in a greater dilution effect). Finally, we ignored possible effects of confounding that might have further diluted effect estimates in the MVIP. With respect to meningitis, we noted that when PCR analysis identified a causative pathogen, only a small percentage were of serotypes preventable by Hib or pneumococcal vaccine, so although RTSS-recipients were more likely to have received Hib and/or pneumococcal vaccine, the confounding effect was likely to be small. With respect to malaria outcomes, midline surveys suggested RTSS coverage did not differ in relation to malaria prevalence at baseline.

Having got estimates of the proportion of vaccinated person time in implementation and comparator areas, in eligible and non-eligible age groups, in each country, we estimated the expected rate ratio for each safety outcome, if the safety signal from the phase 3 occurred in the MVIP, in each country, as R'=[(Rc+1-c)/(Rd+1-d)]/[(Rf+1-f)/(Rg+1-g)], where c=proportion of vaccinated person time in implementation areas in eligible age groups, d=proportion in comparison areas in eligible age groups, and f and g are the corresponding values in non-eligible groups, for that country. The estimates used were c=0.611 in Malawi,0.690 in Ghana and 0.668 in Kenya; the corresponding proportions in comparison areas were d=0.016, 0.056, 0.087, and in non-eligible age groups in implementation areas, f=0.016 in Malawi and 0.027 in Ghana. In Kenya, older age groups were not surveyed, we assumed the same value for f as in Ghana.

The corresponding results using the final data, described earlier:

Table 25: Comparison of rate ratios for safety outcomes with the signals observed in the phase 3 trial

Outcome	Signal in the phase 3 trial (95%CI)	Diluted value	Rate ratio MVIP	z	p
Meningitis	10.5 (1.41,78.0)	4.09 (1.23,30.41)	0.98 (0.63,1.51)	2.20	0.0280
Cerebral malaria	2.15 (1.10,4.30)	1.62 (1.05,3.21)	0.94 (0.63,1.38)	1.86	0.0624
Cerebral malaria (subset)		1.62 (1.05,3.20)	1.03 (0.69,1.55)	1.49	0.1355
Mortality interaction	2.61 (1.29,5.26)	1.87 (1.18,3.77)	1.04 (0.93,1.15)	2.46	0.0140

References

[1] Milligan P. *Statistical Analysis Plan for the Malaria Vaccine Pilot Evaluation*, London, UK: London School of Hygiene & TropicalMedicine and World Health Organization 2021. https://clinicaltrials.gov/ProvidedDocs/65/NCT03806465/SAP_001.pdf. Accessed July 11, 2021.

[2]] WHO (2019) Framework for policy decision on RTS,S/AS01 malaria vaccine. https://www.who.int/immunization/sage/meetings/2019/april/1_Session_7_Framework_for_Policy_Decision_on_RTSS-AS01_-_MALARIA_VACCINE_(for_print).pdf

[3] Ma X, Milligan P, Lam KF, Cheung YB. Ratio estimators of intervention effects on event rates in cluster randomized trials. Stat Med. 2022;41(1):128-45.

[4] Milligan P, Moore KM. Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced World Health Organisation 2021 [Available from: https://terrance.who.int/mediacentre/data/sage/SAGE_eYB_Oct2021.pdf.