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STATISTICAL ANALYSIS PLAN FOR THE DELAYED MALARIA PASSIVE SURVEILLANCE STUDY

Title:

A study of morbidity from malaria in children who had received four years of seasonal malaria chemoprevention, seasonal vaccination with the RTS,S/AS01$_E$ malaria vaccine or both interventions during their first five years of life, including the three-year period after the interventions were discontinued.

Brief Title: A delayed malaria study of RTS,S/AS01$_E$ and/or SMC: the passive surveillance study.

(Protocol Identifying Number: TMA2019SFP-)

Revisions to the statistical analysis plan:

Revision Number	Date of Revision	Page Number(s)	Details

Table of Contents

List of Abbreviations and Acronyms

ABBREVIATION/ ACRONYM	DEFINITION
AZ	Azithromycin
CI	Confidence Interval
CHUSS	Centre Hospitalier Universitaire Souro Sanou
GPS	Global positioning system
ID	Identification
IRR	Incidence Rate Ratio
IRSS	Institut de Recherche en Science de la Santé
ITN	Insecticide Treated Bed Net
LSHTM	London School of Hygiene & Tropical Medicine
MRTC	Malaria Research and Training Center
RDT	Rapid Diagnosis Test
RTS,S	RTS,S/AS01$_E$ malaria vaccine
SAP	Statistical Analysis Plan
SMC	Seasonal Malaria Chemoprevention
SP + AQ	Sulfadoxine-pyrimethamine plus Amodiaquine
WHO	World Health Organization

1. Summary Study Information

1.1 Study title

A study of morbidity from malaria in children who had received four years of seasonal malaria chemoprevention, seasonal vaccination with the RTS,S/AS01$_E$ malaria vaccine or both interventions during their first five years of life, including the three-year period after the interventions were discontinued.

1.2 Clinical trial registration

This epidemiological study is an extension of earlier clinical trials, NCT04319380 and NCT03143218: 'A comparative trial of seasonal vaccination with the malaria vaccine RTS,S/AS01$_E$, seasonal malaria chemoprevention, and of the two interventions combined.' and 'Seasonal vaccination with the RTS,S/AS01E malaria vaccine given with or without seasonal malaria chemoprevention: extension of a randomised, double-blind Phase 3 trial until children reach the age of five years.'

1.3 Study duration

April 2017 – March 2024

1.4 Study sites

Houndé district, Burkina Faso and Bougouni district, Mali.

1.5 Preceding trials to which this study is linked and their objectives

1.5.1 The initial trial

The original trial sought to determine -

1. Whether seasonal vaccination with the RTS,S/AS01$_E$ malaria vaccine was non-inferior to four, monthly courses of seasonal malaria chemoprevention (SMC) with sulphadoxine-pyrimethamine plus amodiaquine (SP+AQ) in preventing clinical malaria and other adverse outcomes.

2. Whether the combination of these two interventions (i.e. seasonal vaccination with RTS,S/AS01$_E$ and SMC with SP+AQ was superior to RTS,S/AS01$_E$ or to SMC given alone in preventing clinical malaria and other adverse outcomes.

These aspects were of equal priority [1, 2].

1.5.2 The extension study

The extension study, undertaken in children aged three or four-years old who had previously received five doses of the RTS,S/AS01$_E$ malaria vaccine or comparator vaccines, together with SMC with SP+AQ or placebo sought to determine whether -

1. Vaccination with a booster dose of the RTS,S/AS01$_E$ malaria vaccine at the beginning of the malaria transmission until children reached the age of five years is non-inferior to SMC in preventing clinical attacks of malaria and would be easier to deliver than SMC [3].

2. Administration of further doses of RTS,S/AS01$_E$ at the beginning of the malaria transmission until children reached the age of five years provides additional protection against clinical episodes of malaria when given together with SMC [3].

Details of the conduct and outcome of these two studies have been published [1-3]

2 Rationale for the delayed malaria study

Subjects repeatedly exposed to malaria gradually develop immunity to the infection, first against severe disease then against uncomplicated clinical episodes of malaria, and finally against malaria infection, although the latter is rarely complete. Thus, there is a risk that protecting children from malaria infections during the first few years of their life through introduction of increasingly effective interventions, or combinations of interventions, will impair their development of natural immunity and result in a shift in the age pattern of malaria with clinical infections, including severe infections, occurring at a later age than would have occurred if the children had not received effective interventions during their first few years of life, a phenomenon now termed 'delayed malaria' [4].

In trials undertaken in Burkina Faso and Mali, children age 5-17 months were randomized to receive either SMC with SP+AQ, seasonal vaccination with the RTS,S/AS01$_E$ malaria vaccine or a combination of the two interventions for a period of four or five years, dependent upon the age at which they were recruited to the trial. RTS,S/AS01$_E$ given alone was non-inferior to SMC given alone and the combination provided an additional 58% protection against clinical episodes of malaria and 67% protection against malaria severe enough to warrant admission to hospital over that obtained with SMC alone, and a similar degree of protection over that seen when RTS,S/AS01$_E$ was given alone. The impact of administration of these effective interventions during the first five years of life when children are normally exposed to repeated malaria infection on the development of naturally acquired immunity to malaria is uncertain. Therefore, the three groups of children in the RTS,S/AS01$_E$ + SMC trial have been followed for a period of three years after the interventions were discontinued through a passive surveillance system which detects hospital admissions with severe malaria, uncomplicated episodes of clinical malaria at health centres and clinics and the prevalence of malaria infection and anaemia at cross-sectional surveys to determine their post intervention experience of malaria.

In addition to the passive surveillance component of the delayed malaria study, a case control study has been undertaken to identify the risk of malaria in children during the post intervention period. Analysis of this component of the delayed malaria study will be covered in a separate statistical analysis plan.

3 Overall design of the delayed malaria study: passive malaria surveillance component

After children had reached the age of five years and were no longer eligible to receive SMC or seasonal malaria vaccination, their parents/guardian were asked whether their child could be included in the delayed malaria follow-up study and, if agreement was given, written informed consent for continuation of follow-up was obtained. No trial interventions were given during the follow-up period, with study children receiving health care through national health care programmes. Passive surveillance for malaria was continued in the same manner as that used during the intervention trial. This included the following -

a. Recording any episode of clinical malaria, defined as a febrile illness with no other obvious cause for the fever, and a *Plasmodium falciparum* parasitaemia ≥ 5,000 parasites and < 250,000 per microliter, in a study child who presented at a health centre.
b. Recording hospital admissions with malaria in study children.
c. Measuring the prevalence of malaria parasitaemia at a cross-sectional survey conducted each year at the end of the malaria transmission season. The prevalence of anaemia and of malnutrition were also recorded during these surveys.
d. Recording any deaths in study children and investigating their likely cause when these occurred outside hospital.

4 Objectives of the passive surveillance component of the delayed malaria study

4.1 Primary objective

The primary objective of this study is determination of whether the incidence of uncomplicated and severe clinical malaria during the first eight years of life (7 years of participation, four years of intervention and three years of passive follow-up) is lower in children who had received the combination of SMC and RTS,S/AS01$_E$ than in children who received either intervention given alone during their first five years of life.

4.2 Secondary objectives

Secondary objectives of the study include –

1. Determination of whether the cumulative incidence of uncomplicated clinical episodes of malaria during the first eight years of life (7 years of participation) in children who received the RTS,S/AS01$_E$ vaccine alone was non-inferior to that observed in children who had received SMC alone during their first five years of life.

2. Determination of whether the incidence of uncomplicated clinical episodes of malaria during the three-year post intervention period is higher in children who had received the

combination of SMC and RTS,S/AS01$_E$ during their first five years of life than in children who had received either SMC or RTS,S/AS01$_E$ alone during this period.

3. Determination of whether the incidence of uncomplicated clinical episodes of malaria during the first year post intervention period is lower in in children who received RTS,S/AS01$_E$ alone during their first five years of life than in those who received SMC alone during this period, due to the persistence of vaccine efficacy.

4. Determination of whether the incidence of severe malaria (deaths from malaria and hospital admissions from malaria) during the three-year post-intervention period is higher in children who had received the combination of SMC and RTS,S/AS01$_E$ during their first five years of life than in children who had received either SMC or RTS,S/AS01$_E$ alone during this period.

5. Determination of whether the incidence of hospitalisation and deaths due to severe malaria during the first eight years of life (7 years of participation) is lower in children who received a combination of SMC and RTS,S/AS01$_E$ than in children who received either intervention given alone during their first five years of life.

6. Determination of whether the cumulative incidence of hospital admissions, excluding external and surgical conditions, and all cause deaths during the first eight years of life (7 years of participation) is lower in children who received a combination of SMC and RTS,S/AS01$_E$ than in children who received either intervention given alone during their first five years of life.

7. Determination of whether the cumulative incidence of uncomplicated clinical malaria during the three years of the post-intervention period is associated with the number of doses of SMC and/or vaccine that children received during the intervention period (their first five years of life).

8. Determination of whether the prevalence of malaria parasitaemia during three annual cross-sectional surveys conducted during the post-intervention period is higher or lower in children who had received the combination of SMC and RTS,S/AS01$_E$ during their first five years of life than in children who had received either SMC or RTS,S/AS01$_E$ alone during this period.

9. Determination of whether the prevalence of moderate anaemia (Hb < 7g/dl) or severe anaemia (Hb < 5g/dl) observed during three cross-sectional surveys conducted during the post intervention period is higher in children who had received the combination of SMC and RTS,S/AS01$_E$ during their first five years of life than in children who had received either SMC or RTS,S/AS01$_E$ alone during this period.

4.3 Exploratory objectives

1. Determination of whether the incidence of uncomplicated or severe malaria during the post- intervention period among children who received RTS,S/AS01$_E$ is higher among children with a high coverage of vaccination during the intervention period than among children in whom vaccine coverage was low.

2. Determination of whether the incidence of uncomplicated or severe malaria during the post intervention period among children who received SMC is higher among children with a high coverage of chemoprevention during the intervention period than among children in whom coverage was low.

3. Determination of whether the prevalence of malaria parasitaemia detected at post-intervention cross-sectional surveys among children who received RTS,S/AS01$_E$ is higher among children with a high coverage of vaccination during the intervention period than among children in whom vaccine coverage was low.

4. Determination of whether the prevalence of malaria parasitaemia among children who received SMC detected during post-intervention cross-sectional surveys is higher among children with a high coverage of chemoprevention during the intervention period than among children in whom coverage was low.

5. Determination of whether the prevalence of moderate or severe anaemia among children who received RTS,S/AS01$_E$ is higher during post-intervention cross-sectional surveys among children with a high coverage of vaccination than among children in whom coverage was low.

6. Determination of whether the prevalence of moderate or severe anaemia among children who received SMC detected during post-intervention cross-sectional surveys is higher among children with a high coverage of chemoprevention during the intervention period than among children in whom coverage was low.

5 Study Populations

5.1 Populations of the initial and extension trials and the interventions they received.

Children of either sex were eligible for inclusion in the trial, provided that they were 5-17 months of age on the scheduled date of first vaccination in April 2017, they were living permanently in the study area, and the consent of a parent or legally acceptable representative was obtained. Detailed description can be found elsewhere [1, 2].

In order to be eligible to participate in the extension study, a child must have been enrolled in the initial phase of the trial of seasonal vaccination with the RTS,S/AS01$_E$ vaccine and their parents or guardian must have provided consent for their inclusion in the extension study. Detailed description can be found elsewhere [3].

Children in the original study were individually randomised to one of three intervention groups. The interventions they received during the initial and extension periods are shown in Table 1. This refers to Cohort one (for detailed description of the Cohort see Section 5.2 Population for the delayed malaria study).

Table 1. Summary of the intervention and timing, both for the main trial and its extension.

	Group		
	1) SMC 'SMC alone'	**2) RTS,S/AS01$_E$ 'RTS,S alone'**	**3) RTS,S/AS01$_E$ +SMC 'Combined group'**
Initial three-year trial			
April/May – June/July 2017 July/Aug – Oct/Nov 2017	Rabies vaccine x 3 SMC x 4	RTS,S/AS01$_E$ x 3 SMC placebo x 4	RTS,S/AS01$_E$ x 3 SMC x 4
June 2018 July-Oct 2018	Hep A vaccine x 1 SMC x 4	RTS,S/AS01$_E$ x 1 SMC placebo x 4	RTS,S/AS01$_E$ x 1 SMC x 4
June 2019 July-Oct 2019	Hep A vaccine x 1 SMC x 4	RTS,S/AS01$_E$ x 1 SMC placebo x 4	RTS,S/AS01$_E$ x 1 SMC x 4
Two-year Extension Study			
June 2020 July-Oct 2020	Tetanus (BF) or Tetanus/Diphtheria toxoids (Mali) x 1[#] SMC x 4	RTS,S/AS01$_E$ x 1 SMC placebo x 4	RTS,S/AS01$_E$ x 1 SMC x 4

5.2 Population for the delayed malaria study

In addition to the eligibility criteria used in the original and extension trials, children who provided consent for their inclusion in the passive surveillance after the end of the intervention were included in the study. Figure 1 indicates shows the numbers of children recruited to each phase of the study and the drop-out rates.

The original trial cohort was recruited in April 2017 when children were aged between 5-17 months. In the two-year extension phase of the original trial, all children received study interventions in 2020. In 2021, children who were who were aged 5 years (60 months) of age on the first of June that year, the start of the malaria transmission, were no longer eligible to receive the trial interventions as is the case in most countries where SMC is deployed. These children, constitute Cohort 1 and are the focus of this analysis. Children whose birth date was earlier than May 31st 2016 continued to receive the trial interventions in 2021 and constitute Cohort 2 (Figure 2). Because children in Cohort 2 received an additional year of interventions, and hence may be at increased risk of malaria when the interventions were discontinued, compared to children in Cohort 1, they will consequently be the subject of a separate analysis. In the text below, the terms 'Cohort 1' or 'older' and 'Cohort 2' or 'younger' children are used as follows:

Cohort 1 or 'older children': children who were above the age of five years on 01 June 2021 (DOB 31/05/2016, or earlier), and who were not eligible for interventions in 2021.

Cohort 2 or 'younger children': children who were five years of age or below on 01 June 2021 (DOB 01/06/2016, or later), and who were eligible to receive trial interventions in 2021.

Children in Cohort 2 are still under follow-up using passive surveillance. A similar statistical analysis plan (SAP), with adjustments to the end of intervention post surveillance periods will be developed for the analysis of post intervention findings in these children. Hence, it will not be discussed any further.

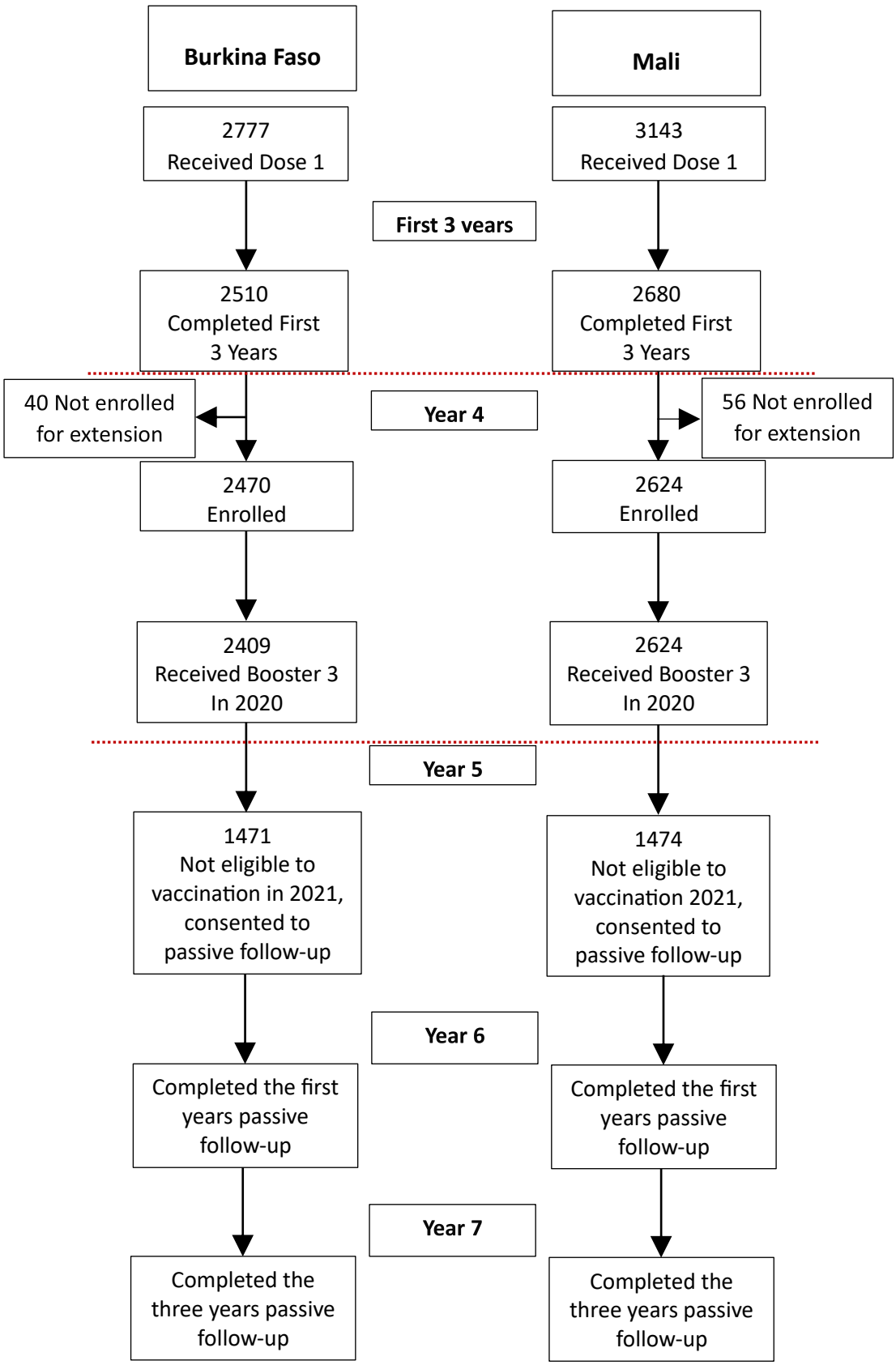


Figure 1. CONSORT chart for the initial phase of the trial and the extension study.

* Some of the numbers in the figure above are provisional and may change for the final analysis once all data cleaning is complete.

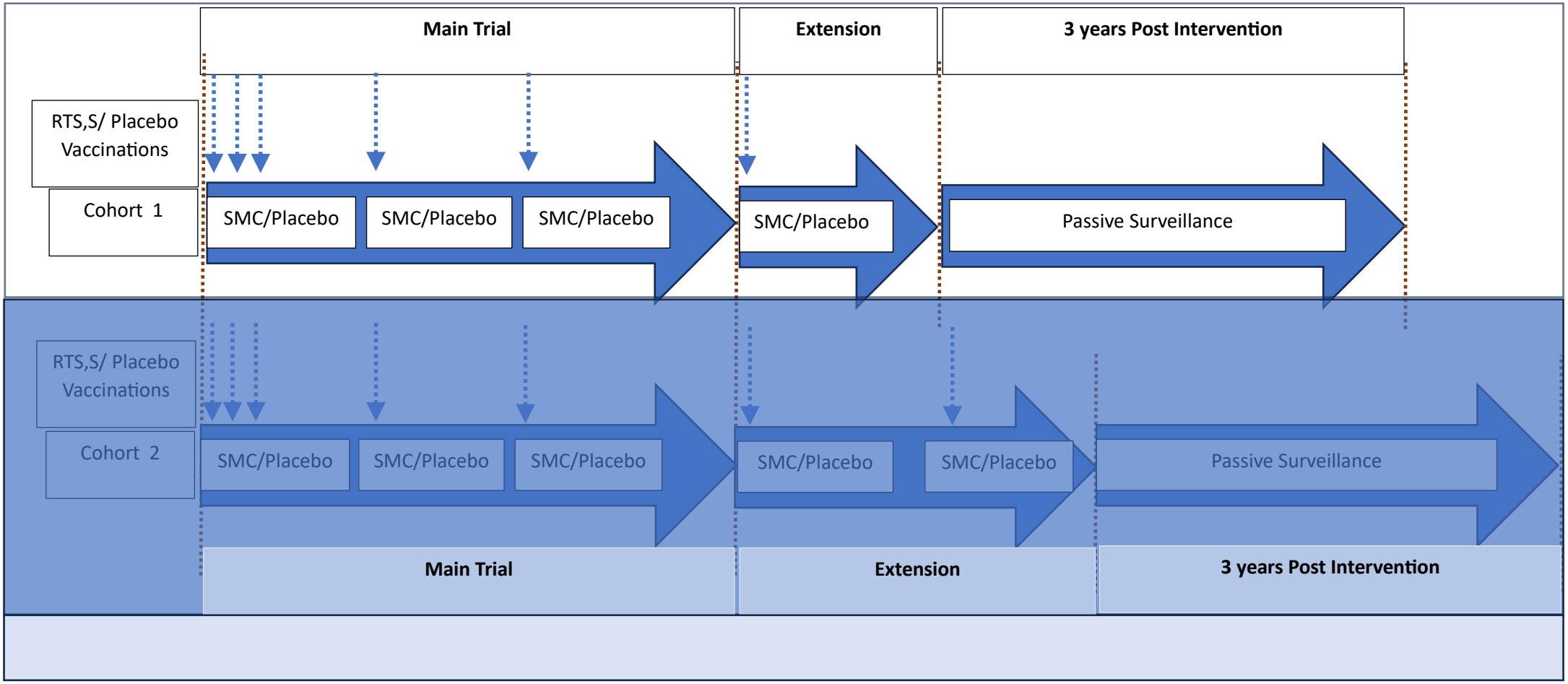


Figure 2. The chronology of the intervention and post-intervention. Cohort 2 is included here only for descriptive purpose; the analysis of findings in this cohort will be the subject of a separate SAP.

6. Study outcomes

6.1 Primary endpoint

The primary endpoint is the incidence of episodes of uncomplicated episodes of clinical malaria defined as an episode of fever (either measured axillary temperature ≥ 37.5°C, or a history of fever within the past 48 hours), and a positive blood film, with a *P. falciparum* parasite density of 5,000 per µl or more. This definition has been used in the intervention period, as well as in many previous trials of malaria vaccines.

All passively detected episodes of clinical malaria will be included in the analysis. This includes visits to outpatient clinics and hospitals, as well as episodes detected at the time of SMC administration or at the end of transmission season survey. These contacts can be considered 'passive' because the caregiver had to bring the child to the contact and because the SMC distribution or survey was conducted at health facility in many cases. As the focus is on passively detected cases, morbidity detected during home visits for serological sampling, or for the weekly parasitaemia survey (which was undertaken only in the initial phase of the study) will be excluded. Morbidity detected at the time of vaccination will also be also excluded, because some children were visited at home and brought to the clinic in order to be vaccinated, so cases found at the time of vaccination cannot be regarded as passively detected.

To avoid double counting of disease episodes which result in more than one healthcare contact, episodes of the primary endpoint documented within 7 days of a previous episode will not be counted. These seven days are not deducted from the person-time at risk [2,3].

6.2 Secondary endpoints

Secondary endpoints - not listed in order of priority - include the following:

6.2.1 Morbidity events detected at study health centres and hospitals.

As for the primary outcome, episodes of the outcomes listed below which occur within 7 days of a previous event of the same type will be discounted. These 7 days were not deducted from the person-time at risk after an episode of malaria [2,3].

6.2.1.1 Clinical malaria with *P. falciparum* parasitaemia of any density. Defined as an episode of fever (either measured temperature ≥ 37.5°C, or a history of fever within the past 48 hours), and a positive blood film for *P. falciparum* parasites. This includes hospitalisations for malaria meeting the above criteria (i.e. fever or history of fever, plus slide confirmed P. *falciparum* malaria of any density).

6.2.1.2 Clinical malaria confirmed by rapid diagnostic test. Defined as an episode of fever (either measured temperature ≥ 37.5°C, or a history of fever within the past 48 hours), and a positive rapid diagnostic test (RDT).

6.2.1.3 Clinical malaria with non-falciparum parasitaemia of any density. Defined as an episode of fever (either measured temperature ≥ 37.5°C, or a history of fever within the past 48 hours), and a positive blood film for non-falciparum *Plasmodium* parasites.

6.2.1.4 Clinical malaria with any Plasmodium spp. infection of any density. Defined as an episode of fever (either measured temperature ≥ 37.5°C, or a history of fever within the past 48 hours), and a positive blood film for any *Plasmodium* spp. parasites with or without *P. falciparum).*

6.2.2 Severe outcomes detected passively at study health centres and hospitals, and through verbal autopsies.

The primary diagnosis in a study child admitted to hospital by a study physician was reviewed by a second independent clinician. A third clinician reviewed cases of disagreement to reach a consensus primary diagnosis. All verbal autopsies were also reviewed by the same process to obtain a consensus cause of death.

The severe outcomes to be considered include -

6.2.2.1 Hospital admissions due to any cause.
6.2.2.2. Hospital admissions excluding those due to external causes or surgical conditions.
6.2.2.3. Hospital admissions due to malaria defined as hospital admissions for which malaria was the primary diagnosis, supported by a positive blood smear. Children who were admitted with a diagnosis of severe anaemia or neurological signs, with documented antimalarial treatment in the past 4 weeks, were also deemed to be due to malaria if their malaria RDT was positive (even if the blood smear result was negative or the blood smear result was not available). Additional analyses of children who meet the WHO criteria for a diagnosis of severe malaria including those with a) cerebral malaria, b) severe anaemia and c) other forms of severe malaria will be undertaken.
6.2.2.4 Blood transfusion.
6.2.2.5 Deaths due to any cause.
6.2.2.6 Deaths due to any cause excluding external causes and surgical conditions.
6.2.2.7 Deaths due to malaria defined as hospital admissions resulting in death, where malaria was recorded as the primary cause of death supported by a positive blood smear. Children who were admitted with a diagnosis of severe anaemia or neurological signs, with documented antimalarial treatment in the past 4 weeks, were also deemed to be due to malaria if their malaria RDT was positive (even if the blood smear result was negative or the blood smear result was not available). Deaths in the community will also be included when malaria is assigned by a panel of three independent physicians as the primary cause of death recorded in a verbal autopsy.

6.2.3 Outcomes measured at cross-sectional surveys at the end of the malaria transmission season.

6.2.3.1 The prevalence of asexual stage *P. falciparum* infection of any density
6.2.3.2 The prevalence of asexual stage *P. falciparum* infection with density ≥ 5000 per ul

6.2.3.3 The prevalence of sexual stages *P. falciparum* infection.
6.2.3.4 The arithmetic mean *P. falciparu*m parasite density, including samples which are parasite negatives as having a density of zero.
6.2.3.5 The prevalence of asexual stage infection with non-falciparum *Plasmodium* species.
6.2.3.6 The prevalence of sexual stage infection with non-falciparum *Plasmodium* species.
6.2.3.7 The mean haemoglobin concentration in g/dL.
6.2.3.8 The prevalence of anaemia, defined as measured Hb < 10 g/dL.
6.2.3.9 The prevalence of moderate anaemia, defined as measured Hb < 7 g/dL.
6.2.3.10 The prevalence of severe anaemia, defined as measured Hb < 5 g/dL.

7. Analysis periods and person-years at risk

Several analysis periods are of interest for the primary outcome of clinical malaria. These are detailed in the figures and text that follow.

Hypothesis testing and p-values will be presented for the whole intervention period (period A characterised below) and for the two periods of interest in the intervention and post-intervention (periods B and C in the list below), see Figure 3. Numbers of events and hazard ratios or other measures of effect (with confidence intervals) will be tabulated for other analysis populations.

Period A. *The whole study period, 7 years (4- year intervention and 3- year post-intervention).*

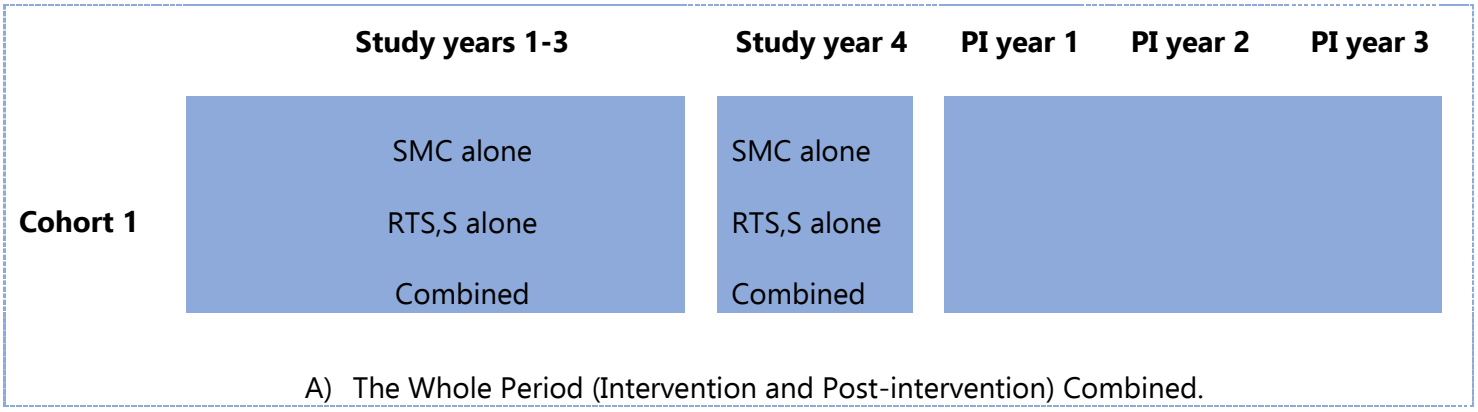
The primary analysis population will be the whole seven-year period (4-year intervention and 3-year post-intervention periods). This is the period starting from enrolment in April 2017 until the end of the passive-surveillance in which children reached 8 years of age (31 March 2024).

Period B. *Intervention period, the 4- year period*

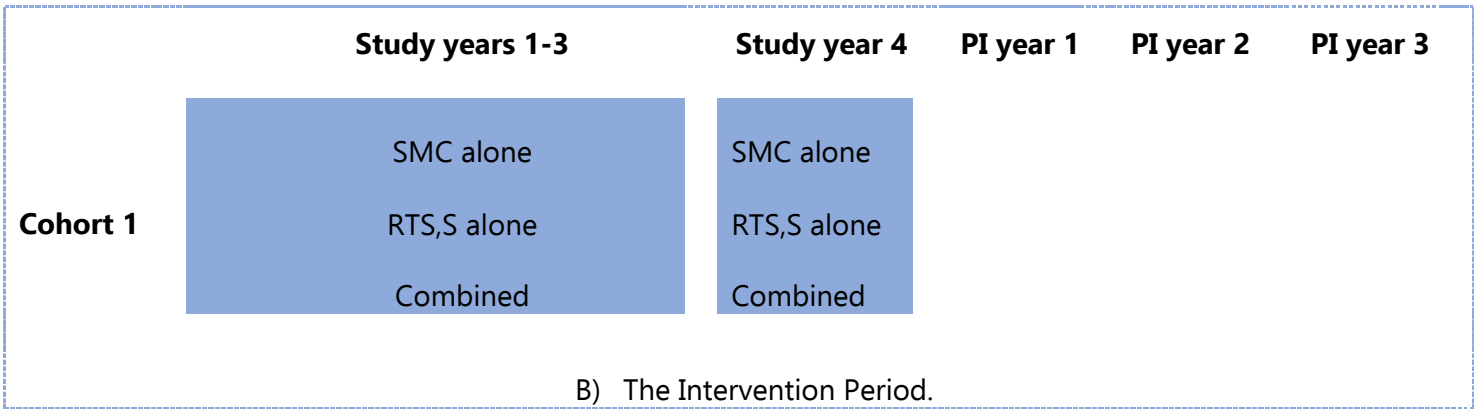
This is the period starts from enrolment in April 2017 until the end of the intervention year in which children reached 5 years of age (31 March 2021).

Period C. *Post-intervention period, the 3- years period*

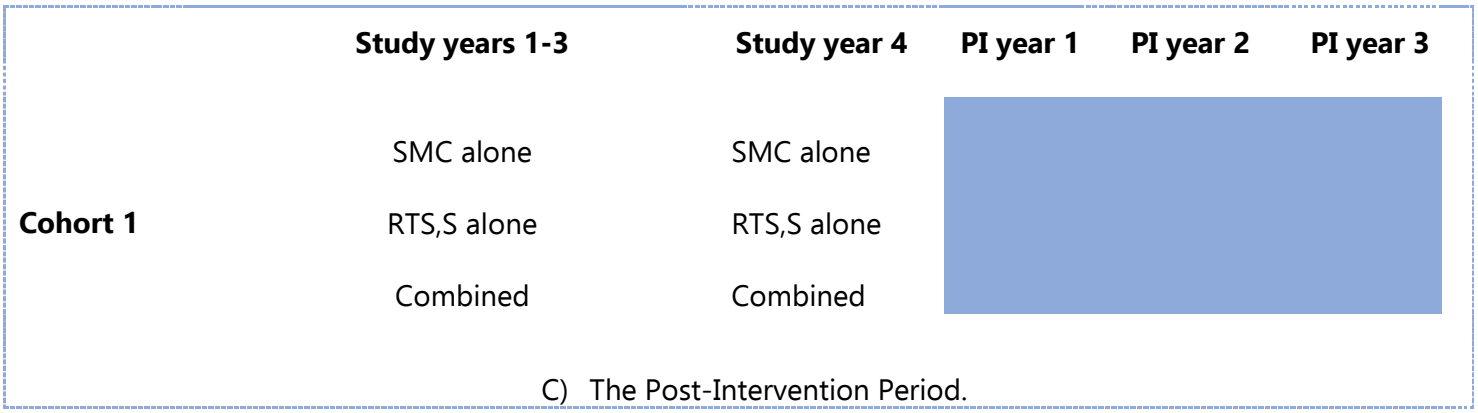
This is the period which starts from 1 April, 2021, when children cease to receive the intervention until the end of the passive-surveillance in which children reaches 8 years of age (31 March 2024).



A) The Whole Period (Intervention and Post-intervention) Combined.



B) The Intervention Period.



C) The Post-Intervention Period.

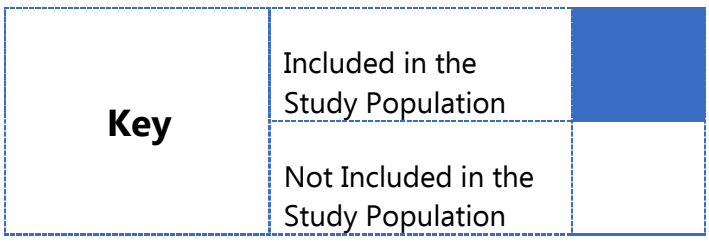


Figure 3: Population Included in Different Analysis Period.

8. Sample size and power considerations

Seasonal malaria chemoprevention given for four months of the year under trial conditions has an efficacy of about 85% during this four-month period. If, without intervention, the peak four months of malaria incidence account for 60% of annual cases (with the other 40% falling during the other months) this equates to an efficacy over 12 months of at least 50%.

The incidence of malaria per child per year during the intervention period of the RTS,S/AS01E + SMC trial was 0.31 in the SMC alone group, 0.32 in the RTS,S/AS01$_E$ alone group, and 0.13 in the combination group [2, 3]. The protective efficacy of the combination (RTS,S/AS01$_E$ and SMC) was 58% compared to SMC alone and 59% compared to RTS,S/AS01$_E$ alone during the four/five year intervention period. It is assumed that the incidence of malaria will increase to 0.5 per child per year in the SMC alone group in the post-intervention period, while the incidence will increase more gradually in the two RTS,S/AS01$_E$ vaccine groups to 0.4 per child per year (20% lower than the SMC alone group) in the first year of post-intervention, as these children will still receive some protection from the vaccine in the year after seasonal vaccination is discontinued, and then increase to 0.5 per child per year (similar to the SMC group) by the third year post-intervention. Thus, over the whole study period that includes the five year intervention and the three year post-intervention period it is assumed that the incidence of malaria will be at least 30% lower in the RTS,S/AS01$_E$ + SMC group compared to SMC alone or RTS,S alone and that the study will have >90% power to detect a protective efficacy of at least 30% for the superiority comparison between the combined intervention group and the two single intervention groups in the 83% of the children eligible to remain within the trial for its full 5 years and who were still being followed at the end of the fifth year of follow-up (n=2099).

As the incidence of malaria was similar in the SMC alone and RTS,S/AS01$_E$ alone groups during the intervention period it is assumed that the incidence of malaria over the entire study period will not be higher in the RTS,S/AS01$_E$ alone group compared to the SMC alone group (RTS,S/AS01$_E$ alone is non-inferior, if not superior, to SMC alone) [2,3]. Hence, the study will also have >90% power to exclude, at the 2.5% significance level, a relative difference in the incidence of clinical malaria of 20% over the 7 year study period between the RTS,S/AS01$_E$ and the SMC alone groups. To determine the level of confidence with which this margin can be excluded, we will also calculate two-sided 90% and 99% confidence intervals. With the anticipated incidence rates, there is adequate power to reject a smaller margin.

The study has more than 80% power to exclude a difference of 15% in the incidence of clinical malaria over the study period, a difference considered to be clinically important. If the lower limit of the 95% does not overlap zero (i.e. it is clear that RTS,S/AS01$_E$ is superior to SMC) then a superiority comparison will be performed as for the combined intervention.

9. Statistical Methods

The number of subjects enrolled, completed, or withdrawn will be summarized. Reasons for withdrawal, when known, will be provided. Demographic data will be summarized by descriptive statistics and will include total number of observations (n), mean, standard deviation (SD) and range for continuous variables, and number and percentages for dichotomous variables.

9.1 Reference group

As SMC is the current standard of care, the SMC alone group will be considered as the reference group for comparisons with RTS,S/AS01$_E$ alone, and the combined group. Comparisons will also be made between RTS,S/AS01$_E$ alone and the combined group.

9.2 Analysis of primary endpoints

To address the primary objective of the study, the passive surveillance data collected throughout the study period that includes both intervention and post-intervention periods will be used. For the reasons outlined above, analyses will be undertaken for A, the entire eight years of life - 7 years of participation (the 4 years of intervention + the 3 years post-intervention), B, the four years of interventions, and C, the three years of the post-intervention surveillance periods.

Comparisons of primary endpoints will be made between the three study groups over the entire study period (first eight years of life), the 4 years of intervention, the 3 years post-interventions, and year by year in the three years post-intervention period. This comparison will be made in the modified intention-to-treat population, which includes all eligible children whose parents or guardians provided consent and who received a first dose of the RTS,S/AS01$_E$ vaccine or placebo in April 2017.

Person-time at risk for the whole study period will be calculated from the time a child received the first priming dose of the RTS,S/AS01$_E$ or the control vaccine until 31 March 2024. Each post-intervention year starts on 1st April and ends on 31 March the following year. Person-times will be censored on the date of death, or date last seen for children lost to follow up or who temporarily travelled out of the trial area, or at the end of the study (31 March, 2024), whichever comes first. Person-time at risk during the post-intervention period for children will be calculated from 1 April 2021 (when they exited the trial) until the date of death, or date last seen for children lost to passive follow up or who temporarily travelled out of the area, or until the end of the surveillance study (31 March 2024), whichever comes first.

The primary endpoint of incidence of all episodes of clinical malaria over the study period will be analysed using Cox regression models with a robust standard error [5] to account for clustering of episodes within individuals (i.e., the Andersen-Gill extension of the Cox model). This will estimate the total effect of the interventions. The Efron method will be used for tied

event times. Protective efficacy, for each study period, will be calculated as 1 minus the hazard ratio (HR), and presented as a percentage.

Hypothesis testing for analyses of the primary outcome will follow the closed testing procedure, to preserve the type I error rate at 5%, whereby there is initially a test of the null hypothesis that the incidence in the three groups is the same. If this is rejected at the 5% level, pairwise comparisons will be performed, also using a 5% significance level. Pairwise comparisons can be considered statistically significant only if the overall null hypothesis is rejected. P-values and 95% confidence intervals will be presented.

Nelson-Aalen Cumulative hazards estimates will be plotted for each group during the study years, and Kaplan-Meier failure estimates, to first malaria episode, will be plotted for each study periods.

Sub-analyses will be conducted by cohorts defined by the countries.

9.3 Analyses of secondary endpoints

Secondary outcomes which are passively detected events, will be analysed in a similar way as for the primary outcome, i.e. estimating the hazard ratio using Cox regression with a robust standard error.

For the non-inferiority comparison of RTS,S/AS01$_E$ to SMC, the two-sided 95% confidence interval for the hazard ratio will be compared to a pre-specified non-inferiority margin (see Sample Size Consideration section).

9.4 Per protocol analysis

As a secondary analysis, the primary outcome of clinical malaria will also be analysed per protocol (PP). The PP population will be defined separately for each year of the study. Children who were vaccinated at all scheduled vaccination contacts in a particular year (3 in 2017, 1 in each subsequent year) and who, in the same year, were also seen at the first SMC/SMC placebo contact each month (4 per year) will be considered as 'per protocol' for that year. Children who attended for SMC administration but who did not receive SMC because they had malaria and were referred for treatment will be included in the per protocol analysis.

'Per protocol' is defined differently for the two interventions (vaccination and SMC). For vaccination, a child must have received all vaccination doses that year; for SMC a child must only have attended all SMC contacts that year. This difference is necessary because the primary outcome of the trial (clinical malaria) can result in a specific SMC dose being missed permanently, whereas if a child had malaria at the time of vaccination, catch-up was attempted later in the season. The per protocol conditions will be applied equally to all three groups, i.e. to be considered as per protocol, a child must have received all doses of vaccine AND attended all SMC contacts, irrespective of which of these were active and placebo.

All secondary outcomes will be analysed by modified intention to treat, as described above.

Prevalence of asymptomatic malaria at the end of the transmission season among treatment groups will be compared using prevalence ratios and 95% CI. The prevalence ratio of secondary endpoints measured at end of season surveys (including *P. falciparum* parasitaemia, anaemia, etc) will be estimated using Poisson regression, with a robust standard error account for clustering of malaria episodes within individuals, as described in Zou, 2004 [6]. Arithmetic mean parasite densities (including in the calculation samples which are parasite negatives, as having density of zero), will be compared between arms using Poisson regression with a robust standard error.

Linear regression models will be used to compare mean haemoglobin concentration between the groups.

To estimate the effect modification by the number of cycles of SMC and doses of RTS,S/AS01$_E$ vaccine, the level of exposure (coverage) will be categorised into Quantiles using scores (assuming 1 booster is equivalent to three priming doses which is also equivalent to four cycles of SMC) based on the frequency distribution.

10. References

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List of Tables

List of Figures

Table 1: Baseline characteristics of children in the three study groups, by country, at initial enrolment into the intervention study.

Total number of children	Chemoprevention alone		RTS.S Alone		Combined RTS,S + chemoprevention		Total	
	No.	%	No.	%	No.	%	No.	%
Age at first vaccination								
Under 8 months								
8-11 months								
12-15 months								
16 months or older								
Sex								
Male								
Female								
LLIN use the night before the 2017 census								
Yes								
No								
Missing								
PCV vaccination								
Yes								
No								
Card not available								
Card incomplete								
Missing								
Penta vaccination								
Yes								
No								
Card not available								
Card incomplete								
Missing								
MenAfriVac vaccination								
Yes								
No								
Missing								

Table 2*:* Baseline characteristics of children in the three study groups, by country, at the beginning of the post-intervention period.

Total number of children	Chemoprevention alone		RTS.S Alone		Combined RTS,S + chemoprevention		Total	
	No.	%	No.	%	No.	%	No.	%
Age at first vaccination								
Under 8 months								
8-11 months								
12-15 months								
16 months or older								
Sex								
Male								
Female								
LLIN use the night before the 2017 census								
Yes								
No								
Missing								
PCV vaccination								
Yes								
No								
Card not available								
Card incomplete								
Missing								
Penta vaccination								
Yes								
No								
Card not available								
Card incomplete								
Missing								
MenAfriVac vaccination								
Yes								
No								
Missing								

Table 3: Adherence to vaccination with RTS,S/AS01$_E$ or control vaccine during the initial and extension periods in the three trial groups.

	Chemoprevention alone		RTS.S Alone		Combined RTS,S + Chemoprevention		Total	
	No.	%	No.	%	No.	%	No.	%
Coverage of vaccine doses								
Study year 1								
Received dose 1								
Received dose 2								
Received dose 3								
Study year 2								
Received booster 1								
Study year 3								
Received booster 2								
Study year 4								
Received booster 3								
Cumulative number of vaccine doses								
Primary series								
First dose only								
First and second dose								
All three doses								
Received fourth dose/booster 1								
Received fourth dose/booster 2								
Received fourth dose/booster 3								
Cumulative vaccine dose Categories								
< 6 doses								
6 doses								

Table 4: Number of SMC or SMC placebo contacts made during the initial and extension periods by children in each of the three trial groups.

	Chemoprevention alone		RTS.S Alone		Combined RTS,S + chemoprevention		Total	
	No.	%	No.	%	No.	%	No.	%
Number of chemoprevention contacts attended								
Study Year 1								
0								
1								
2								
3								
4								
Study Year 2								
0								
1								
2								
3								
4								
Study Year 3								
0								
1								
2								
3								
4								
Study Year 4								
0								
1								
2								
3								
4								

Table 5: Number of prevention/Placebo Courses Received during the initial and extension periods by children in each of the three trial groups.

	Chemoprevention alone		RTS.S Alone		Combined RTS,S + Chemoprevention		Total	
	No.	%	No.	%	No.	%	No.	%
Number of Chemoprevention contacts attended								
Study Year 1								
0								
1								
2								
3								
4								
Study Year 2								
0								
1								
2								
3								
4								
Study Year 3								
0								
1								
2								
3								
4								
Study Year 4								
0								
1								
2								
3								
4								
Cumulative SMC Cycles								
<12 SMC cycles								
12-15 SMC cycles								
16 SMC Cycles								
Cumulative RTS,S and SMC Cycles combined								
<6 doses + <12 SMC cycles								
<6 doses + 12-15 SMC cycles								
6 doses + <12 SMC cycles								
6 doses + 12-15 SMC cycles								
6 doses + 16 SMC Cycles								

Table 6: Characteristics of children censored during the four-year intervention period.

Total number of children	Child was not censored		Child censored during the study		Odds ratios [95% CI]
	No.	%	No.	%	
Age at first vaccination					
Under 8 months					
8-11 months					
12-15 months					
16 months or older					
Sex					
Male					
Female					
LLIN use the night before the 2017 census					
Yes					
No					
Missing					
PCV vaccination					
Yes					
No					
Card not available					
Card incomplete					
Missing					
Penta vVaccination					
Yes					
No					
Card not available					
Card incomplete					
Missing					
MenAfriVac vaccination					
Yes					
No					
Missing					

Table 7: Incidence of uncomplicated clinical malaria (Modified Intention-to-treat Analysis) by intervention period, country and trial group.

Variable	Person-yr at Risk	Events	Incidence (95% CI)	Protective efficacy, Vaccine Alone or Combination vs Chemoprevention (95% CI)	Protective efficacy, Combination vs Vaccine Alone (95% CI)
		No.	No. of events per 1000 person-yr at risk		
Initial and post intervention periods combined					
Burkina Faso and Mali					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					
Burkina Faso					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					
Mali					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					
Four-year intervention period					
Burkina Faso and Mali					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					
Burkina Faso					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					
Mali					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					
Three-year ears post-intervention					
Burkina Faso and Mali					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					
Burkina Faso					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					
Mali					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					
First post-intervention year					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					

Second post-intervention year					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					
Third post-intervention year					
Chemoprevention alone				Reference	
Vaccine alone					Reference
Combination					

Table 8: Cause of hospital admission by study group during the intervention and post-intervention period combined.

	Chemoprevention alone		RTS.S Alone		Combined RTS,S + chemoprevention		Total	
	No.	%	No.	%	No.	%	No.	%
Non-fatal hospital admissions								
Excluded								
External cause								
Surgical conditions								
Included								
Severe malaria meeting WHO criteria								
Cerebral malaria								
Cerebral malaria and severe anaemia								
Severe malaria								
Severe malaria anaemia								
Severe malaria with hyperparasitaemia								
Severe malaria with hypoglycaemia								
Severe malaria with jaundice								
Malaria not meeting WHO criteria								
Cerebral malaria								
Malaria								
Severe malaria								
Severe malaria with convulsions								
Severe malaria with prostration								
Severe malaria with repeated vomiting								
Febrile convulsions								
Pneumonia/other respiratory infections								
Gastroenteritis								
HIV								
Sickle Cell Anaemia								
Measles								
Urinary tract infection								
Malnutrition								
Non-malaria anaemia								

Table 9: Cause of fatal hospital admission by study group during the intervention and post-intervention period combined.

	Chemoprevention alone		RTS.S Alone		Combined RTS,S + Chemoprevention		Total	
	No.	%	No.	%	No.	%	No.	%
Fatal hospital admissions								
Excluded								
External cause								
Included								
Severe malaria meeting WHO criteria								
Cerebral malaria								
Cerebral malaria and severe anaemia								
Severe malaria anaemia								
Severe malaria with convulsions								
Severe malaria with hypoglycaemia								
Severe malaria with respiratory distress								
Malaria not meeting WHO criteria								
Severe malaria with convulsions								
Other Febrile Illness								
Pneumonia/Other respiratory infections								
Gastroenteritis								
Malnutrition								

Table 10: Incidence of hospitalisation according to treatment group by trial group and period of follow-up (modified intention-to-treat analysis).

Variable	Person-year at risk	Events	Incidence (95% CI)	Protective efficacy, vaccine alone or combination vs chemoprevention (95% CI)	Protective efficacy, combination vs vaccine Alone (95% CI)
		No.	No. of events per 1000 person-yr at risk		
Hospitalisations					
Intervention and post-intervention periods combined					
Any reason, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					
Four-year intervention period					
Any reason, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					
Three-year post-Intervention period					
Any reason, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					

Table 11: Cause of death by study group during the intervention and post-intervention period combined.

	Chemoprevention alone		RTS.S Alone		Combined RTS,S + chemoprevention		Total	
	No.	%	No.	%	No.	%	No.	%
Deaths outside hospital								
Excluded								
External cause								
Surgical conditions								
Included								
Severe malaria meeting WHO criteria								
Cerebral malaria								
Cerebral malaria and severe anaemia								
Severe malaria								
Severe malaria anaemia								
Malaria not meeting WHO criteria								
Malaria								
Severe malaria with prostration								
Other febrile illness								
Pneumonia/other respiratory infections								
Gastroenteritis								
HIV								
Malnutrition								
Non-malaria anaemia								
Sudden infant death								
Unknown								

Table 12: Incidence of death according to intervention group (Modified Intention-to-treat Analysis).

Variable	Person-yr at Risk	Events	Incidence (95% CI)	Protective efficacy, Vaccine Alone or Combination vs Chemoprevention (95% CI)	Protective efficacy, Combination vs Vaccine Alone (95% CI)
		No.	No. of events per 1000 person-yr at risk		
Intervention and post-intervention periods combined					
All, including external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
All, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					
The four-year intervention period					
All, including external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
All, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					
The three-year post intervention period					
All, including external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
All, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					

Table 13: Prevalence of malaria parasitaemia and anaemia at cross sectional surveys in the post-intervention period by intervention group (Modified Intention-to-treat Analysis).

Variable	Children	Prevalence (95% CI)	Prevalence Ratio, Vaccine Alone or Combination vs Chemoprevention (95% CI)	Prevalence Ratio, Combination vs Vaccine Alone (95% CI)
	No./total no. (%)			
Prevalence of *falciparum* infection at end-of-season surveys				
First-year post-intervention				
Chemoprevention alone				
Vaccine alone				
Combination				
Second-year post-intervention				
Chemoprevention alone				
Vaccine alone				
Combination				
Third-year post-intervention				
Chemoprevention alone				
Vaccine alone				
Combination				
Prevalence Moderate or severe anaemia; Hb <7g/dL				
The Seven-years combined				
Chemoprevention alone				
Vaccine alone				
Combination				
The four-year post intervention				
Chemoprevention alone				
Vaccine alone				
Combination				
The three-year post Intervention combined				
Chemoprevention alone				
Vaccine alone				
Combination				
The first-year post intervention				
Chemoprevention alone				
Vaccine alone				
Combination				
The second-year post intervention				
Chemoprevention alone				
Vaccine alone				
Combination				
The third-year post intervention				
Chemoprevention alone				
Vaccine alone				
Combination				

Table 14: Incidence of uncomplicated clinical malaria according to SMC/vaccine coverage.

Variable	Person-yr at Risk	Events	Incidence (95% CI)	Hazard ratio, vaccine alone or combination vs chemoprevention (95% CI)	Hazard ratio, combination vs vaccine Alone (95% CI)
		No.			
Three-year post-intervention period					
Chemoprevention alone					
<12 SMC cycles				Reference	
12-15 SMC cycles					
16 SMC Cycles					
Vaccine alone					
Up to 3 Priming + 1 Booster					Reference
3 Priming + 2 Booster					
3 Priming + 3 Booster					
Combination					
< 6 doses + <12 SMC cycles					
6 doses + <12 SMC cycles					
< 6 doses + 12-15 SMC cycles					
6 doses + 12-15 SMC cycles					
6 doses + 16 SMC cycles					

Table 15: Incidence of uncomplicated clinical malaria according to SMC/Vaccine coverage by year during the post intervention period.

Variable	Person-yr at Risk	Events	Incidence (95% CI)	Hazard Ratio, Vaccine Alone or Combination vs Chemoprevention (95% CI)	Hazard Ratio, Combination vs Vaccine Alone (95% CI)
		No.	No. of events per 1000 person-year at risk		
First post intervention year (year 5)					
Chemoprevention alone					
<12 SMC cycles				Reference	
12-15 SMC cycles					
16 SMC Cycles					
Vaccine alone					
Up to 3 Priming + 1 Booster					Reference
3 Priming + 2 Booster					
3 Priming + 3 Booster					
Combination					
< 6 doses + <12 SMC cycles					
6 doses + <12 SMC cycles					
< 6 doses + 12-15 SMC cycles					
6 doses + 12-15 SMC cycles					
6 doses + 16 SMC cycles					
Second post-intervention year (year 6)					
Chemoprevention alone					
<12 SMC cycles				Reference	
12-15 SMC cycles					
16 SMC Cycles					
Vaccine alone					
Up to 3 Priming + 1 Booster					Reference
3 Priming + 2 Booster					
3 Priming + 3 Booster					
Combination					
< 6 doses + <12 SMC cycles					
6 doses + <12 SMC cycles					
< 6 doses + 12-15 SMC cycles					
6 doses + 12-15 SMC cycles					
6 doses + 16 SMC cycles					
Third post-intervention year (Year 7) Year 7					
Chemoprevention alone					
<12 SMC cycles				Reference	
12-15 SMC cycles					
16 SMC Cycles					
Vaccine alone					
Up to 3 Priming + 1 Booster					Reference
3 Priming + 2 Booster					
3 Priming + 3 Booster					
Combination					
< 6 doses + <12 SMC cycles					
6 doses + <12 SMC cycles					

< 6 doses + 12-15 SMC cycles					
6 doses + 12-15 SMC cycles					
6 doses + 16 SMC cycles					

Table 16: Incidence of severe malaria according to SMC/vaccine coverage.

Variable	Person-yr at Risk	Events	Incidence (95% CI)	Hazard Ratio, Vaccine Alone or Combination vs Chemoprevention (95% CI)	Hazard Ratio, Combination vs Vaccine Alone (95% CI)
		No.	No. of events per 1000 person-yr at risk		
The 3 Years Post-intervention					
Chemoprevention alone					
<12 SMC cycles				Reference	
12-15 SMC cycles					
16 SMC Cycles					
Vaccine alone					
Up to 3 Priming + 1 Booster					Reference
3 Priming + 2 Booster					
3 Priming + 3 Booster					
Combination					
< 6 doses + <12 SMC cycles					
6 doses + <12 SMC cycles					
< 6 doses + 12-15 SMC cycles					
6 doses + 12-15 SMC cycles					
6 doses + 16 SMC cycles					

Table 17: Prevalence of malaria parasitaemia detected at cross-sectional surveys during the three -year post-intervention according to overage during the intervention period.

Variable	Children	Prevalence (95% CI)	Prevalence Ratio, Vaccine Alone or Combination vs Chemoprevention (95% CI)	Prevalence Ratio, Combination vs Vaccine Alone (95% CI)
	No./total no. (%)			
First year post-intervention				
Chemoprevention alone				
<12 SMC cycles				
12-15 SMC cycles				
16 SMC Cycles				
Vaccine alone				
Up to 3 Priming + 1 Booster				
3 Priming + 2 Booster				
3 Priming + 3 Booster				
Combination				
< 6 doses + <12 SMC cycles				
6 doses + <12 SMC cycles				
< 6 doses + 12-15 SMC cycles				
6 doses + 12-15 SMC cycles				
6 doses + 16 SMC cycles				
Second year post-intervention				
Chemoprevention alone				
<12 SMC cycles				
12-15 SMC cycles				
16 SMC Cycles				
Vaccine alone				
Up to 3 Priming + 1 Booster				
3 Priming + 2 Booster				
3 Priming + 3 Booster				
Combination				
< 6 doses + <12 SMC cycles				
6 doses + <12 SMC cycles				
< 6 doses + 12-15 SMC cycles				
6 doses + 12-15 SMC cycles				
6 doses + 16 SMC cycles				
Third year post-intervention				
Chemoprevention alone				
<12 SMC cycles				
12-15 SMC cycles				
16 SMC Cycles				
Vaccine alone				
Up to 3 Priming + 1 Booster				
3 Priming + 2 Booster				
3 Priming + 3 Booster				
Combination				
< 6 doses + <12 SMC cycles				
6 doses + <12 SMC cycles				
< 6 doses + 12-15 SMC cycles				
6 doses + 12-15 SMC cycles				
6 doses + 16 SMC cycles				

Table 18: Prevalence of moderate or severe anaemia detected at cross-sectional surveys during the three - year post-intervention according to overage during the intervention period.

Variable	Children	Prevalence (95% CI)	Prevalence Ratio, Vaccine Alone or Combination vs Chemoprevention (95% CI)	Prevalence Ratio, Combination vs Vaccine Alone (95% CI)
	No./total no. (%)			
First year post-intervention				
Chemoprevention alone				
<12 SMC cycles				
12-15 SMC cycles				
16 SMC Cycles				
Vaccine alone				
Up to 3 Priming + 1 Booster				
3 Priming + 2 Booster				
3 Priming + 3 Booster				
Combination				
< 6 doses + <12 SMC cycles				
6 doses + <12 SMC cycles				
< 6 doses + 12-15 SMC cycles				
6 doses + 12-15 SMC cycles				
6 doses + 16 SMC cycles				
Second year post-intervention				
Chemoprevention alone				
<12 SMC cycles				
12-15 SMC cycles				
16 SMC Cycles				
Vaccine alone				
Up to 3 Priming + 1 Booster				
3 Priming + 2 Booster				
3 Priming + 3 Booster				
Combination				
< 6 doses + <12 SMC cycles				
6 doses + <12 SMC cycles				
< 6 doses + 12-15 SMC cycles				
6 doses + 12-15 SMC cycles				
6 doses + 16 SMC cycles				
Third year post-intervention				
Chemoprevention alone				
<12 SMC cycles				
12-15 SMC cycles				
16 SMC Cycles				
Vaccine alone				
Up to 3 Priming + 1 Booster				
3 Priming + 2 Booster				
3 Priming + 3 Booster				
Combination				
< 6 doses + <12 SMC cycles				
6 doses + <12 SMC cycles				
< 6 doses + 12-15 SMC cycles				
6 doses + 12-15 SMC cycles				
6 doses + 16 SMC cycles				

Table 19: Incidence of uncomplicated clinical malaria (Per-protocol Analysis) during the intervention and post intervention periods by country and study group.

Variable	Person-yr at Risk	Events	Incidence (95% CI)	Protective efficacy, Vaccine Alone or Combination vs Chemoprevention (95% CI)	Protective efficacy, Combination vs Vaccine Alone (95% CI)
		No.	No. of events per 1000 person-yr at risk		
Intervention and post-intervention periods combined					
Burkina Faso and Mali					
Chemoprevention alone					
Vaccine alone					
Combination					
Burkina Faso					
Chemoprevention alone					
Vaccine alone					
Combination					
Mali					
Chemoprevention alone					
Vaccine alone					
Combination					
The four-year intervention period					
Burkina Faso and Mali					
Chemoprevention alone					
Vaccine alone					
Combination					
The three-year post-intervention period					
Burkina Faso and Mali					
Chemoprevention alone					
Vaccine alone					
Combination					
Burkina Faso					
Chemoprevention alone					
Vaccine alone					
Combination					
Mali					
Chemoprevention alone					
Vaccine alone					
Combination					
The first year of the post-intervention period (Year 5)					
Chemoprevention alone					
Vaccine alone					
Combination					
The second year of the post-intervention period (Year 6)					
Chemoprevention alone					
Vaccine alone					
Combination					

The third year of the post-intervention period (Year 7)					
Chemoprevention alone					
Vaccine alone					
Combination					

Table 20: Incidence of hospitalisation according to treatment group (Per Protocol Analyses).

Variable	Person-yr at Risk	Events	Incidence (95% CI)	Protective efficacy, Vaccine Alone or Combination vs Chemoprevention (95% CI)	Protective efficacy, Combination vs Vaccine Alone (95% CI)
		No.	No. of events per 1000 person-yr at risk		
Hospitalisations					
Intervention and post-intervention periods combined					
Any reason, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					
The four year intervention period					
Any reason, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					
The three-year post-Intervention period					
Any reason, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					

Table 21: Incidence of death according to treatment group (Per Protocol Analyses).

Variable	Person-yr at Risk	Events	Incidence (95% CI)	Protective efficacy, Vaccine Alone or Combination vs Chemoprevention (95% CI)	Protective efficacy, Combination vs Vaccine Alone (95% CI)
		No.	No. of events per 1000 person-yr at risk		
The intervention and post-intervention periods combined					
All, including external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
All, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					
The four-year Intervention period					
All, including external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
All, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					
The three-year post Intervention period					
All, including external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
All, excluding external causes and surgery					
Chemoprevention alone					
Vaccine alone					
Combination					
Severe Malaria					
Chemoprevention alone					
Vaccine alone					
Combination					