Seasonal vaccination with RTS,S/AS01$_E$ vaccine with or without seasonal malaria chemoprevention in children up to the age of 5 years in Burkina Faso and Mali: a double-blind, randomised, controlled, phase 3 trial

Alassane Dicko, Jean-Bosco Ouedraogo*, Issaka Zongo, Issaka Sagara, Matthew Cairns, Rakiswendé Serge Yerbanga, Djibrilla Issiaka, Charles Zoungrana, Youssoufa Sidibe, Amadou Tapily, Frédéric Nikièma, Frédéric Sompougdou, Koualy Sanogo, Mahamadou Kaya, Hama Yalcouye, Oumar Mohamed Dicko, Modibo Diarra, Kalifa Diarra, Ismaila Thera, Alassane Haro, Abdoul Aziz Sienou, Seydou Traore, Almahamoudou Mahamar, Amagana Dolo, Irene Kuepfer, Paul Snell, Jane Grant, Jayne Webster, Paul Milligan, Cynthia Lee, Christian Ockenhouse, Opokua Ofori-Anyinam, Halidou Tinto, Abdoulaye Djimde, Daniel Chandramohan†, Brian Greenwood†*

Summary

Background Seasonal vaccination with the RTS,S/AS01$_E$ vaccine combined with seasonal malaria chemoprevention (SMC) prevented malaria in young children more effectively than either intervention given alone over a 3 year period. The objective of this study was to establish whether the added protection provided by the combination could be sustained for a further 2 years.

Methods This was a double-blind, individually randomised, controlled, non-inferiority and superiority, phase 3 trial done at two sites: the Bougouni district and neighbouring areas in Mali and Houndé district, Burkina Faso. Children who had been enrolled in the initial 3-year trial when aged 5–17 months were initially randomly assigned individually to receive SMC with sulphadoxine-pyrimethamine and amodiaquine plus control vaccines, RTS,S/AS01$_E$ plus placebo SMC, or SMC plus RTS,S/AS01$_E$. They continued to receive the same interventions until the age of 5 years. The primary trial endpoint was the incidence of clinical malaria over the 5-year trial period in both the modified intention-to-treat and per-protocol populations. Over the 5-year period, non-inferiority was defined as a 20% increase in clinical malaria in the RTS,S/AS01$_E$-alone group compared with the SMC alone group. Superiority was defined as a 12% difference in the incidence of clinical malaria between the combined and single intervention groups. The study is registered with ClinicalTrials.gov, NCT04319380, and is complete.

Findings In April, 2020, of 6861 children originally recruited, 5098 (94%) of the 5433 children who completed the initial 3-year follow-up were re-enrolled in the extension study. Over 5 years, the incidence of clinical malaria per 1000 person-years at risk was 313 in the SMC alone group, 320 in the RTS,S/AS01$_E$-alone group, and 133 in the combined group. The combination of RTS,S/AS01$_E$ and SMC was superior to SMC (protective efficacy 57·7%, 95% CI 53·3 to 61·7) and to RTS,S/AS01$_E$ (protective efficacy 59·0%, 54·7 to 62·8) in preventing clinical malaria. RTS,S/AS01$_E$ was non-inferior to SMC (hazard ratio 1·03 [95% CI 0·95 to 1·12]). The protective efficacy of the combination versus SMC over the 5-year period of the study was very similar to that seen in the first 3 years with the protective efficacy of the combination versus SMC being 57·7% (53·3 to 61·7) and versus RTS/AS01$_E$-alone being 59·0% (54·7 to 62·8). The comparable figures for the first 3 years of the study were 62·8% (58·4 to 66·8) and 59·6% (54·7 to 64·0%), respectively. Hospital admissions for WHO-defined severe malaria were reduced by 66·8% (95% CI 40·3 to 81·5), for malarial anaemia by 65·9% (34·1 to 82·4), for blood transfusion by 68·1% (32·6 to 84·9), for all-cause deaths by 44·5% (2·8 to 68·3), for deaths excluding external causes or surgery by 41·1% (–9·2 to 68·3), and for deaths from malaria by 66·8% (–2·7 to 89·3) in the combined group compared with the SMC alone group. No safety signals were detected.

Interpretation Substantial protection against malaria was sustained over 5 years by combining seasonal malaria vaccination with seasonal chemoprevention, offering a potential new approach to malaria control in areas with seasonal malaria transmission.

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For the French translation of the abstract see **Online** for appendix 1

*Joint first authors

†Joint senior authors

Department of Infectious Disease Epidemiology (M Cairns PhD, Prof P Milligan PhD, P Snell PhD), **Department of Disease Control** (Prof D Chandramohan PhD, J Grant MSc, Prof B Greenwood MD, I Kuepfer PhD, Prof J Webster PhD), **London School of Hygiene & Tropical Medicine, London, UK; Institut des Sciences et Techniques–Institut de Recherche en Sciences de la Santé, Bobo-Dioulasso, Burkina Faso** (I Zongo PhD, R S Yerbanga PhD, C Zoungrana MD, F Nikièma MD, F Sompougdou MD, A Haro MSc, A A Sienou MSc, Prof H Tinto PhD, Prof J-B Ouedraogo PhD); **The Malaria Research and Training Center, University of Science, Technology and Techniques of Bamako, Bamako, Mali** (Prof A Dicko MD, Prof I Sagara MD, D Issiaka MD, Y Sidibe MD, A Tapily MD, K Sanogo MD, M Kaya MD, H Yalcouye MD, O M Dicko, MD, M Diarra MD, K Diarra PharmD, S Traore MD, A Mahamar PhD, I Thera MPH, Prof A Dolo PhD, Prof A Djimde PhD); **PATH, Seattle, USA** (C Lee PhD,

Introduction

In 2021, there were an estimated 241 million cases of malaria and an estimated 619 000 malaria deaths worldwide, over 90% of which occurred in sub-Saharan Africa.[1] In the Sahel and sub-Sahelian regions of sub-Saharan Africa, where malaria remains a major cause of

C Ockenhouse PhD); **GSK, Wavre, Belgium** (O Ofori-Anyinam PhD)

Correspondence to:
Prof Brian Greenwood, Department of Disease Control, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK
brian.greenwood@lshtm.ac.uk

Research in context

Evidence before this study

In many of the countries where the burden of malaria remains persistently high, malaria transmission is highly seasonal. Seasonal Malaria Chemoprevention (SMC), which involves administration of sulphadoxine–pyrimethamine and amodiaquine to children at monthly intervals during the peak malaria transmission season each year until they reach the age of 5 or 10 years is a highly successful intervention. However, malaria remains a major cause of death and severe illness in many areas where SMC is deployed effectively, and additional control measures are needed. The malaria vaccine RTS,S/AS01$_E$ is now recommended for use in high malaria burden countries by WHO. When given in an age-based schedule of three priming doses in the first year of life and a booster dose in the second year of life, RTS,S/AS01$_E$ provides only a modest amount of protection during the first 3 or 4 years of life. However, a high amount of protection is obtained in the first few months after the priming doses or after a booster dose is given. Thus, it has been suggested that in areas of seasonal malaria transmission, the fourth dose should be given as a seasonal vaccine just before the start of the malaria transmission season rather than through an age-based schedule. A trial done in young children in Burkina Faso and Mali to evaluate this approach showed that three priming and two seasonal booster doses of RTS,S/AS01$_E$ given alone was non-inferior in protecting against severe or uncomplicated malaria than SMC given alone and that further substantial reductions in deaths from malaria, hospital admissions with severe malaria and clinical attacks of malaria were achieved when the two interventions were combined. In Burkina Faso and Mali, the R21 malaria vaccine is being given to children in communities where SMC is also being administered through the national malaria control programme, but a formal evaluation of the effect of R21 with SMC is not being done in these trials. A search of PubMed from database inception to Feb 21, 2023 for relevant published research articles which used the terms "malaria vaccine", "RTS,S vaccine", "chemoprevention", "SMC/seasonal malaria chemoprevention", and"PMC/perennial malaria chemoprevention/IPTi/intermittent preventive treatment in infants" did not identify any papers describing other studies of the effect of combining SMC and seasonal malaria vaccination.

Added value of this study

The added value of the study described in this paper is that it shows that in Burkina Faso and Mali, and probably in the many neighbouring countries with seasonal malaria transmission, the burden of malaria remains high until children reach the age of at least 5 years and that children require optimum protection until they reach this age, when they might become eligible for the school-age malaria chemopreventive programmes currently being explored in several countries where the burden of malaria remains high. The study in Burkina Faso and Mali has shown that a combination of immunological and chemopreventive approaches to malaria control might have a synergistic effect and that this could be exploited in other ways, for example by combining chemoprevention with the antimalarial monocolonal antibodies currently being evaluated with promising initial results.

Implications of all the available evidence

No single intervention provides the high amount of protection needed by young children living in the many areas of the Sahel and sub-Sahel with a high burden of seasonal malaria. Combining chemopreventive and immunological approaches, including seasonal vaccine or monoclonal antibodies, provides a potential approach. Perennial malaria chemoprevention (PMC) in young children resident in areas with perennial malaria transmissions is now being promoted by WHO and other institutions. It will be important to establish whether combination of PMC with malaria vaccination will be as effective as the combination of seasonal malaria vaccination with RTS,S/AS01$_E$ and SMC has proven to be.

morbidity and mortality in young children, malaria transmission is highly seasonal.[2] Seasonal malaria chemoprevention (SMC), which comprises monthly administration of sulphadoxine–pyrimethamine plus amodiaquine given to young children four or five times during the peak malaria transmission season, was recommended by WHO for malaria control in areas of the Sahel and sub-Sahel with highly seasonal transmission in 2012.[3] This strategy is now widely deployed with approximately 45 million children receiving SMC in 2021.[1] Despite the high effectiveness of SMC,[4] malaria remains the primary cause of hospital admissions and deaths in young children in many seasonal malaria transmission areas in sub-Saharan Africa,[5] and additional control tools are needed to control the infection in these regions. A trial done in young children in Burkina Faso and Mali showed that the addition of seasonal vaccination with the malaria vaccine RTS,S/AS01$_E$ to SMC substantially reduced the incidence of clinical malaria, severe malaria, and deaths from malaria in young children over a 3 year period.[6] These findings contributed to the historic decision by WHO in October, 2021 to recommend the deployment of RTS,S/AS01$_E$ for the prevention of *Plasmodium falciparum* malaria in children living in regions with moderate to high transmission in sub-Saharan Africa, including an option for countries with seasonal malaria transmission to provide two seasonal booster doses.[7] The objective of this study was to assess whether the marked reduction in the incidence of clinical and severe malaria achieved by combining RTS,S/AS01$_E$ and SMC seen in the first 3 years of the trial in Burkina Faso and Mali could be sustained until study children reached the age of 5 years, the age at which SMC is no longer given in these

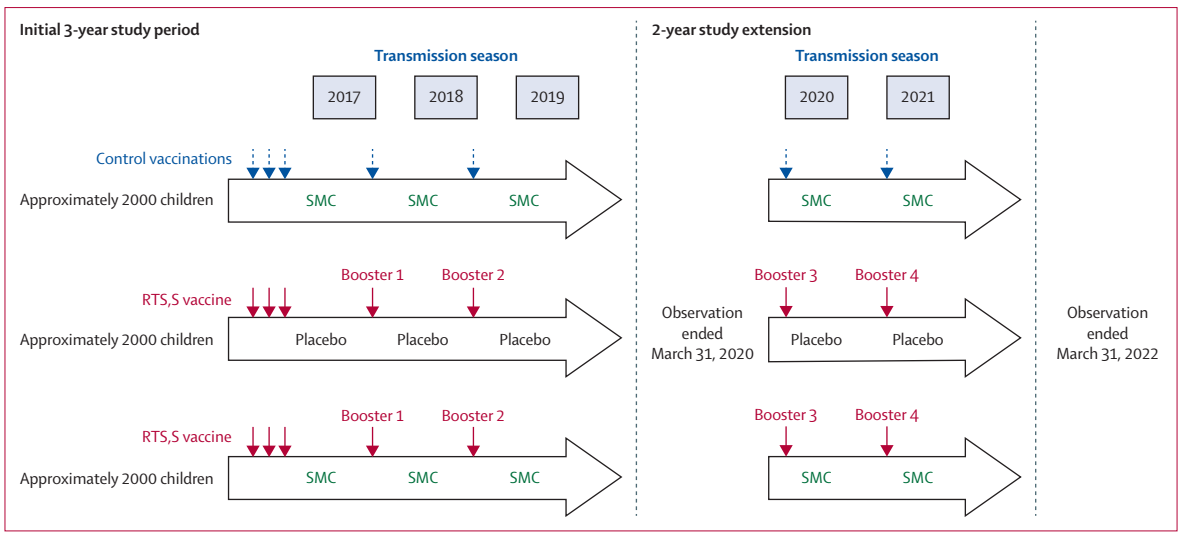

Figure 1: **Overall study design**
Only children aged below 5 years on June 1, 2021 were eligible to receive study interventions in 2021. SMC=seasonal malaria chemoprevention.

countries, and also to assess the safety of administration of repeated booster doses of the RTS,S/AS01$_E$vaccine, as an increase in the incidence of meningitis and in female mortality was noted in those who had received the vaccine during the phase 3 RTS,S/AS01$_E$ trial.[8]

Methods

Study design and participants

This was a double-blind, individually randomised, controlled, non-inferiority and superiority, phase 3 trial done at two sites: the Bougouni district and neighbouring areas in Mali and Houndé district, Burkina Faso. Research team staff were based at the district hospitals and community health centres in these areas. Children who had been enrolled in the initial 3-year trial were eligible for inclusion in the extension study if their parents or guardian gave their written informed consent. Children with a previous allergic reaction to one of the study drugs or vaccines, or who had febrile convulsions on more than one occasion following vaccination, or who had developed a serious underlying illness since initial enrolment were not eligible for re-enrolment. Children who reached the age of 5 years before June 1, 2021 exited the extension study at the end of the fourth year (the first year of the extension); the remaining children were followed for a fifth year (the second year of the extension study). The epidemiology of malaria in the trial areas has been described previously.[5,6] The overall trial design is summarised in figure 1. The trial protocol (appendix 2) was reviewed and approved by the ethics committees of the London School of Hygiene & Tropical Medicine, UK; the University of Science, Techniques, and Technologies, Bamako, Mali; the ethics committee for health research, Burkina Faso; and the regulatory authorities in Burkina Faso and Mali.

Randomisation and masking

Enrolment, randomisation, and masking procedures for the initial part of the trial have been described previously.[6] Briefly, randomisation to one of three groups—the SMC alone group, the RTS,S/AS01$_E$ malaria vaccine alone group, or the combined SMC and RTS,S/AS01$_E$ group—was done by an independent statistician. The randomisation list used permuted blocks after sorting according to age, sex, area of residence, and previous receipt of chemoprevention. Tablet computers with the randomisation list were accessible to the study pharmacists, but all other investigators and trial staff were unaware of treatment assignments. Study children were given a new photographic identity card with a quick reference code. At the time of vaccination or administration of chemoprevention, these cards were scanned to ensure that the correct intervention was administered. The investigators, trial staff, and participants remained masked to treatment allocation until the database was locked and archived with the data safety and monitoring board in July, 2022.

Procedures

All study children were given a piperonyl butoxide long-lasting insecticide-treated net (YORKOOL long lasting insecticidal net; YORKOOL Group, Tianjin, China) at initial enrolment and on enrolment into the extension study. During the extension study, children in the RTS,S/AS01$_E$-alone or combined groups received a sixth dose of RTS,S/AS01$_E$ (GSK, Rixensart, Belgium) in June, 2020 and a seventh in June, 2021 (figure 1). Children in the SMC alone group received tetanus or tetanus–diphtheria toxoid vaccine (Serum Institute of India, Pune, India) in June, 2020 and June, 2021. Vaccines were administered intramuscularly as described previously.[6] Children in the SMC alone and the combined groups received four cycles

See Online for appendix 2

of sulphadoxine–pyrimethamine plus amodiaquine at monthly intervals each year; the RTS,S/AS01$_E$-alone group received four cycles of a sulphadoxine–pyrimethamine plus amodiaquine placebo at the same times. In 2021, a fifth cycle of SMC with sulphadoxine–pyrimethamine plus amodiaquine or placebo was given to children in Burkina Faso, in line with national guidelines. Sulphadoxine–pyrimethamine plus amodiaquine was administered according to WHO recommendations.[3] A course of SMC for children older than 1 year comprised a single treatment of sulphadoxine–pyrimethamine (500 mg/25 mg) and amodiaquine 150 mg on day 1 and amodiaquine 150 mg on days 2 and 3. Infants received half of these doses. Sulphadoxine–pyrimethamine and amodiaquine and matching placebo were provided by Guilin Pharmaceuticals (Shanghai, China), a GMP-certified supplier. All treatments were given under observation.

Outcomes

The primary trial endpoint was the incidence of clinical episodes of malaria, defined as a measured temperature of at least 37·5°C, or a history of fever within the past 48 h, and *Plasmodium falciparum* parasitaemia of more than 5000/µL, in children who presented at a health facility. Prespecified secondary endpoints included all-cause deaths, deaths excluding external causes and surgery, deaths from malaria, hospital admission with malaria, malaria anaemia, blood transfusion, and prevalence of malaria parasitaemia at the end of the malaria transmission season.[6]

Children in the trial who attended a health centre with suspected malaria were tested with a rapid diagnostic test. Children who tested positive were treated with artemether–lumefantrine for uncomplicated malaria or injectable artesunate for severe malaria. Blood smears were obtained from all suspected malaria cases and read by two independent microscopists. Discrepant readings were resolved by a third reader, following a standardised algorithm.[9]

Yearly cross-sectional surveys of all available study children were carried out at the end of the malaria transmission season to establish malaria parasite prevalence and to measure haemoglobin concentration (HemoCue, AB Leo Diagnostics, Helsingborg, Sweden). At the time of these surveys, 200 randomly selected schoolchildren aged 6–12-years (not eligible for SMC) resident in the study areas were tested for malaria by microscopy. To establish the in vivo efficacy of the chemopreventive regimen, study children with asymptomatic malaria parasitaemia detected at the final cross-sectional survey in 2021 were treated with sulphadoxine–pyrimethamine plus amodiaquine, and blood films were collected for microscopy on days 1, 2, 4, 7, 14, and 28 post-treatment to test for the efficacy of the chemopreventive regimen in treating asymptomatic malaria parasitaemia.

Home visits were done daily for 7 days post-vaccination for approximately 150 randomly selected study children in each country each year to assess the frequency of local and systemic adverse events following repeated booster doses of RTS,S/AS01$_E$ or control vaccine. Serious adverse events were recorded and reported throughout the study period. Deaths that occurred outside health facilities were assessed by verbal autopsy.[10] Assignment of causes of hospital admissions or deaths inside or outside health facilities was made by two physicians masked to a child's study group. A third independent physician reviewed cases with an initial disagreement and a consensus was reached.

Statistical analysis

The rationale for the trial's sample size is described in the statistical analysis plan (appendix 2). Over the 5-year period, for the non-inferiority comparison, the study had greater than 90% power to exclude, at the 2·5% significance level, a 20% increase in clinical malaria in the RTS,S/AS01$_E$-alone group compared with the SMC alone group. For the superiority comparisons, the study had 90% power to detect a 12% difference in the incidence of clinical malaria between the combined and single intervention groups. The primary analysis population was modified intention to treat (mITT), which included all eligible children enrolled in April, 2017 who subsequently enrolled in the extension study. The primary outcome was also analysed per protocol, as defined in the statistical analysis plan (appendix 2). Secondary outcomes were analysed only by mITT. Person-time at risk was calculated from the date of first vaccination until the censoring date for that child (March 31, 2020 for children who did not join the extension study; March 31, 2021 for children who joined the extension study but reached 5 years of age by June 1, 2021; and March 31, 2022 for children who joined the extension study and were younger than 5 years on June 1, 2021); the date of death; the date of permanent emigration; or the date on which the child was last seen or consent was withdrawn.

Hazard ratios (HRs) were estimated by means of Cox regression models, stratified by study centre, with robust standard errors. Protective efficacy was calculated as $(1-HR)\times100$, with two-sided 95% CIs. To preserve the type-I error rate at the 5% level, the closed testing procedure was used: the Wald test of the null hypothesis of equal HRs comparing all three groups was done. If this was rejected at the 5% significance level, pairwise comparisons were done by means of a 5% significance level. Rate differences were estimated by means of the method of Xu and colleagues,[11] and the number of cases averted per 1000 was estimated as the difference in cumulative hazards.

The statistical analysis was done by means of Stata version 16.

Oversight of the trial was provided by a data safety and monitoring board, and by a trial steering

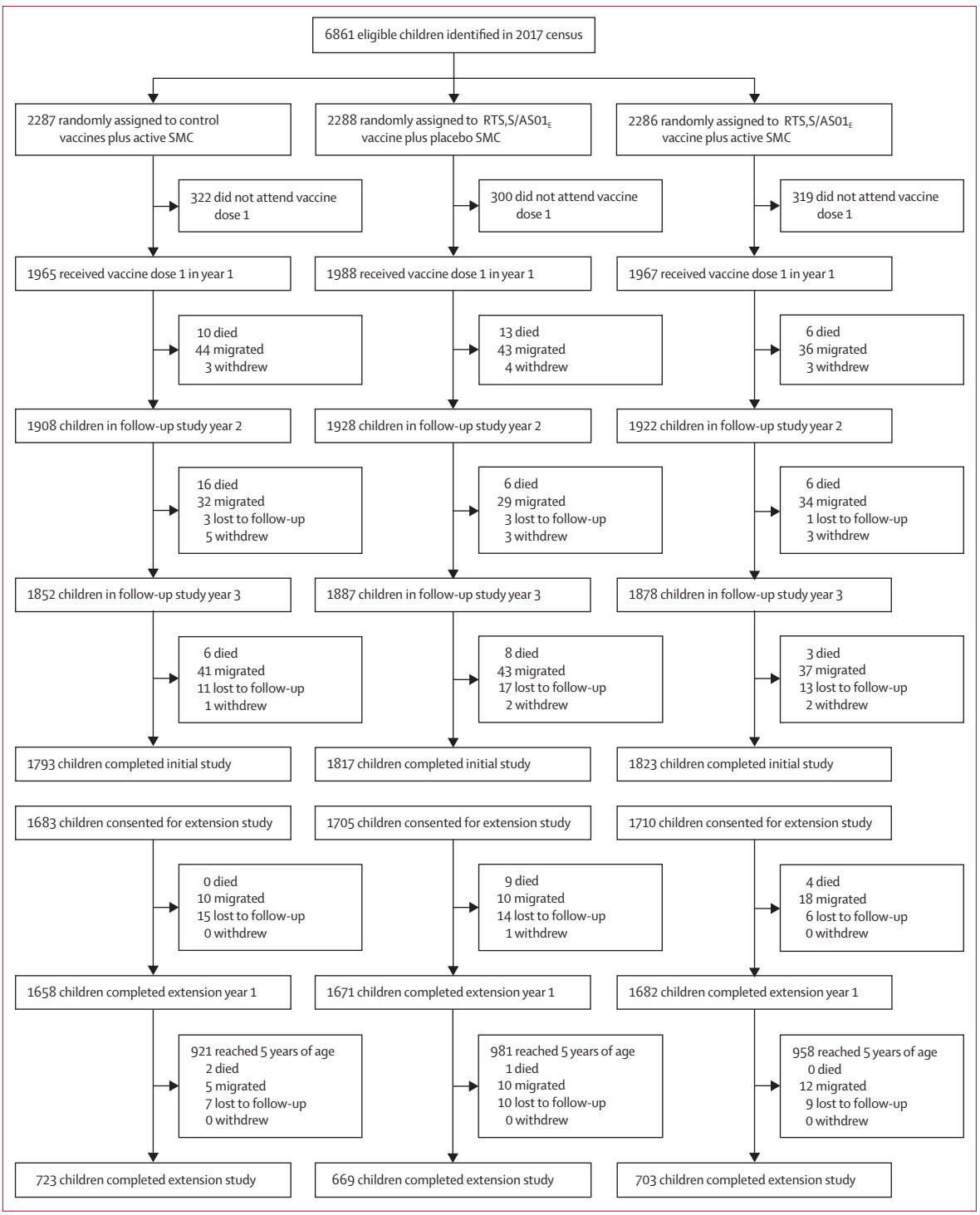

Figure 2: **Trial profile**
The number of children noted to have completed the first phase of the study successfully is larger than reported in the study by Chandramohan and colleagues[6] as different criteria for study completion were used in this secondary analysis.

committee. We use the CONSORT reporting guidelines.[12] The trial is registered on ClinicalTrials.gov, NCT04319380.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation,

	Child-years at risk	Events	Rate per 1000 child years at risk	Protective efficacy (95% CI) combined *vs* seasonal malaria chemoprevention alone	Protective efficacy (95% CI) combined *vs* RTS,S/AS01$_E$ alone
Whole study, both countries					
Seasonal malaria chemoprevention alone	7887·0	2472	313·4 (301·3 to 326·0)	1 (ref)	..
RTS,S/AS01$_E$-alone	7937·8	2537	319·6 (307·4 to 332·3)	−3·0% (−11·8 to 5·2)	1 (ref)
Combined	7957·4	1055	132·6 (124·8 to 140·8)	57·7% (53·3 to 61·7)	59·0% (54·7 to 62·8)
Whole study, Burkina Faso					
Seasonal malaria chemoprevention alone	3775·0	1482	392·6 (373·1 to 413·1)	1 (ref)	..
RTS,S/AS01$_E$-alone	3695·6	1617	437·6 (416·7 to 459·4)	−11·5% (−22·1 to −1·8)	1 (ref)
Combined	3799·0	678	178·5 (165·5 to 192·4)	54·7% (49·2 to 59·6)	59·3% (54·4 to 63·7)
Whole study, Mali					
Seasonal malaria chemoprevention alone	4111·9	990	240·8 (226·2 to 256·2)	1 (ref)	
RTS,S/AS01$_E$-alone	4242·2	920	216·9 (203·3 to 231·3)	9·60% (−5·67 to 22·6)	1 (ref)
Combined	4158·4	377	90·7 (82·0 to 100·3)	62·3% (54·8 to 68·6)	58·3% (49·9 to 65·4)
Year 4, both countries					
Seasonal malaria chemoprevention alone	1669·4	562	336·7 (309·9 to 365·7)	1 (ref)	..
RTS,S/AS01$_E$-alone	1687·6	648	384·0 (355·5 to 414·7)	−14·9% (−30·5 to −1·2)	1 (ref)
Combined	1695·4	300	176·9 (158·0 to 198·1)	47·5% (38·8 to 54·9)	54·3% (47·0 to 60·6)
Year 5, both countries					
Seasonal malaria chemoprevention alone	729·2	249	341·5 (301·6 to 386·6)	1 (ref)	..
RTS,S/AS01$_E$-alone	679·1	349	513·9 (462·7 to 570·7)	−49·5% (−79·3 to −24·6)	1 (ref)
Combined	713·1	131	183·7 (154·8 to 218·0)	46·8% (33·2 to 57·7)	64·4% (55·8 to 71·4)

Table 1: **Protective efficacy against cases of clinical malaria during the 5-year study period and during the 2-year extension period**

writing of the report, or the decision to submit for publication.

Results

An initial 6861 children were recruited in April, 2017; 1793 children in the SMC alone group, 1817 in the RTS,S/AS01$_E$-alone group, and 1823 in the combined group completed the initial 3 year follow-up period.[6] At the time of first vaccination, 51·8% of children were male and 48·2% female. 94% of children in each group were reconsented and re-enrolled for the extension study. At the end of the trial in March 2022, 2095 (82·8%) of 2530 of children eligible to remain within the trial for its full 5 years were still being followed. Reasons for drop-out are shown in the CONSORT chart (figure 2).

Coverage with RTS,S/AS01$_E$ or a control vaccine remained very high throughout the 5 years of the study (appendix 2 p 1), and was similar between study groups. In year 1, 93·4% of children received all three doses of study vaccines; in year 2, 95·1% of children still in follow-up received booster doses of vaccine; in year 3, 94·7%; in year 4, 98·7%; and in year 5, 96·3%. The coverage with SMC was also high over the course of the study and was similar between study groups ranging from 82·8% in the first year of the study to 94·7% in the last year. (appendix 2 pp 2–3). In 2021, a fifth dose of SMC was given to children in Burkina Faso with a coverage of 90·7%.

The incidence of clinical malaria and protective efficacy estimates during the whole study period and during the 2-year extension period are presented in table 1. The mean number of clinical malaria cases per child over the 5-year period of the trial and the incidence of clinical malaria by calendar month over the study period are shown in figure 3 (panel A and panel B, respectively). 6064 clinical malaria episodes occurred among study children during the 5-year study period. The incidence rate of clinical malaria per 1000 person-years at risk (PYAR) was 313 in the SMC alone group, 320 in the RTS,S/AS01$_E$-alone group, and 133 in the combined group. Protective efficacy in the combined group was 57·7% (95% CI 53·3–61·7) compared with SMC alone and 59·0% (54·7–62·8) compared with RTS,S/AS01$_E$-alone. Thus, the protective efficacy of the combination versus SMC over the 5-year period of the study was very similar to that seen in the first 3 years of the trial when the protective efficacy of the combination versus SMC was 62·8 % (58·4–66·8) and the protective efficacy of the combination versus RTS,S/AS01$_E$ was 59·6% (54·7–64·0). Overall, RTS,S/AS01$_E$-alone was non-inferior to SMC alone, (HR 1·03; 95% CI 0·95–1·12), and the efficacy findings were similar in Burkina Faso and Mali (table 1). Over the whole study period, the rate differences per 1000 PYAR were 180·7 (95% CI 159·5–201·9) between the SMC alone and the combined group, and 188·9 (167·5–210·2) between the RTS,S/AS01$_E$-alone and the combined groups (appendix 2 pp 4–5). The estimated total number of cases averted per 1000 children in the combined group (derived from the cumulative hazard functions) was 876 (95% CI 796–957) relative to the SMC alone group, and 1015 (929–1101)

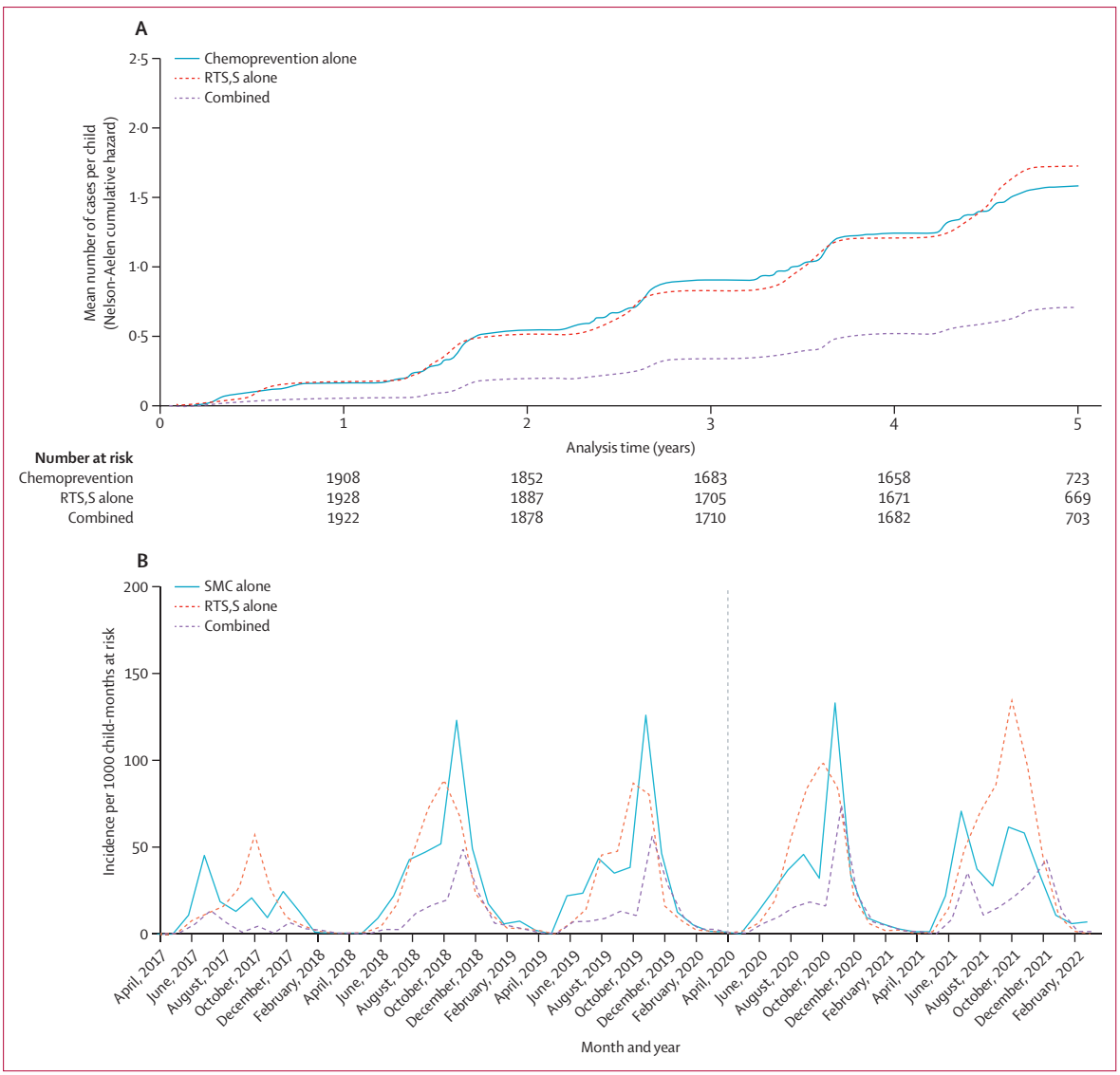

Figure 3: **Clinical malaria cases**

(A) Cumulative mean number of clinical malaria cases per child over the 5-year period of the trial in the three study groups. (B) Incidence of the clinical malaria in the three study groups by calendar month and year. Panel A indicates the mean number of clinical malaria episodes per child over the study period (equal to the Nelson-Aalen estimate of the cumulative hazard). The number at risk drops in year 5 as children who had reached 5 years of age, were aged out of the cohort. Panel B gives the incidence rate per 1000 child-months at risk, in each calendar month of the study. Note that in the fifth year of the study, 5-monthly cycles of SMC were administered in Burkina Faso, matching the standard of care provided to children outside of the study through the national malaria control programme. The low incidence of malaria in all groups in the first year of the study is likely to be associated with the much lower than average rainfall in that year (2017) and the young age of the study children at that time.

relative to the RTS,S/AS01$_E$-alone group. Analysis of data from the 2-year extension period showed that the combined group was superior to SMC alone in year 4 (protective efficacy 47·5%; 95% CI 38·8–54·9) and in year 5 (protective efficacy 46·8%; 33·2–57·7) and superior to RTS,S/AS01$_E$-alone in year 4 (protective efficacy 54·3%; 47·0–60·6) and in year 5 (protective efficacy 64·4%; 55·8–71·4). Rate differences comparing the combined group with the SMC alone or RTS,S/AS01$_E$-alone groups remained large during the extension period, in year 4; these were respectively 159·7 cases per 1000 (95% CI 121·6–197·8) and 209·3 (169·9–248·7), and in year 5, 159·9 (102·0–217·8) and 332·1 (262·8–401·3; appendix 2 pp 4–5). Results from per-protocol analyses were similar to mITT analyses (appendix 2 p 6). During the last year of the study the incidence of clinical episodes of malaria was substantially higher in the RTS,S/AS01$_E$-alone group (513·9 [462·7–570·7] per 1000 child years at risk) compared with the SMC alone group (341·5 [301·6–386·6]), with the difference being most marked at the end of the transmission season (figure 3B). The difference between groups was much more marked in Burkina Faso than in

	Events	Rate per 1000 person-years at risk (95% CI)	Protective efficacy (95% CI) *vs* SMC alone	Protective efficacy (95% CI) *vs* RTS,S alone
Hospitalisations (all causes)				
Seasonal malaria chemoprevention alone	86	10·9 (8·83 to 13·5)	..	..
RTS,S/AS01$_E$-alone	95	12·0 (9·79 to 14·6)	−11·1% (−51·0 to 18·3)	..
Combined	78	9·80 (7·85 to 12·2)	9·7% (−23·5 to 34·1)	18·7% (−11·1 to 40·6)
Hospitalisations (excluding external causes and surgery)				
Seasonal malaria chemoprevention alone	68	8·62 (6·80 to 10·90)	..	..
RTS,S/AS01$_E$-alone	87	11·0 (8·88 to 13·50)	−29·0% (−79·6 to 7·3)	..
Combined	61	7·67 (5·96 to 9·85)	10·7 (−26·6 to 37·0)	30·8% (2·58 to 50·8)
Hospitalisation for malaria				
Seasonal malaria chemoprevention alone	57	7·23 (5·57 to 9·37)	..	..
RTS,S/AS01$_E$-alone	67	8·44 (6·64 to 10·7)	−18·9% (−71·5 to 17·6)	..
Combined	36	4·52 (3·26 to 6·27)	37·1% (3·3 to 59·1)	47·1% (19·0 to 65·4)
Hospitalisation for malaria meeting WHO definition of severe malaria				
Seasonal malaria chemoprevention alone	45	5·71 (4·26 to 7·64)	..	..
RTS,S/AS01$_E$-alone	43	5·42 (4·02 to 7·30)	3·6% (−47·4 to 37·0)	..
Combined	15	1·89 (1·14 to 3·13)	66·8% (40·3 to 81·5)	65·6% (38·0 to 80·9)
Hospitalisation for severe malarial anaemia				
Seasonal malaria chemoprevention alone	35	4·44 (3·19 to 6·18)	..	..
RTS,S/AS01$_E$-alone	30	3·78 (2·64 to 5·41)	13·3% (−42·0 to 47·1)	..
Combined	12	1·51 (0·86 to 2·66)	65·9% (34·1 to 82·4)	60·7% (23·6 to 79·8)
Blood transfusions				
Seasonal malaria chemoprevention alone	28	3·55 (2·45 to 5·14)	..	..
RTS,S/AS01$_E$-alone	25	3·15 (2·13 to 4·66)	10·3% (−55·0 to 48·1)	..
Combined	9	1·13 (0·59 to 2·17)	68·1% (32·6 to 84·9)	64·4% (23·4 to 83·5)
Deaths (all causes)				
Seasonal malaria chemoprevention alone	34	4·31 (3·08 to 6·03)	..	..
RTS,S/AS01$_E$-alone	37	4·66 (3·38 to 6·43)	−8·8% (−73·1 to 31·7)	..
Combined	19	2·39 (1·52 to 3·74)	44·5% (2·77 to 68·3)	49·0% (11·4 to 70·6)
Deaths (excluding external causes and surgery)				
Seasonal malaria chemoprevention alone	27	3·42 (2·35 to 4·99)	..	..
RTS,S/AS01$_E$ alone	28	3·53 (2·44 to 5·11)	−4·0% (−76·2 to 38·7)	..
Combined	16	2·01 (1·23 to 3·28)	41·1% (−9·24 to 68·3)	43·4% (−4·52 to 69·3)
Deaths from malaria				
Seasonal malaria chemoprevention alone	12	1·52 (0·864 to 2·68)	..	..
RTS,S/AS01$_E$-alone	15	1·89 (1·14 to 3·13)	−25·8% (−168·6 to 41·1)	..
Combined	4	0·503 (0·189 to 1·34)	66·8% (−2·68 to 89·3)	73·6% (20·8 to 91·2)

Table 2: **Severe outcomes over the whole 5-year study period, both countries combined**

Mali. In Burkina Faso the incidence rate was 672·9 (589·6–768·0) in the RTS,S/AS01$_E$-alone group compared with 377·4 (317·3–448·7) in the SMC alone group. In Mali, the incidence was 366 (308·2–435·3) in the RTS,S/AS01$_E$-alone group and 310 (259·6–370·8) in the SMC alone group. In Burkina Faso, an additional, fifth round of SMC was given at the end of the malaria transmission season whereas only four rounds of SMC were given in Mali.

Over the 5 years of follow-up, the combined intervention provided a high amount of protection compared with SMC alone or RTS,S/AS01$_E$-alone against the following prespecified secondary endpoints: admission to hospital for WHO-defined severe malaria, severe malaria anaemia, and blood transfusion (table 2). Point estimates for death from all causes, death excluding external causes and surgery, and death from malaria were also substantially lower during the whole study period in the combined group than in the RTS,S/AS01$_E$-alone or SMC alone groups (table 2). During the 2-year extension period, the incidence of WHO-defined severe malaria was lower than in the first 3 years but remained relatively high with a rate of 3·3/1000 per year in the SMC-alone group (appendix 2 p 7). During the 2-year extension period, there were 12 deaths excluding deaths from external causes: two in the SMC alone group, six in the RTS,S/AS01$_E$-alone group, and four in the combined group (appendix 2 p 8). Five deaths attributed to malaria

were reported during the extension period: one in the SMC alone group, three in RTS,S/AS01$_E$-alone group, and one in the combined group.

The prevalence of *P falciparum* parasitaemia at the end of the malaria transmission season in the SMC alone group was 15·2% in 2020 and 8·2% in 2021. Prevalence was reduced by 51% (prevalence ratio 0·49; 95% CI 0·40–0·60) in 2020 and by 46% (prevalence ratio 0·54; 0·35–0·82) in 2021 in the combined group compared with the SMC alone group (appendix 2 pp 9–10). Parasite prevalence in school-age children at the end of malaria transmission season was 54·5% in Houndé, Burkina Faso in 2020 and 56·0% in 2021. The respective figures in Bougouni, Mali were 18·5% and 15·5%.

An in vivo treatment study with sulphadoxine–pyrimethamine plus amodiaquine was done in 195 study children with asymptomatic malaria parasitaemia detected during the cross-sectional survey in 2021, which showed that *P falciparum* remained sensitive to the sulphadoxine–pyrimethamine plus amodiaquine combination in the study areas with only two early unsuccessful treatment outcomes (one in each country), no further unsuccessful clinical or parasitological outcomes, and no reinfections between day 7 and day 28, giving an adequate clinical and parasitological response rate of response rate of 99·3% (95% CI 95·3–99·9) in Burkina Faso and 97·9% (95% CI 86·2–99·7) in Mali (appendix 2 p 11).

Local and systemic adverse events following priming or booster doses of RTS,S/AS01$_E$ were mostly minor and were similar in frequency to those observed with the control vaccines. Five children had febrile convulsions the day after vaccination with RTS,S/AS01$_E$ during the first 3 years of the study, all of whom recovered completely; no febrile convulsions were observed following administration of third or fourth booster doses. The overall incidence of febrile convulsions following RTS,S/AS01$_E$ vaccination was approximately one per 4500 doses. Ten possible cases of meningitis were investigated by lumbar puncture, eight during the first 3 years of the study, and two during the extension period. Cerebrospinal fluid examination excluded a diagnosis of meningitis in all of these children. As noted in the first 3 years of the study, there was no evidence of an interaction between study group and sex for deaths or hospital admissions (table 3). The all-cause death rate per 1000 PYAR was 4·25 (95% CI 3·05–5·92) in boys versus 2·74 (1·79–4·21) in girls. When external causes and surgery were excluded, the incidence rates were 3·16 (95% CI 2·15–4·63) in boys and 2·35 (1·48–3·73) in girls (table 4).

	Events	Person-years at risk	Rate (95% CI) per 1000 person-years at risk
Seasonal malaria chemoprevention alone—male participants	16	4068·7	3·93 (2·41–6·42)
Seasonal malaria chemoprevention alone—female participants	11	3818·2	2·88 (1·60–5·20)
RTS,S/AS01$_E$-alone—male participants	14	4143·4	3·38 (2·00–5·71)
RTS,S/AS01$_E$-alone—female participants	14	3794·3	3·69 (2·19–6·23)
Combined group—male participants	12	4096·3	2·93 (1·66–5·16)
Combined group—female participants	4	3861·1	1·04 (0·39–2·76)
RTS,S/AS01$_E$-alone and combined group (pooled)—male participants	26	8239·7	3·16 (2·15–4·63)
RTS,S/AS01$_E$-alone and combined group (pooled)—female participants	18	7655·5	2·35 (1·48–3·73)

Table 3: **All-cause deaths (excluding external causes and surgery) by study groups and sex**

	Hazard ratio (95% CI)	Gender interaction parameter (95% CI)
Combined *vs* seasonal malaria chemoprevention alone in males	0·75 (0·35–1·58)	0·48 (0·12–1·88)*
Combined *vs* seasonal malaria chemoprevention alone in females	0·36 (0·11–1·13)	..
Combined *vs* RTS,S/AS01$_E$-alone in males	0·86 (0·40–1·86)	0·32 (0·08–1·25)*
Combined *vs* RTS,S/AS01$_E$-alone in females	0·28 (0·09–0·85)	..
RTS,S/AS01$_E$-alone *vs* seasonal malaria chemoprevention alone in males	0·87 (0·42–1·78)	1·48 (0·51–4·31)*
RTS,S/AS01$_E$-alone *vs* seasonal malaria chemoprevention alone in females	1·29 (0·59–2·83)	..
Pooled RTS,S/AS01$_E$ groups *vs* seasonal malaria chemoprevention alone in males	0·81 (0·43–1·51)	1·01 (0·38–2·68)†
Pooled RTS,S/AS01$_E$ groups *vs* seasonal malaria chemoprevention alone in females	0·82 (0·39–1·73)	..
Female–male mortality ratios within each group		
SMC alone	0·72 (0·34–1·56)	..
RTS,S/AS01$_E$-alone group	1·07 (0·51–2·25)	..
Combined group	0·35 (0·11–1·07)	..
Pooled group (RTS,S/AS01$_E$ plus seasonal malaria chemoprevention and RTS,S/AS01$_E$-alone groups)	0·73 (0·40–1·33)	..

Interaction parameter and 95% CI indicates evidence for effect modification by gender (1 indicates no effect modification). *Model fitted with the three study groups. †Model fitted with RTS,S/AS01$_E$ groups pooled.

Table 4: **All cause deaths (excluding external causes and surgery)—between group comparisons**

Discussion

Combining seasonal vaccination with RTS,S/AS01$_E$ with SMC reduced substantially the incidence of clinical episodes of malaria, hospitalisations with WHO-defined severe malaria, severe malaria anaemia, blood transfusion, and death in children exposed to a high degree of malaria transmission from early in life until the age of 5 years. How this apparent synergy between vaccine and drugs is brought about is not clear, but one possibility is that the immune response induced by the vaccine, and by natural exposure, is more effective when faced with a low density parasitaemia induced by the drugs, than when faced by parasitaemia at high density. In Year 5 of the study, a higher incidence of clinical malaria was seen in children in the RTS,S/AS01$_E$-alone group compared with those in the SMC alone group. That this difference was much more marked in Burkina Faso than in Mali strongly suggests that this was due largely to the fact that in Burkina Faso, but not in Mali, a fifth round of SMC was given at the end of the malaria season. This finding strongly supports the decision by the Burkinabe

National Malaria programme to deliver five rounds of SMC in parts of the country where the malaria transmission season is longest. Despite the findings in the final year of the trial, over the 5 years of the study, children who received only RTS,S/AS01$_E$ had a similar amount of protection to those who received only SMC. This is important because if seasonal malaria vaccination is introduced at scale in countries deploying SMC, it is likely that although a majority of children will receive both interventions, some children might receive only RTS,S/AS01$_E$ or only SMC.

Repeated doses of RTS,S/AS01$_E$ were safe. Only five episodes of post-vaccination febrile convulsions were recorded, all in the first 3 years of the study; no cases of meningitis were detected, and there was no evidence of an excess of deaths in girls in children who received RTS,S/AS01$_E$, as had been noted in the RTS,S/AS01$_E$ phase 3 trial. The findings of the current study and those of the ongoing RTS,S/AS01$_E$ pilot implementation suggest that the safety signals recorded in the RTS,S/AS01$_E$ phase 3 trial were chance findings. However, this issue is still generating concern. [13] During the last 2 years of the study, there were more deaths in children in the RTS,S/AS01$_E$ alone and combined groups than in the SMC alone group (six, four, and two respectively). But with these small numbers, this difference is likely to be due to chance.

This study has shown that in the study areas there remains a high burden of malaria in children receiving SMC even though SMC remains highly effective, reflecting the very intense rates of transmission in the study areas. In the SMC alone group the incidence of clinical malaria among children aged 4–5 years was similar to that seen among children aged 1–3 years and more than 0·3 episodes per child per year, whereas the incidence of severe malaria was lower among the children aged 4–5 years compared with the children aged 1–3 years (3·3/1000 *vs* 6·7/1000 PYAR). This high incidence of clinical malaria and severe malaria seen in older children warrants continuation of the combination of SMC and seasonal vaccination at least until children reach the age of 5 years.

A limitation of this study is that as SMC is standard of care in Burkina Faso and Mali, the trial could not include a control group receiving neither RTS,S/AS01$_E$ or SMC, and so the absolute efficacy of the combination cannot be estimated directly. However, during the course of the trial the incidence of clinical episodes of malaria per year in children in the combined group was 0·18 episodes per child per year in Burkina Faso and 0·09 episodes per child per year in Mali, far lower than incidence rates of 2·88 and 1·79 recorded in children of a similar age in Burkina Faso and Mali in 2008 by means of similar surveillance and laboratory techniques who were protected by insecticide treated nets only.[14,15] This suggests that deployment of seasonal vaccination with RTS,S/AS01$_E$ combined with a long-lasting insecticide-treated net and SMC has the potential to reduce very substantially the burden of malaria in children up to the age of 5 years in many parts of sub-Saharan Africa. A second limitation of the study is that there was a 13·7% dropout of children between initial consenting and first vaccination due out migration and families changing their mind about volunteering their child for the study. However, analysis of the scarce information available for these children suggests that there were no major demographic differences between the two groups and that the children who were vaccinated were representative of their communities.

In areas of high transmission, older children acquire some protection against malaria, in particular against severe malaria, through naturally acquired immunity induced by repeated exposure to the malaria parasite. Thus, there is a risk that stopping administration of effective interventions abruptly could lead to an increase in the risk of malaria in subsequent years (rebound or delayed malaria).[16] Therefore, children in the RTS,S/AS01$_E$ plus SMC trial are being followed-up for 2 years after ceasing to receive RTS,S/AS01$_E$ and SMC through passive surveillance and a case control study to assess whether they are at any increased risk of malaria.

A phase 2b trial of the R21/Matrix-M malaria vaccine done in Nanoro, Burkina Faso, an area with similar malaria epidemiology to that of Houndé, Burkina Faso, where this trial was done and where SMC is also deployed, found a substantial reduction in the incidence of clinical malaria following priming and a seasonal booster dose of the vaccine.[17] A phase 3 trial of this vaccine is now underway at five sites in four countries, two of which have seasonal malaria transmission and where SMC is given (ClinicalTrials.gov, NCT04704830). Provided that the results of the phase 3 study confirm those of the phase 2 trial, R21/Matrix-M might become the second malaria vaccine to be approved for deployment in high transmission areas, with evidence to support its use as a seasonal malaria vaccine in areas where this is appropriate.

The WHO recommendation on the deployment of RTS,S/AS01$_E$ states that countries with highly seasonal malaria, or with perennial malaria transmission with seasonal peaks, might consider providing the vaccine seasonally,[7] and several African countries are considering this option. It is now important to establish how seasonal vaccination with RTS,S/AS01$_E$ or R21 could be delivered at scale most effectively when sufficient doses of these vaccines become available to support national programmes that wish to follow this recommendation. Potential options include delivery of seasonal vaccination once a year through routine Expanded Programme on Immunization clinics or through an annual mass vaccination campaign.[18] The efficacy, feasibility, and acceptability of these different options now need to be explored.

Contributors

The first draft of the paper was written by ADi and J-BO. No paid support was employed in writing the paper. DC and BG coordinated the trial; IZ, IS, J-BO, and ADi managed the field operations and reviewed substantially the draft; and MC wrote the analytical plan, did the statistical analysis, and reviewed substantially the draft. RSY, DI, CZ, YS, AT, FN, KS, MK, HY, OMD, MD, KD, ST, AM, and ADo contributed substantially to data collection and reviewed the draft; IT, AH, AAS, IK, and PS managed the data and reviewed the draft; JG assisted with the coordination of the trial; PM provided statistical support and reviewed the draft; and CL, JW, CO, OO-A, HT, and AD contributed to the overall trial oversight and reviewed the draft. MC and PM accessed and verified the database. All authors read and approved the final version of the manuscript. BG and ADi had final responsibility for the decision to submit for publication.

Declaration of interests

OO-A is an employee of the GSK group of companies and has restricted shares in the GSK group of companies. All of the authors declare no competing interests.

Data sharing

Individual de-identified data on trial participants, and the data dictionary, protocol, and statistical analysis plan will be made available to qualified investigators following a request for use of these materials, and will be held at the London School of Hygiene & Tropical Medicine (https://datacompass.lshtm.ac.uk/). Data will be available from the end of 2023 following analysis of secondary endpoints defined in the statistical analysis plan. Requests for access to trial data should be addressed to the corresponding author (brian.greenwood@lshtm.ac.uk).

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