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Title

Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced (September 2021, v1.2)

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This report was reviewed by the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Group (MPAG) in October 2021 and was used to support the development of the recommendation included in the *WHO Guidelines for malaria*. It is being made publicly available for transparency purposes and information, in accordance with the *WHO handbook for guideline development, 2nd edition* (2014).

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Annex 3: Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced

Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced

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Contents

Background: 4
Evaluation design: 4
Statistical methods: 5
Results: 6
Vaccine delivery and uptake: 6
Hospital surveillance: 8
Mortality surveillance: 8
Safety: 9
Meningitis: 9
Cerebral malaria: 9
Mortality: 10
Impact: 10
Hospital admission with severe malaria among children eligible to have received three doses of RTS,S/AS01: 10
Hospital admissions of patients with a positive malaria test: 11
All-cause hospital admission: 11
Strengths and limitations: 11
Key points: 13
Figures and Tables: 14
Figure 1. Distribution by age of total person years, up to April 30 2021, in children eligible to have received at least one dose of RTS,S/AS01, in each country. 15
Figure 2: Total Number of first RTSS doses (RTSS-1) administered per month, in each country, up to April 2021. 15
Figure 3. A: Estimated proportion of vaccinated person time, by age, in eligible age groups in implementation areas in Malawi, Ghana and Kenya. 16
Figure 4. Age distribution of meningitis cases (probable and confirmed cases) admitted to sentinel hospitals from both implementation and comparison areas, up to April 30 2021, in age groups who would have been eligible to receive (at least one dose of) the malaria vaccine, in each country. 17
Figure 5. Age distribution of severe malaria cases from comparison areas admitted to sentinel hospitals up to April 30 2021, in age groups who would have been eligible to receive (at least 1 dose) of the malaria vaccine. 18
Figure 6: Age distribution of deaths due to any cause except injury, occurring in comparison areas up to March 31 2021, in age groups who would have been eligible to have received at least one dose of RTS,S/AS01, in each country. 19
Table 1: Summary of impact outcomes: 20
Table 2: Comparison with safety signals observed in the phase 3 trial[1] 21

Table 3. Baseline characteristics of the malaria vaccine pilot area (variables used for randomisation constraints):.....22

Table 4. Baseline characteristics of the malaria vaccine pilot area, restricted to clusters within the pre-defined sentinel hospital areas 23

Table 5. RTS,S/AS01 vaccine uptake from household surveys of children aged 12-23 months.....24

Annex 1: Calculation of incidence rate ratios 24

Figure A1. Probable or confirmed meningitis: Rate Ratios for the association between the introduction of RTS,S/AS01 and probable or confirmed meningitis in children age-eligible to receive dose 1. 25

Figure A2. Cerebral malaria: Rate Ratios for the association between the introduction of RTS,S/AS01 and cerebral malaria (including children with malaria and impaired consciousness with unknown meningitis status) in children age-eligible to receive dose 1.....26

Figure A3. Severe malaria: Rate Ratios for the association between the introduction of RTS,S/AS01 and severe malaria (including children with malaria and impaired consciousness or convulsions with unknown meningitis status) in children age-eligible to have received dose 3.....26

Figure A4. Mortality excluding accidents and trauma (impact population): Rate Ratios for the association between the introduction of RTS,S/AS01 and death (excluding those due to accidents or trauma) in children age-eligible to have received dose 3. 27

Background:

The RTS,S/AS01 malaria vaccine was introduced in pilot schemes in Malawi, Ghana and western Kenya in 2019, to evaluate safety, and effectiveness before the vaccine could be recommended more widely.

The evaluation, planned over 4 years, aims to assess the feasibility of achieving high uptake of the vaccine, and to measure the effect that introducing the malaria vaccine has in reducing child deaths and hospital admissions with severe malaria, in areas with year-round malaria transmission. The evaluation also addresses three safety signals that were observed in the phase 3 trial but whose significance was unclear: an unexplained excess of meningitis cases in RTS,S/AS01 recipients, an excess in cerebral malaria cases among RTS,S/AS01 recipients, and an excess of deaths among girls who received RTS,S/AS01.

It was anticipated that sufficient data to assess the safety signals and the initial impact on the incidence of hospital admission with severe malaria was likely to be available after the first 2 years of the evaluation. The primary analysis of these outcomes would be done at that time. These results, if favourable, would be sufficient to support a recommendation for wider use of the vaccine. Information which would follow later would include uptake of the fourth dose and the impact of vaccine introduction on all-cause mortality.

Evaluation design:

Within the pilot region in each country, districts or similar areas were randomized to introduce the vaccine in 2019, or to delay introduction until a decision is reached about safety and effectiveness. The scale of the introduction and duration of the evaluation was chosen in order to be able to measure the impact of vaccine introduction on child survival. A total of 158 areas were randomized (66 districts in Ghana; 46 sub-counties in western Kenya; and 46 groups of immunization clinics and their associated catchment areas, in Malawi). Each area had a total population of about 100,000 and an expected birth cohort of about 4,000 per year. The areas where introduction was delayed serve as comparison areas for the purpose of the evaluation. Household surveys were conducted throughout the implementation and comparison regions in each country, before vaccine introduction, to assess at baseline the coverage of EPI vaccines, use of insecticide-treated bednets and malaria prevalence in children, and information about care-seeking for children who are unwell (with reported fever).

The vaccine schedule involves four doses, at 6,7,9 and 24 months of age in Ghana and Kenya and at 5,6,7 and 22 months in Malawi. The RTS,S/AS01 vaccine is delivered by national immunization programmes through their routine systems. This has involved adding three vaccination visits to the EPI schedule in Ghana and Kenya and four additional visits in Malawi. In each country the fourth dose is given 15 months after the third dose, three months earlier than in the phase 3 trial.

Delivery of RTS,S/AS01 in each country is being monitored by the EPI programme, and uptake of the vaccine is being assessed independently through household surveys, conducted about 18 months and 30 months after introduction of the malaria vaccine. Surveillance for severe malaria and other conditions is being maintained through sentinel hospitals where diagnostic procedures have been strengthened, and surveillance for mortality has been established in the community throughout the implementation and comparison areas. Mortality surveillance aimed to build on, and substantially expand, existing vital registration systems. Hospital and mortality surveillance started in each country when the malaria vaccine was introduced or shortly afterwards.

At the start of the evaluation, the pilot areas in all three countries had high coverage of the routine childhood vaccines in the first year of life. The percentage of children 12-23 months who had received their third dose of DTP-containing vaccine[1] was 95% in Ghana, 95% in Malawi and 92% in Kenya, and 89%, 93% and 90% respectively had received their first dose of measles-containing vaccine. With respect to vaccines in the second year of life, among children 24-35 months of age, the percentage that had received their second dose of measles-containing vaccine was 82% in Ghana. Among children aged 5-48 months 91% slept under an long-lasting insecticide-treated bednet (LLIN) in Malawi, where an LLIN distribution campaign had been completed just prior to the survey, 64% in Ghana, and 87% in Kenya, and the prevalence of recent or current *P.falciparum* infection in this age group, as measured by rapid diagnostic test, was 21% in Ghana, 22% in Malawi and 22% in Kenya.

The evaluation continues until 2023 but by April of 2021 sufficient data had accrued to address the safety signals observed in the phase 3 trial, and to provide evidence of the impact of vaccine introduction on the incidence of hospital admission with severe malaria. This analysis of safety and impact on severe malaria is the primary analysis on which decisions about wider use of the vaccine will be based.

Statistical methods:

For each outcome of interest, the incidence rate ratio was estimated comparing the incidence rate among children eligible to have received the malaria vaccine in regions where the vaccine was introduced, with that in the corresponding age groups in comparison areas. The method of estimation takes advantage of the fact that surveillance is maintained for all children between 1 and 59 months of age, including both eligible children, and children who are not eligible for vaccination because they are too young or were too old when the vaccine was introduced. If the vaccine has no effect, the ratio of the number of events in eligible versus non-eligible children should be the same in intervention and comparator areas. The ratio of these ratios, is an estimate of the incidence rate ratio associated with vaccine introduction in the vaccine-eligible age group. Confidence intervals are estimated using standard methods (Annex 1). Events are classified as belonging to vaccine-eligible children, or non-eligible children. To avoid contamination, children who were just too old to be eligible, by up to two months, were excluded from analysis, as the vaccine uptake in this group is unknown. For this reason, the total events in eligible and non-eligible categories is slightly less than the total number of events for that outcome.

By using the data for the non-eligible children in each region there is an adjustment for underlying differences in disease burden or access to hospital between implementation and comparison regions, in so far as these factors will tend to be highly correlated between different age groups. Pre-intervention data on the incidence of the outcomes of interest could serve this purpose but surveillance was established only when the vaccine was introduced and vaccine introduction could not have been delayed in order to obtain such data. A second advantage is that reliance on population denominators, which are challenging to estimate reliably, is avoided when estimating incidence rate ratios.

[1] Vaccine status documented from the home-based record (HBR) or according to caregiver recall, except at baseline in Ghana where vaccine status was determined only from children with an HBR (in Ghana 88% of children 12-23months surveyed had an HBR).

For safety outcomes, the research question[2] was whether the excess of cases of meningitis and cerebral malaria, and the excess mortality in girls, which were unexplained, were causally related to the vaccine. We therefore estimated the number of events required for 90% power to detect rate ratios for these safety signals, if they were of the magnitude observed in vaccinated children the phase 3 trial[3], after allowing for dilution due to vaccine coverage being less than 100%, and allowing for effects of contamination[4]. We also allowed for potential confounding whereby, in the case of meningitis, if RTS,S/AS01 recipients have also received Hib and pneumococcal vaccine, which protect against meningitis, this could to some extent mask a safety signal (in practice this was a small effect due to the fact that vaccine-preventable serotypes were relatively uncommon causes of meningitis). We calculated that the meningitis signal in the phase 3 trial would equate to a rate ratio of 4 to 5 if vaccine coverage was 60% to 70% in implementation areas and 5% in comparison areas. The cerebral malaria signal would equate to a rate ratio of 1.7 to 2, and the mortality signal in girls to a mortality ratio of 1.4 to 1.6. (These values were used in the power calculations. More accurate estimates were made later, when data on RTS,S/AS01 coverage from the household surveys was available). We estimated that 90 cases of meningitis and 400 cases of cerebral malaria, in eligible and non-eligible age groups combined, would be required for 90% power, and that 2000 deaths in vaccine-eligible ages would allow 90% power to detect a gender interaction. For impact outcomes, we estimated that a total of about 3000 severe malaria cases (eligible and non-eligible groups combined) would be required for 80% power to detect a reduction of 24% and 4000 for 90% power. Based on event rates observed in the first year of the evaluation we anticipated that the required number of events for each outcome would have accrued by approximately the same time, at about 24 months after the first introduction of the vaccine (April 2021), if data for all three countries were combined. By April 30 2021, there was a total of 134 cases of meningitis, and 572 of cerebral malaria, and by March 31 2021, 4280 deaths with cause of death. Deaths that occurred in April 2021 were excluded as verbal autopsies were not complete.

Results:

Vaccine delivery and uptake:

In Malawi the first child was vaccinated on April 23 2019, in Ghana on April 30 2019, and in Kenya on September 13 2019. By April 30 2021, a total of 652,673 children had received their first dose, 226,498 in Malawi, 238,318 in Ghana and 187,857 in Kenya, representing 76% of the estimated target population of eligible children over that period in Malawi, 70% in Ghana and 82% in Kenya. A total of 494,745 children had received their third dose (173,552 in Malawi, 200,398 in Ghana and 120,795 in Kenya), respectively 64%, 67% and 69% of the estimated target number. When

[2] SAGE/MPAC (2015) Evidence-to-recommendations table on the use of malaria vaccines, 2015. Available at: https://www.who.int/immunization/policy/position_papers/malaria_evidence_recommendations_table.pdf WHO (2016) Malaria vaccine: WHO position paper – January 2016. Weekly epidemiological record Jan 2016 no. 4. 91:33–52 http://www.who.int/wer

[3] In the phase 3 trial, 21 cases of meningitis occurred in RTS,S/AS01 recipients, a rate of 1.05/1000, and one case in control children, a rate of 0.1/1000; the rate ratio was 10.5 (95%CI 1.41,78.0). There were 43 cases of cerebral malaria in RTS,S/AS01 recipients and 10 cases in control children, a rate ratio of 2.15 (1.1,4.3). There were 67 deaths in girls who received RTS,S/AS01 and 17 in girls in the control group, a mortality ratio of 2, while in boys there were 45 deaths in RTS,S/AS01 recipients and 29 in boys in the control group, mortality ratio 0.8. The relative mortality ratio (girls:boys) was 2.61 (95%CI 1.29,5.26).

[4] Statistical Analysis Plan for the MVPE. V3.42, July 2021. https://www.clinicaltrials.gov/ProvidedDocs/65/NCT03806465/SAP_001.pdf
Protocol V9.0, April 2020. https://www.clinicaltrials.gov/ProvidedDocs/65/NCT03806465/Prot_ICF_000.pdf

vaccination coverage was assessed in Malawi in a survey conducted in March 2021 in children 12-23 months of age, who were due for their first dose between Sep 2019 and Aug 2020, 72.5% had received their first dose of RTS,S/AS01 according to the home-based record (HBR) or caregiver recall, and 62.3% had received three doses. The median age at dose 3 was 8.5 months, with 90% of third doses received by 13 months of age. In Ghana, a survey in November 2020, assessing uptake in children due for dose 1 between June 2019 and May 2020, found 75% of children 12-23 months of age had received the first dose and 67% three doses. Among those who received three doses the median age of the third dose was 9.7 months and 90% of third doses were received by 13.4 months of age. In Kenya, a survey in May to July 2021, assessing coverage in children due for dose 1 between Dec 2019 and Jan 2021, found 78.6% of children 12-23 months of age had received the first dose and 62.3% the third dose. The median age of the third dose was 9.0 months and 90% of third doses were received by 11.0 months of age.

In each country, uptake of RTS,S/AS01 appeared equitable, with similar coverage across wealth rankings based on household assets, and by gender.

When uptake of RTS,S/AS01 was compared in relation to whether the child had slept under a treated bednet the night before the survey, in Ghana 60% of those not using a net had received three doses of the malaria vaccine compared to 71% among those who did use a net, while in Malawi the corresponding estimates were 55% in those not using a net and 66% among net users, and in Kenya, 51.4% among non-users and 63.2% among net users.

Preliminary results from the surveys in Ghana and Malawi indicate that RTS,S/AS01 introduction did not influence uptake of other childhood vaccines, or use of insecticide-treated bednets, and there was no evidence of changes in care-seeking behaviour associated with receipt of the malaria vaccine.

In each country, coverage of the first dose of RTS,S/AS01 was less than for the first dose of measles-containing vaccine, indicating that there are missed opportunities for RTS,S/AS01 vaccination when children attend for measles vaccine. In Ghana, coverage of the first dose of RTS,S/AS01 was 75.0% compared to 88.3% for the first dose of measles-containing vaccine. The corresponding estimates in Malawi were 72.5% for the first dose of RTS,S/AS01 and 79.7% for the first dose of measles vaccine, and in Kenya, 78.6% for RTSS-1 and 90.9% for measles vaccine.

The first children were eligible for their fourth dose of vaccine in September 2020 in Malawi, in November 2020 in Ghana and in March 2021 in Kenya. By April 2021, a total of 79,523 children had received their fourth dose, 33,509, 35,209 and 10,805 in Malawi, Ghana and Kenya, representing 40%, 40% and 64% of the respective estimated target numbers. Coverage of the 4th dose will be assessed through surveys in 2022.

In comparison areas, the survey in Ghana found that 6% of children 12-23 months with an HBR had documented receipt of RTS,S/AS01, and in Malawi 1.9%, and in Kenya 10.2%. RTS,S/AS01 was not provided in comparison areas but children may have visited a facility in a neighbouring area where the vaccine was available, or could have moved to live in a comparator area having previously lived and received vaccines in an implementation area.

In children in implementation areas who were under 48 months of age but were too old, by at least 2 months, when the vaccine was introduced to have been eligible to receive RTS,S/AS01, (again out of those with an HBR), 1.9% of children in Malawi and 2.9% in Ghana had documented receipt of RTS,S/AS01. Older children were not surveyed in Kenya.

By April 2021, the youngest children to be vaccinated at the start of vaccine introduction, who were aged 5 months in Malawi and 6 months in Ghana and Kenya, would have been aged 29 months in Malawi, 30 months in Ghana, and 30 months in Kenya. In Kenya, at the start of vaccine introduction, children up to 11 months of age could be vaccinated with their first dose. Thus the oldest child to have been vaccinated in Kenya at the start of the programme would have been aged 30 months by April 2021. Guidelines in Ghana at the start of vaccine introduction limited administration of the first dose to children 6 and 7 months old, and in Malawi to children aged 5 months. Therefore, the results of the evaluation to April 2021 refer to children aged between 5 and 30 months (Figure 1).

Hospital surveillance:

Across the three countries there was a total of 27,678 admissions to sentinel hospitals in children 1-59 months, during the period from vaccine introduction until the end of April 30th 2021, 13,918 in areas where the vaccine was provided (implementation areas), of which 4,853 were vaccine-eligible based on their date of birth, and 13,760 in comparison areas, 5,141 being eligible by the same criteria. Among vaccine-eligible children, 2,156 of the admissions in implementation areas were for conditions unlikely to be directly affected by the malaria vaccine (patients who did not have malaria or anaemia, and also excluding patients with meningitis), compared to 2,245 admissions in children who were too young to receive the malaria vaccine, or too old when the malaria vaccine was introduced. In comparison areas, the number corresponding number of admissions (excluding malaria, anaemia and meningitis), was in a similar ratio, 2,003 among those who would have been eligible for the malaria vaccine and 2,062 among those who would not have been eligible. The pooled estimate across the three countries of the incidence rate ratio for hospital admission with conditions excluding malaria and anaemia (and meningitis), among vaccine-eligible children, in implementation areas compared to comparison areas, was 1.05 (95% confidence interval 0.95, 1.17), indicating that the implementation and comparison areas were broadly comparable with respect to admission with conditions that were unlikely to be affected directly by the malaria vaccine.

Mortality surveillance:

A total of 13682 deaths 1-59 months of age were reported to March 31 2021 (deaths in April 2021 were excluded because verbal autopsies have not all been completed). Of the deaths to March, 4729 were in vaccine-eligible age groups, and 95.5% of these had verbal autopsies completed (or, in the case of facility deaths in Malawi, hospital records obtained), and a cause of death (categorized as due to injury, or other causes) established for 4280/4729 (90.5%). In Malawi, it was possible to estimate population denominators using data from the 2018 census and then to compare the rates of mortality with mortality estimates from the census. The population under 5 years of age in each areas in the implementation and comparison regions was estimated using projections from the 2018 census and population estimates for facility catchments provided by the EPI programme. The age structure was estimated based on projected number of births in each area and census estimates of the infant and child survival for each district. The total person time in children aged 1-59 months, during the surveillance period, was 1,681,572 person years, during this time a total of 7359 deaths were reported in this age group, a rate of 4.38/1000 (both sexes combined). This is similar to the national estimate derived from the 2018 census of 5.08[5] (both sexes combined). In Kenya and Ghana recent census data are not available (in Kenya, full results from the 2019 census are not available yet, in Ghana the 2021 census was recently completed).

[5] The national estimate of under-5 mortality, ${}_5q_0$, in Malawi from the 2018 census is 44 per 1000 live births. Subtracting the neonatal mortality of 19.8/1000, and converting to mortality rate per 1000 person years, gives a national mortality rate 1-59 months of 5.08/1000 person years. The weighted average of district estimates from the census gives an estimate of 5.17/100 person years 1-59 months for MVIP areas.

Safety:

Meningitis:

A total of 4,311 suspected cases of meningitis were investigated. Lumbar punctures were performed in 2,652 (62%) of these patients, and polymerase chain reaction (PCR) analysis of samples of cerebro-spinal fluid (CSF) was available for 2,249 patients (52%). A total of 51 cases of probable or confirmed meningitis (identified based on examination of CSF, or a positive PCR result) were seen in sentinel hospitals among age groups of children eligible for the malaria vaccine, 27 from implementation areas and 24 from comparison areas (Figure 4). Among the age groups that were not eligible for the malaria vaccine, there were 79 probable or confirmed cases, 44 from implementation areas and 35 from comparison areas. The incidence rate ratio comparing rates of admission with meningitis in implementation and comparison areas, among vaccine-eligible children, was 0.81 (95%CI 0.43, 1.55). There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with meningitis, and there were sufficient cases, and high coverage of the vaccine, to detect an excess of the magnitude observed in the phase 3 trial, if it had occurred. Of the patients with probable or confirmed meningitis in vaccine-eligible age groups from implementation areas, 41% (11/27) had received RTS,S/AS01 vaccine, compared to 53% (2491/4672) of all other hospital admissions in this age group from implementation areas (odds ratio, adjusted for country and age, 0.73 (95%CI 0.31,1.71). The PCR results showed that only 15% (8/55) samples from confirmed cases, were of vaccine serotypes preventable by Hib or pneumococcus vaccines (i.e. *Haemophilus influenzae* type b, or vaccine serotypes of *Streptococcus pneumoniae*).

Cerebral malaria:

There were 1,405 cases of severe malaria (*P. falciparum* infection with severe anaemia, or respiratory distress, or with impaired consciousness or convulsions but not meeting criteria for meningitis) among children who were eligible to have received at least one dose of the malaria vaccine, 558 from implementation areas and 847 from comparison areas (Figure 5). Among these, there were 55 cases of cerebral malaria (positive for *P.falciparum* by rapid diagnostic test or microscopy, with impaired consciousness (i.e. a Glasgow coma score <11 or Blantyre coma score <3 or assessed as P or U on the AVPU (“Alert, Voice, Pain, Unresponsive”) score, in whom lumbar puncture had been performed to exclude cases with probable meningitis), 25 from implementation areas and 30 from comparison areas. Among age groups of children not eligible to have received the malaria vaccine, there were 241 cases of cerebral malaria, 115 from implementation areas and 126 from comparison areas. The incidence rate ratio comparing rates of admission to hospital with cerebral malaria in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.77 (95%CI 0.44, 1.35). The incidence rate ratio for admission with other forms of severe malaria excluding cerebral malaria was 0.70 (95%CI 0.54, 0.89). There was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria (relative rate ratio 0.94 (95%CI 0.57, 1.56) and test of interaction p-value 0.808). When the analysis was broadened to include cases meeting the criteria for cerebral malaria but in whom lumbar puncture had not been performed, there was a total of 103 cases in age-groups eligible to have received at least one dose of the malaria vaccine, 49 from implementation areas and 54 from comparison areas, and there were 455 cases in non-eligible age groups, 230 from implementing areas and 225 from comparison areas. The incidence rate ratio comparing rates of admission to hospital with cerebral malaria (with the broader case definition) in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.96 (95%CI 0.61, 1.52). Again there was no evidence that impact differed between cerebral malaria and other forms of severe malaria (test of interaction p-value 0.470). Similar results were obtained when cerebral

malaria was limited to cases defined as U (unresponsive) on the AVPU score. Among children eligible to have received the vaccine, 20 of the cases from implementation areas and 25 from comparison areas met this stricter criterion, and the estimate of the rate ratio was 0.66 (95%CI 0.31, 1.43).

Of the patients with cerebral malaria in vaccine-eligible age groups from implementation areas, 47% (23/49) had received RTS,S/AS01 vaccine, compared to 53% (2479/4650) of all other admissions in this age group from implementation areas (odds ratio, adjusted for country and age, 1.03, 95%CI 0.56,1.90; the odds ratio among cases meeting the stricter definition requiring an LP, was 1.58, 95%CI 0.66,3.80).

There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with cerebral malaria.

Mortality:

Excluding deaths due to injury, among children eligible to have received three doses of RTS,S/AS01, there were a total of 2864 deaths reported, 1421 from implementing regions and 1443 from comparison regions (Figure 6). In children who were not eligible to have received the vaccine there were 4218 deaths in implementing regions and 3874 in comparison regions. The mortality ratio in the vaccine-eligible age group (eligible for three doses) between implementing and comparison regions, was 0.93 (95%CI 0.84,1.03), a 7% reduction (95%CI -3%,16%). There was no evidence that the mortality ratio differed between girls and boys, the p-value for this interaction was 0.343. The mortality ratio in girls was 0.98 and in boys 0.90, the relative mortality ratio (girls:boys) was 1.08 (95%CI 0.92,1.28). When analysis was extended to children eligible to have received at least one dose of vaccine, similar results were obtained (ratio of mortality ratios: 1.08 (95%CI 0.93, 1.25), p value for the interaction 0.321). Similar results were also obtained when the analysis was repeated for different age groups of eligible children (mortality ratio girls:boys, in eligible children under 18 months of age, was 1.10, 95%CI 0.94, 1.29, and in eligible children aged 18 months and above, 0.95, 95%CI 0.70, 1.31).

Vaccination status of vaccine-eligible children who died in implementation areas was similar in girls and boys (58.9% and 57.0% respectively). According to the household surveys in 12-23month olds, coverage of the first dose of RTS,S/AS01 was slightly higher in girls than boys (77.6% in girls and 73.0% in boys in Ghana and 75.1% in girls and 70.1% in boys in Malawi, and 79.0% in girls and 78.2% in boys in Kenya), and similarly for the third dose ().

Impact:

Hospital admission with severe malaria among children eligible to have received three doses of RTS,S/AS01:

Among children eligible to have received all three primary doses of RTS,S/AS01, there was a total of 1107 admissions with severe malaria (*P. falciparum* infection with severe anaemia, or respiratory distress, or with impaired consciousness or convulsions but not meeting criteria for meningitis), 418 from implementation areas and 689 from comparison areas. Among children who were not eligible to have received any doses of RTS,S/AS01 there were 1313 patients admitted from implementation areas and 1390 from comparison areas. The incidence rate ratio comparing incidence of admission with severe malaria between implementing and comparison areas was 0.70 (95%CI 0.54, 0.92), a reduction of 30% (95%CI 8%, 46%), again there was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria. When cases were excluded if they had impaired consciousness or convulsions but had not had an LP performed to exclude meningitis, and they did not fulfil other criteria for severe malaria (severe anaemia or respiratory distress), there was a total

of 873 severe malaria cases in age groups eligible to have received three doses of malaria vaccine, 324 from implementation areas and 549 from comparison areas. In non-eligible age groups there were 989 cases from implementation areas and 1026 from comparison areas. The incidence rate ratio comparing incidence of admission with severe malaria between implementing and comparison areas was 0.65 (95%CI 0.49, 0.86).

Of the patients with severe malaria in vaccine-eligible age groups from implementation areas, 30% (123/415) had received 3 doses of RTS,S/AS01 vaccine, compared to 47% (1384/2951) of all other admissions in this age group from implementation areas (odds ratio, adjusted for country and age, 0.49, 95%CI 0.39,0.61).

Of the severe malaria cases in children eligible for three doses of RTS,S/AS01, a total of 284/1107 patients had severe malaria anaemia (26%). The incidence rate ratio for this subgroup of severe malaria was 0.78 (95%CI 0.55, 1.09), with no evidence that effectiveness differed when compared to that for other forms of severe malaria (interaction test p-value 0.529).

Hospital admissions of patients with a positive malaria test:

Patients admitted to sentinel hospitals were routinely tested for malaria infection by RDT or microscopy, out of a total of 27,678 patients admitted, test results were available for 88%. Among children eligible to have received three vaccine doses, the number of patients admitted with a positive malaria test was 2630, 1075 from implementation areas and 1555 from comparison areas. The rate ratio comparing the incidence of hospital admission with a positive malaria test between implementation and comparison areas was 0.79 (95%CI 0.68, 0.93), a reduction of 21% (95%CI 7%,32%).

All-cause hospital admission:

Severe malaria represented 19% of all admissions to sentinel hospitals (with at least one overnight stay) in comparison areas, among children who would have been eligible to have received three doses of malaria vaccine. In this age group there was a total of 3196 admissions to sentinel hospitals in implementation areas and 3569 in comparison areas. The rate ratio comparing the incidence of all-cause hospital admission between implementation and comparison areas, for this age group, was 0.92 (95%CI 0.83, 1.03), a reduction of 8% (95%CI -3%, 17%).

Strengths and limitations:

The evaluation was well powered to detect safety signals observed in the phase 3 trial if they had occurred. Hospital surveillance was strengthened and standardised to optimize detection and diagnosis of meningitis and severe malaria. Where we were able to assess completeness of mortality surveillance, in Malawi, the rates of mortality were similar to estimates from the recent census. Using data from household surveys on coverage and timing of the first dose of RTS,S/AS01 we estimated that the proportion of vaccinated person time in implementation areas would have been at least 60%, and less than 5% in comparison areas, and less than 2% in non-eligible age groups in implementation areas (Figure 3). We estimated that the meningitis signal in the phase 3 trial would then translate to a rate ratio of 3.9, and the cerebral malaria signal would translate to a rate ratio of 1.6. The 95% confidence intervals for the pooled estimates obtained during this evaluation exclude these values (Table 2). The relative mortality ratio between girls and boys in the phase 3 trial (i.e. the ratio of mortality in girls who received RTS,S/AS01 to that in girls in the control group, divided by the corresponding ratio in boys) was 2.6, this would translate to a relative mortality ratio of 1.8 if it occurred in the pilot implementation areas. The estimate of the mortality ratio between implementation and comparison regions, for girls, was similar to that for boys, and the ratio of the effect in girls to that in boys was 1.08, with a narrow confidence interval (95%CI 0.93,1.25) that

excludes a gender interaction such as that observed in the phase 3 trial. There was similarly no evidence of interaction when analysis was limited to eligible children above 18 months of age.

The impact on severe malaria is consistent with impact that would be expected on the basis of the efficacy observed in the phase 3 trial and given the level of uptake of the vaccine in implementation areas[6].

The observed reductions in all-cause hospital admissions, and all cause mortality, were associated with more uncertainty, but the point estimates were consistent with the impact on severe malaria. Severe malaria accounted for about 20% of all admissions to sentinel hospitals in eligible age groups in comparison areas, so a reduction of 30% in severe cases equates to about an expected 6% reduction in all cause admissions, similar to what was observed. If vaccine effectiveness against malaria deaths is similar to that for admission with severe malaria, the point estimate of a reduction of 7% in mortality would be consistent with about 23% of deaths (excluding injuries) being caused by malaria in these populations and age groups.

The use of data for non-eligible age groups aimed to control for underlying differences between intervention and comparator areas. Randomization balance was assessed, for hospital surveillance, in terms of comparability in admissions with conditions unlikely to be affected by the vaccine, which appeared well balanced overall. But imbalance with respect to the outcomes of interest cannot be excluded and may have influenced results. There was variability in point estimates of effects between countries but there was wide uncertainty around these. The analyses were powered only for pooled analysis across the three countries.

Contamination due to the malaria vaccine being received by children in comparison areas, or by children in non-eligible age groups in implementing areas, could have diluted estimates of effects. These effects have been allowed for, using survey estimates of the proportion of children in comparison areas who received the malaria vaccine, and of the proportion of non-eligible children in comparison and implementation areas who received the vaccine. Misclassification of events to clusters or age groups, could have occurred. Efforts were made to verify cluster assignments based on village of residence, but there could have been some misclassifications. Children just outside the age range for eligibility, but who might have received the vaccine, were excluded from the non-eligible group during analysis to reduce bias. Dates of birth were verified from documents where possible but errors in age could have led to misclassification of age group.

However, the fact that the impact observed against severe malaria was consistent with the expected impact, and the consistent point estimates for other impact outcomes, argue against dilution effects having been significantly under-estimated.

Confounding, whereby malaria vaccine uptake is associated with underlying risks of malaria, meningitis or mortality, could influence estimates of effects. However, we found no association between EPI coverage and malaria prevalence during baseline surveys, and with respect to

[6] We estimated, using data for Malawi as an example, the proportion of person time accounted for by children who had received their third dose and among these the proportion of person time within 6 months of the third dose, when the vaccine is most effective, the proportion 6-12 months since the third dose, and the proportion more than 12 months since the third dose. These periods were associated with vaccine efficacies against clinical malaria of 67.6%, 38.9% and 27.9% in the phase 3 trial. The proportions of person time in these periods were estimated using information on age of receipt of RTS,S/AS01 doses in the coverage surveys. These proportions were 0.6, 0.32, 0.08, giving a mean efficacy of 55%. The fraction of person time vaccinated with 3 doses was 45%. The product (0.55x0.45) gives an expected reduction in the incidence of malaria of 25% in Malawi.

meningitis, although children who received the malaria vaccine were more likely to have previously received pneumococcal vaccine and Hib vaccine than children who did not receive the malaria vaccine, which might mask an effect of the malaria vaccine on meningitis risk, we observed that vaccine serotypes of Hib and pneumococcus were relatively uncommon when CSF samples were investigated by PCR .

Vaccination status was assessed from the home-based records where possible, and otherwise from caregiver recall, but caregiver recall of vaccination status appeared unreliable. This was a limitation of the analysis of vaccination status of children who died, as vaccine documentation was available for only 40% of deaths. Vaccine documentation was better for hospital patients. Records were available for 82% of vaccine-eligible hospital patients from implementation areas. And during the household surveys, a high proportion of children had a vaccine record available, over 90% of children in Ghana and over 80% in Malawi and Kenya.

Key points:

- High, equitable coverage of the primary three doses of RTS,S/AS01 was achieved in all three countries. In Malawi, where 86.2% of children 12-23months old had received DTP3, and 72.5% had received their first dose of RTS,S/AS01 and 62.3% received their third dose. In Ghana, where DTP3 coverage was 93.4%, 75% of children had received the first dose of RTS,S/AS01 and 67% three doses. In Kenya, DTP3 coverage was 93.7%, 78.6% of children had received the first dose of RTS,S/AS01 and 62.35 the third dose.
- The evaluation over the first 24 months of the MVPE was well powered to detect effects of RTS,S/AS01 introduction on the incidence of hospital admission with meningitis and with cerebral malaria in pooled analysis of the data from the three MVIP countries. Sufficient events were observed to allow effects of the magnitude observed in the phase 3 trial to be detected if they occurred, with 90% power, after allowing for the level of vaccine coverage.
- There was no evidence that RTS,S/AS01 introduction increased incidence of hospital admission with meningitis. The incidence rate ratio (RTS,S:comparator) was 0.81 (95%CI 0.43,1.55).
- There was no evidence that RTS,S/AS01 introduction was associated with an increase in hospital admission with cerebral malaria. The incidence rate ratio for admission with cerebral malaria was 0.77 (95%CI 0.44,1.35), and 0.96 (0.61,1.52) when a broader definition was used, and 0.66 (95%CI 0.31, 1.43) when a narrower definition was used. There was also no evidence that RTS,S/AS01 introduction was less effective against hospital admission with cerebral malaria than with other forms of severe malaria.
- The evaluation was not powered at this time point to assess impact of vaccine introduction on mortality but the evaluation was well powered to detect gender imbalance in all-cause mortality of the magnitude observed in the phase 3 trial, in children up to about 2yrs of age. There was no evidence that the effect of RTS,S/AS01 introduction on all-cause mortality differed between girls and boys in this age group.
- RTS,S/AS01 introduction was associated with a reduction in incidence of hospital admission with severe malaria, the reduction of 30% was consistent with the reduction that would be expected on the basis of the efficacy observed in the phase 3 trial, given the level of coverage of 3 doses of RTS,S/AS01 achieved in the evaluation areas.

- Continued evaluation will assess the impact of the 4th dose in each country, and impact of vaccine introduction on mortality.

Figures and Tables:

The age distribution of eligible children in the pilot areas in each country is shown in Figure 1. The number of children given their first dose of RTS,S/AS01 in each month, is shown in Figure 2, and the estimated proportion of eligible children who had received their first dose of RTS,S/AS01, by month of age, is shown in Figure 3. Figures 4-6 show the number of cases of meningitis, severe malaria, and the number of deaths, by age, in eligible age groups in each country.

Table 1 shows the rate ratios for the impact outcomes. Table 2 gives a comparison of the rate ratios for the safety outcomes with the rate ratios that would have been expected if the safety signals in the phase 3 trial had occurred during the pilot implementations. Tables 3 and 4 give the baseline characteristics of implementation and comparison areas that were used during randomization. Table 5 summarises results from the household surveys of RTS,S/AS01 coverage.

Statistical methods, and country-specific estimates for each outcome, are given in Annex 1.

Figure 1. Distribution by age of total person years, up to April 30 2021, in children eligible to have received at least one dose of RTS,S/AS01, in each country.

In Malawi, the estimates are based on denominators derived from the 2018 national census (estimates for the population in comparison areas in hospital catchments, are shown). In Ghana and Kenya, exact denominators have not been estimated, the approximate age pattern is shown. In Malawi, the first dose of RTS,S/AS01 was provided for children aged 5 months, starting on April 23 2019. In Ghana, the first dose was provided for children aged 6 and 7 months, starting April 30 2019. In Kenya, the first dose was given to children from 6 to 11 months of age, starting Sep 13 2019.

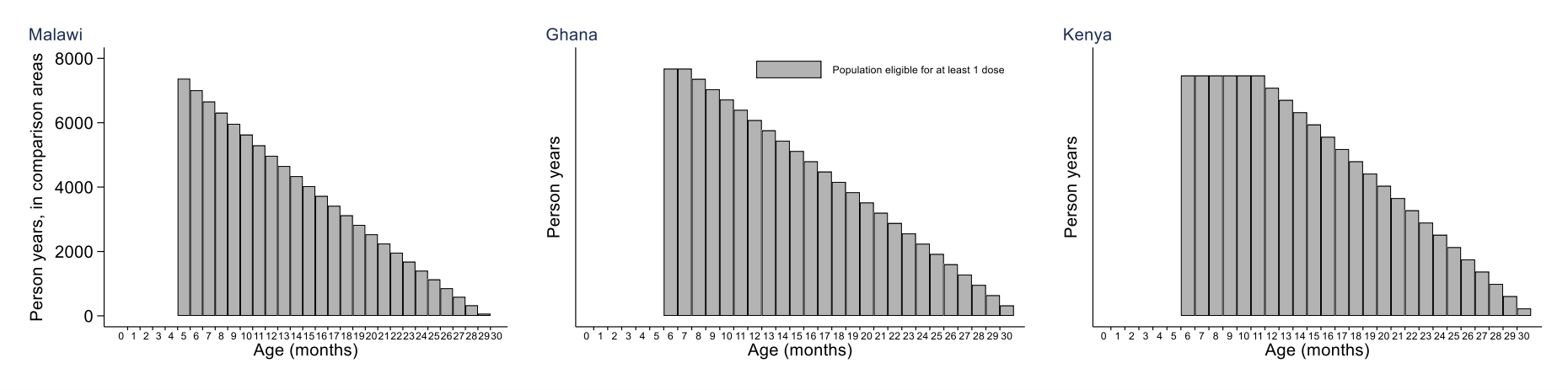


Figure 2: Total Number of first RTSS doses (RTSS-1) administered per month, in each country, up to April 2021.

When the vaccine was first introduced, in Malawi, vaccine administration was limited to children 5 months of age; in Ghana, to children 6 and 7 months of age, and in Kenya, to children 6 to 11 months of age. Vaccine administration started on April 23 2019 in Malawi, and Sep 13 2019 in Kenya, the data for the first month therefore reflects that vaccine was delivered for only part of the month. In Ghana, delivery started on April 30 2019.

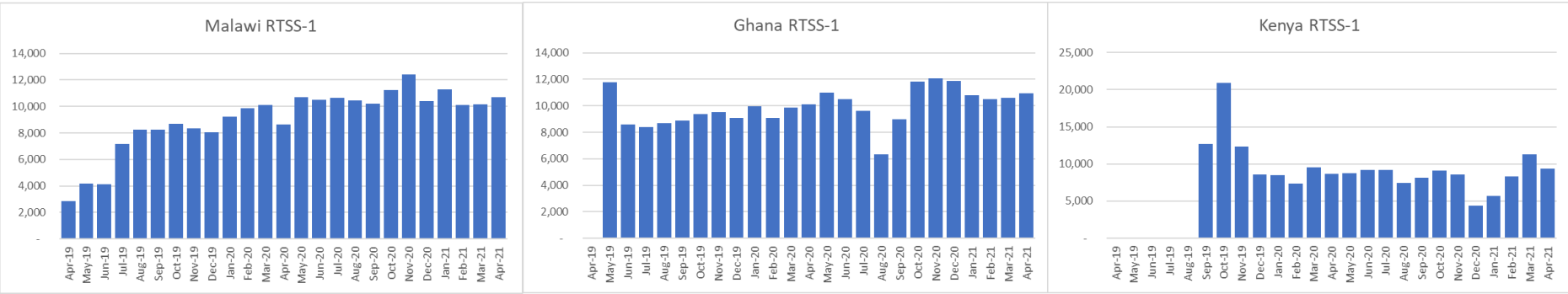


Figure 3. A: Estimated proportion of vaccinated person time, by age, in eligible age groups in implementation areas in Malawi, Ghana and Kenya.

The proportion of children in implementation areas who had received their first dose of RTS,S/AS01 was estimated for each month of age, was estimated from the household surveys in each country. The overall proportion of vaccinated person time, across all ages, was 0.668 (Kenya), 0.690 (Ghana) and 0.611 (Malawi).

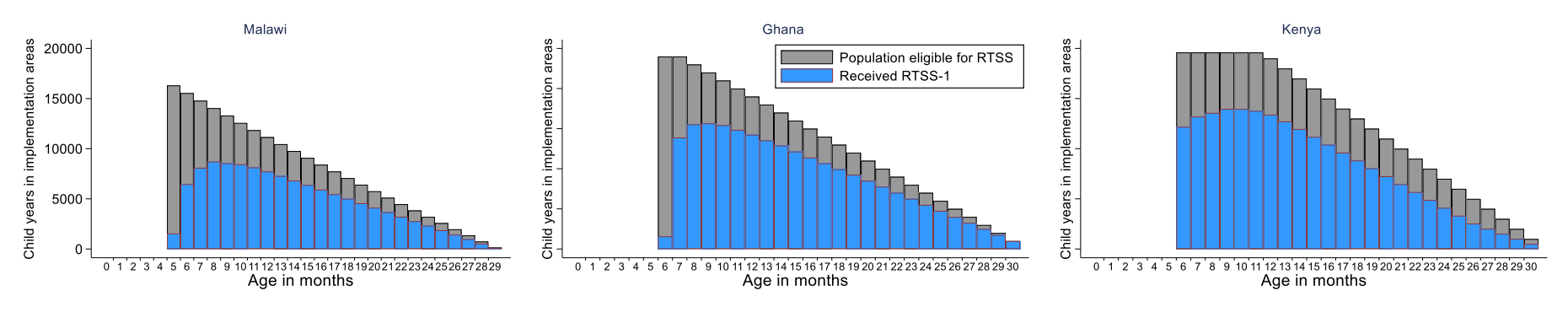


Figure 4. Age distribution of meningitis cases (probable and confirmed cases) admitted to sentinel hospitals from both implementation and comparison areas, up to April 30 2021, in age groups who would have been eligible to receive (at least one dose of) the malaria vaccine, in each country.

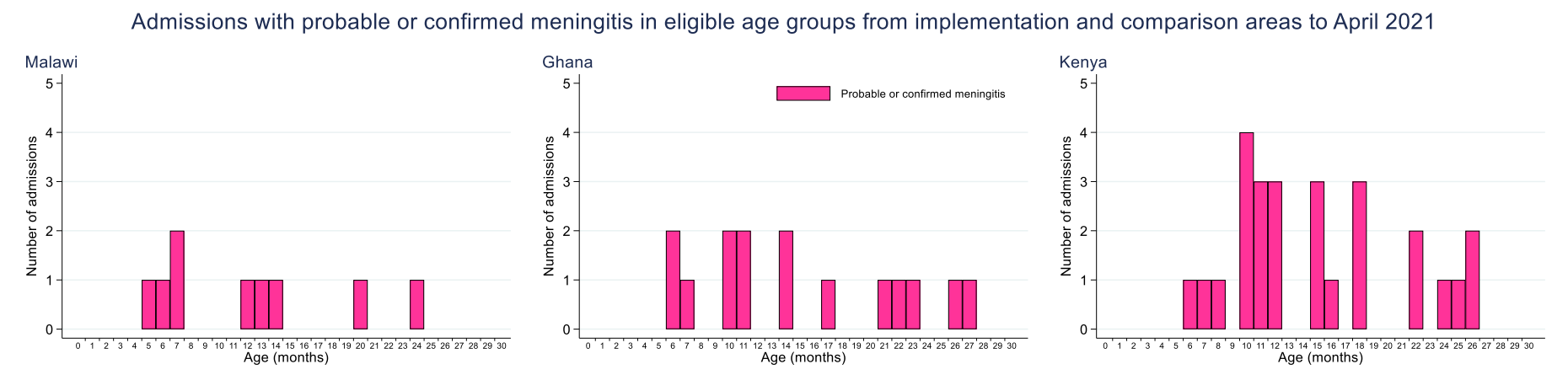


Figure 5. Age distribution of severe malaria cases from comparison areas admitted to sentinel hospitals up to April 30 2021, in age groups who would have been eligible to receive (at least 1 dose) of the malaria vaccine.

The bars indicate the number of severe cases, the number of these that had severe malaria anaemia, and the number that had cerebral malaria. (The figure is not intended to show the degree of overlap between the different forms of severe malaria).

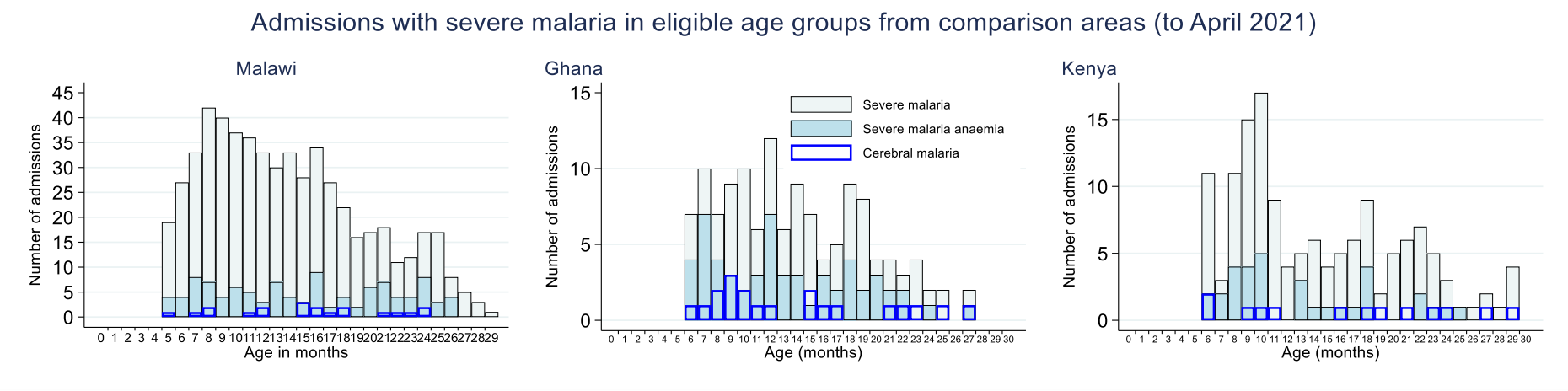


Figure 6: Age distribution of deaths due to any cause except injury, occurring in comparison areas up to March 31 2021, in age groups who would have been eligible to have received at least one dose of RTS,S/AS01, in each country.

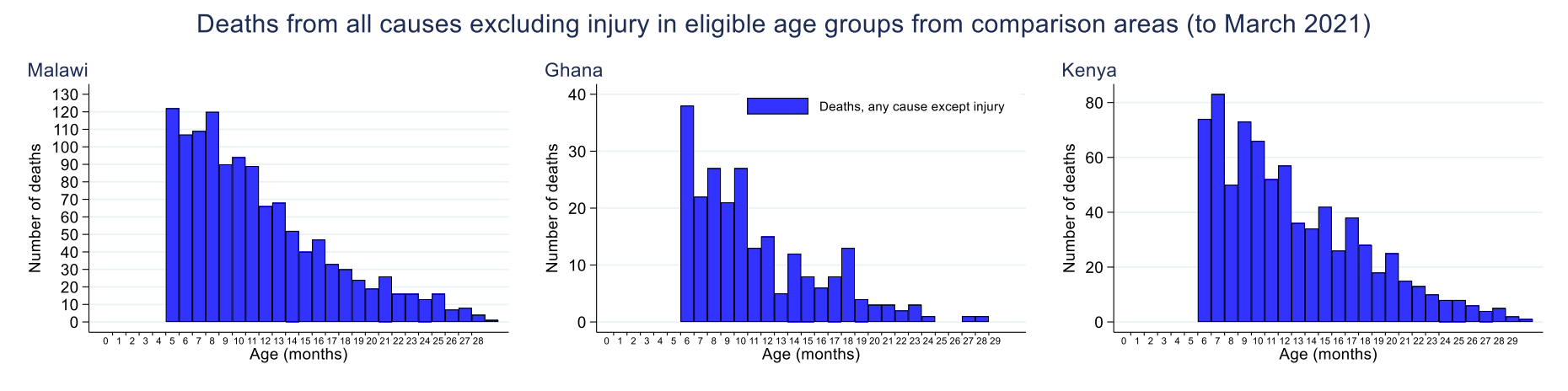


Table 1: Summary of impact outcomes:

Outcome	No. of events in eligible age groups[1]		Rate ratio (95%CI)	% impact[2] (95% confidence interval)
	Implementing	Comparison		
Hospital admission with severe malaria[3]	418	689	0.70 (0.54, 0.92)	30% (8.0%,46%)
Hospital admission with severe malaria[4]	324	549	0.65 (0.49, 0.86)	35% (14%,51%)
Mortality due to all causes excluding injuries[5]	1421	1443	0.93 (0.84,1.03)	7.0% (-3.0%,16%)
Hospital admission for any cause[6]	3340	3678	0.92 (0.83, 1.03)	8.0% (-3.0%,17%)
Hospital admission with a positive malaria test	1119	1606	0.79 (0.68, 0.93)	21% (7.0%,32%)
Hospital admission with severe malaria anaemia	131	153	0.78 (0.55, 1.09)	22% (-9.0%,45%)

1: Number of cases by area are given for the age-eligible population. Rate ratios were estimated by comparing the ratio of events in eligible to non-eligible children in implementation areas, with the corresponding ratio in comparison areas (Annex 1).

2: percentage reduction in incidence associated with introduction of the RTS,S/AS01 vaccine, among the age group of children eligible to have received three doses of the vaccine.

3: Severe malaria definition: *P. falciparum* infection detected by RDT microscopy AND one or more of the following: a) impaired consciousness (Glasgow coma score<11, Blantyre coma score<3, or assessed as P or U on the AVPU score and CSF findings not consistent with probable or confirmed meningitis; b) multiple of atypical convulsions (more than two episodes within 24 hours or prolonged (>15minutes), or focal) and CSF findings not consistent with probable or confirmed meningitis; c) respiratory distress (manifested as chest indrawing or deep breathing); d) severe malaria anaemia (haemoglobin concentration <5g/dL or haematocrit <15%).

4: Severe malaria, defined as above, but excluding cases if they had impaired consciousness or convulsions but had not had an LP performed to exclude meningitis, and they did not fulfil other criteria for severe malaria (severe anaemia or respiratory distress).

5: Death due to any cause excluding injury (InterVA code 12).

6: A stay in hospital/inpatient facility for at least one night, (and patients who were admitted but died before an overnight stay was completed).

Table 2: Comparison with safety signals observed in the phase 3 trial[1]

Outcome	Rate ratio in the phase 3 trial[2] (95%CI)	Rate ratio of the phase 3 trial, adjusted for MVIP coverage[3] (95%CI)	Rate ratio in the MVIP (95%CI)	z	p-value
Meningitis	10.5 (1.41,78.0)	3.92 (1.22,12.6)	0.81 (0.43, 1.55)	2.31	0.0207
Cerebral malaria[4]	2.15 (1.1,4.3)	1.60 (1.05,2.43)	0.77 (0.44, 1.35)	2.06	0.0397
Cerebral malaria[5]		1.60 (1.05,2.43)	0.96 (0.61, 1.52)	1.62	0.1049
Mortality ratio[6]	2.61 (1.29,5.26)	1.83 (1.17,2.85)	1.08 (0.93, 1.25)	2.19	0.0285

1: If the safety signals observed in the phase 3 trial occurred in the MVIP, the magnitude of the effect we would observe would be smaller than in the phase 3 trial, since not all children will have received the vaccine. Any effects would be further diluted if there was contamination due to some children in comparison areas, or children in non-eligible age groups, receiving the vaccine. We used estimates of coverage and timing of malaria vaccine doses from the household surveys in each country to estimate the person time in vaccinated children as a proportion of total person time, and the degree of contamination. These estimates were used to calculate the expected effect in each country, if the safety signals in the phase 3 trial had occurred in the pilot. The average of these effects for each outcome is shown in column 2, and compared with the observed rate ratio from the MVIP (column 3) using a z-test. For each safety outcome, the observed rate ratio in the MVIP was inconsistent with the signal in the phase 3 trial. The hypothesis that the signal observed in the phase 3 trial occurred in the MVIP, given the degree of dilution that was estimated, was rejected ($p<0.05$), except when the broader case definition for cerebral malaria was used (including cases in whom lumbar puncture had not been performed), when the p-value was 0.1049.

2: Rate ratio in the phase 3 trial comparing the combined vaccine groups (R3R and R3R) with the control group, from month 0 to study end.

3: In each country the expected rate ratio for each safety outcome, if the safety signal from the phase 3 were to have occurred in the MVIP, was estimated as $R'=[(Rc+1-c)/(Rd+1-d)]/[(Rf+1-f)/(Rg+1-g)]$, where R is the rate ratio in the phase 3 trial, c is the proportion of vaccinated person time in implementation areas in eligible age groups, d the proportion in comparison areas in eligible age groups, and f and g are the corresponding values in non-eligible groups, for that country. The average across the three countries was calculated as $\exp[\Sigma w_i \log(R_i')]$, where the weights w_i are the normalised weights used to obtain the pooled estimate of the rate ratio (column 3) for that outcome (as detailed in Annex 1), so that the comparison is based on the same relative weightings of the three countries. The estimates used were c=0.611 in Malawi, 0.690 in Ghana and 0.668 in Kenya (Figure 3); the corresponding proportions in comparison areas were d=0.016, 0.056, 0.087, and in non-eligible age groups in implementation areas, f=0.016 in Malawi and 0.027 in Ghana and Kenya. We (conservatively) assumed g=0 in each country.

4: Cerebral malaria, MVIP cases in which lumbar puncture had been performed to exclude cases with probable meningitis.

5: Cerebral malaria, using, for MVIP, a case definition broadened to include cases in which lumbar puncture had not been performed.

6: The mortality ratio, in the phase 3 trial, was defined as the ratio of the mortality rate between vaccine recipients and controls, for girls, relative to that for boys.

Table 3. Baseline characteristics of the malaria vaccine pilot area (variables used for randomisation constraints):

	Ghana		Kenya		Malawi	
	Vaccinating	**Comparison**	**Vaccinating**	**Comparison**	**Vaccinating**	**Comparison**
Number of clusters, N	33	33	23	23	23	23
Surviving infants, N (Total; cluster-level median [min-max])	128624; 3490 [912-7026]	133702; 3700 [1202-8954]	126698; 5296 [3736-8805]	125747; 5275 [2702-10739]	107728; 4536 [2816-6931]	113997; 4831 [3026-8112]
Parasite prevalence, % (cluster-level median [min-max])	22% [12-52]	21% [11-45]	21% [7-43]	19% [5-43]	19% [6-39]	20% [6-46]
Coverage of pentavalent dose 1, % (cluster-level mean [min-max])	99% [61-162]	97% [51-141]	71% [26-126]	74% [55-94]	89% [60-114]	93% [59-135]
Coverage of pentavalent dose 3, % (cluster-level mean [min-max])	96% [61-138]	99% [50-140]	63% [26-113]	66% [51-85]	85% [54-103]	87% [57-151]
Coverage of measles dose 1, % (cluster-level mean [min-max])	93% [67-136]	95% [46-172]	65% [31-120]	66% [52-83]	83% [51-107]	81% [49-122]
Number of hospitals, N	39; 1.45 [0-5]	42; 1.55 [0-5]	30; 1.35 [0-3]	30; 1.30 [0-4]	10; 1.08 [0-2]	10; 1.08 [0-2]
Number of health centers, N (Total; cluster-level median [min-max])	153; 4.22 [2-13]	155; 3.76 [1-15]	90; 3.27 [1-10]	93; 3.43 [0-10]	66; 2.84 [0-6]	66; 2.64 [1-5]
Number of dispensaries, N (Total; cluster-level median [min-max])	799; 21.73 [9-62]	776; 21.14 [6-47]	314; 11.90 [5-32]	320; 12.90 [6-29]	18; 1.60 [0-3]	18; 1.19 [0-3]

Table 4. Baseline characteristics of the malaria vaccine pilot area, restricted to clusters within the pre-defined sentinel hospital areas

	Ghana		Kenya		Malawi	
	Vaccinating	**Comparison**	**Vaccinating**	**Comparison**	**Vaccinating**	**Comparison**
Number of sentinel hospitals	8		6		4	
Number of clusters, N	15	17	16	12	8	9
Surviving infants, N (Total; cluster-level median [min-max])	71992; 4419 [1379-7026]	76097; 3994 [1202-8954]	87824; 5222 [3736-8805]	67836; 5414 [3487-10739]	37908; 4490 [2816-6931]	49039; 5309 [3670-8112]
Parasite prevalence, % (cluster-level median [min-max])	21% [12-52]	19% [11-45]	23% [9-43]	19% [10-43]	15% [6-36]	21% [10-46]
Coverage of pentavalent dose 1, % (cluster-level mean [min-max])	99% [63-162]	93% [51-109]	69% [26-126]	76% [59-94]	86% [63-100]	90% [78-117]
Coverage of pentavalent dose 3, % (cluster-level mean [min-max])	94% [61-137]	95% [50-118]	61% [26-113]	67% [53-82]	84% [56-103]	84% [70-118]
Coverage of measles dose 1, % (cluster-level mean [min-max])	91% [67-136]	91% [46-117]	64% [31-120]	69% [52-83]	82% [51-103]	78% [63-99]
Number of hospitals, N	25; 1.92 [0-5]	26; 1.94 [0-5]	21; 1.36 [0-3]	15; 1.29 [0-2]	3; 1.41 [0-2]	5; 1.19 [0-2]
Number of health centers, N (Total; cluster-level median [min-max])	73; 4.26 [2-13]	82; 4.08 [1-12]	58; 3.11 [1-8]	56; 3.99 [2-10]	24; 3.12 [0-6]	26; 2.74 [2-5]
Number of dispensaries, N (Total; cluster-level median [min-max])	423; 25.74 [10-62]	433; 22.54 [6-47]	214; 12.04 [5-27]	152; 11.68 [6-22]	4; 1.00 [0-1]	7; 1.12 [0-2]

Table 5. RTS,S/AS01 vaccine uptake from household surveys of children aged 12-23 months

	Ghana	Kenya	Malawi
Month of survey	November 2020	May – July 2021	March 2021
Period when children surveyed were due to have received their first dose of RTS,S/AS01	Jun 2019 – May 2020	Dec 2019-Jan 2021	Sep 2019 – Aug 2020
No. with home-based record of vaccination (HBR)/no. surveyed (%)	1082/1179 (91.8%)	1395/1438 (98.0%)	1082/1184 (91.4%)
Coverage of 1st dose by HBR (by HBR or recall)	79.7% (75.2%)	79.5% (78.6%)	74.1% (72.5%)
Coverage of 3rd dose by HBR (by HBR or recall)	71.2% (67.0%)	65.5% (62.3%)	65.2% (62.3%)
median age of receiving dose 3	9.7 months	9.0 months	8.5 months
90th percentile of age at dose 3	13 months	11.0 months	13 months
% received RTSS-1 in comparison areas by HBR	6.1%	10.2%	1.9%
% received RTSS-1 in older age groups in implementation areas, by HBR	1.1%	Not surveyed	1.9%

Annex 1: Calculation of incidence rate ratios

In each country, the log of the rate ratio comparing the incidence in eligible age groups in RTS,S/AS01 implementation areas with that in comparison areas, was estimated as:

$D = \log(R_1) - \log(R_0)$, where R_1 is the ratio of the number of events in eligible age-groups to the number of events in non-eligible age groups, in implementation areas, and R_0 is the corresponding ratio in comparison areas. The variance of D is $V(D) = V(R_1)/R_1^2 + V(R_0)/R_0^2$, where

$$V(R_j) = \left(\frac{m_j}{(m_j-1)n_{j,B}^2}\right)\sum_{i=1}^{m_j}\left(n_{j,i,A} - R_j n_{j,i,B}\right)^2 \qquad j = 0,1$$

Where m_j is the number of clusters in implementation areas (j=1) or comparison areas (j=0), $n_{j,i,A}$ is the number of events in eligible age groups in cluster i in implementation areas (j=1) or comparison areas (j=0), and $n_{j,i,B}$ the corresponding number in non-eligible age groups, and $n_{j,B}$ is the total events in non-eligible groups in implementation (j=1) or comparison (j=0) areas.

The estimates of D for each country, D_1, D_2 and D_3, were combined to give a pooled estimate $\overline{D} = \sum D_i/V(D_i)/\sum 1/V(D_i)$, i=1..3, with variance $V(\overline{D}) = 1/\sum[1/V(D_i)]$. The pooled rate ratio was then calculated as $\exp(\overline{D})$ and the 100(1-α)% confidence interval given by $\exp[\overline{D} +/- t_{\alpha/2,C-6}\sqrt{V(\overline{D})}]$, with df equal to the total number of clusters C less 2x3=6.

Figure A1. Probable or confirmed meningitis: Rate Ratios for the association between the introduction of RTS,S/AS01 and probable or confirmed meningitis in children age-eligible to receive dose 1.

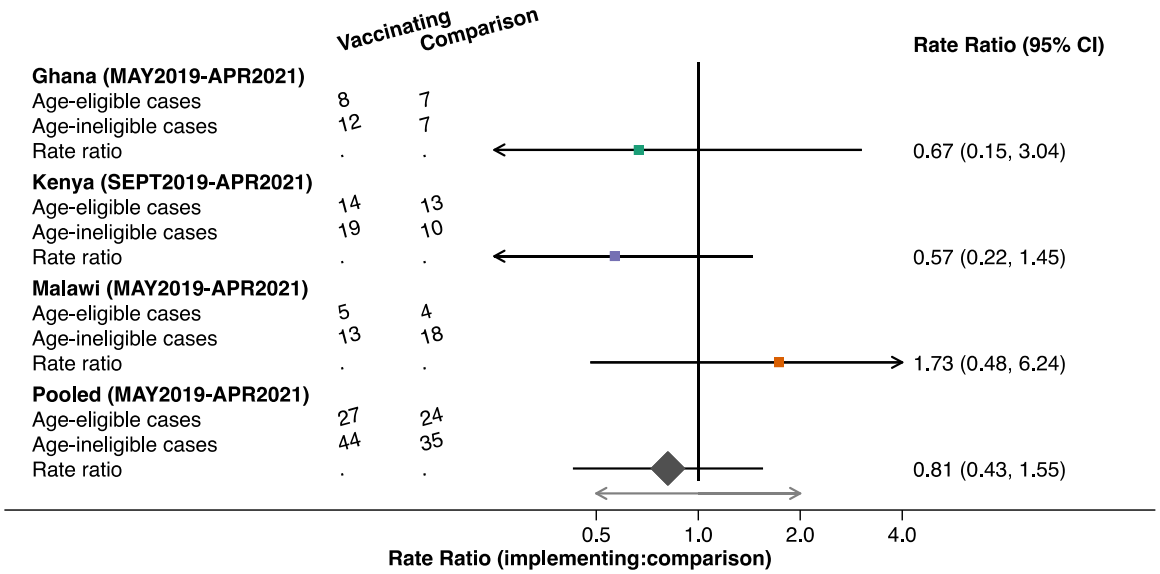


Figure A2. Cerebral malaria: Rate Ratios for the association between the introduction of RTS,S/AS01 and cerebral malaria (including children with malaria and impaired consciousness with unknown meningitis status) in children age-eligible to receive dose 1.

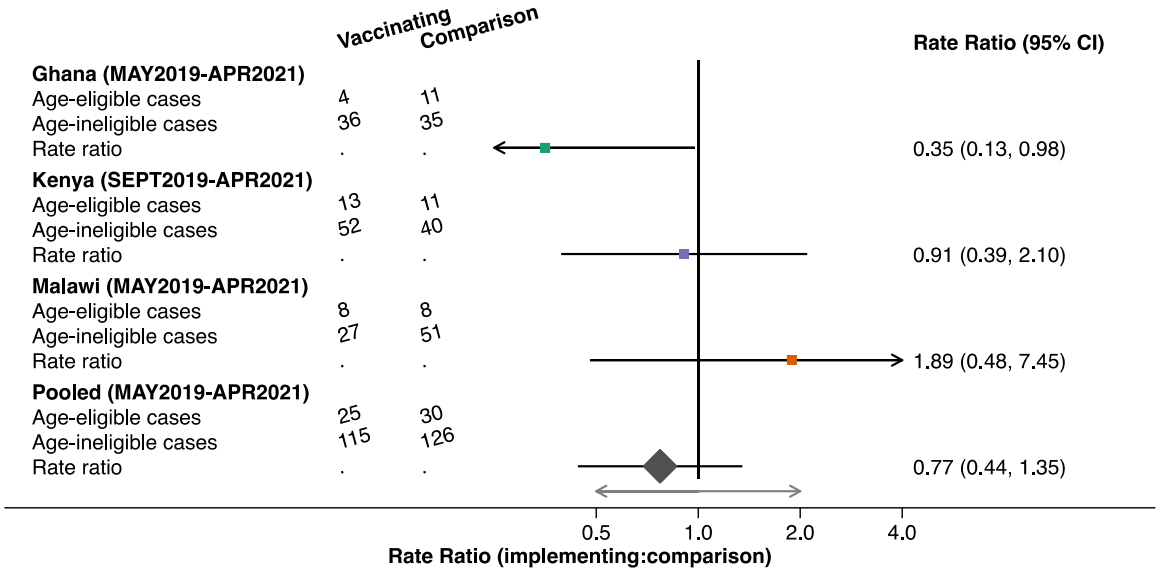


Figure A3. Severe malaria: Rate Ratios for the association between the introduction of RTS,S/AS01 and severe malaria (including children with malaria and impaired consciousness or convulsions with unknown meningitis status) in children age-eligible to have received dose 3.

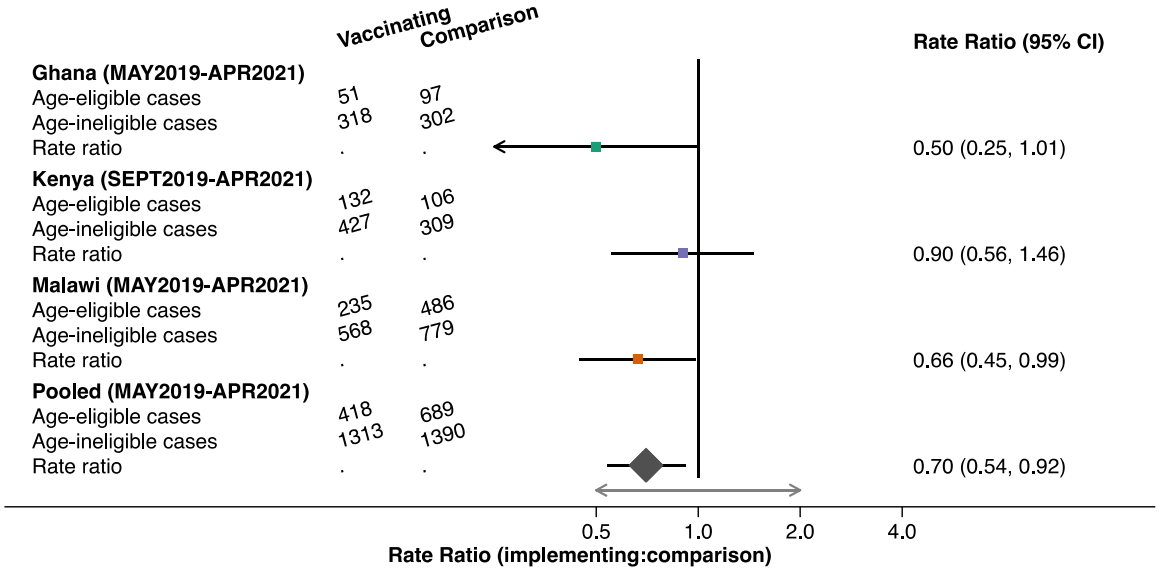
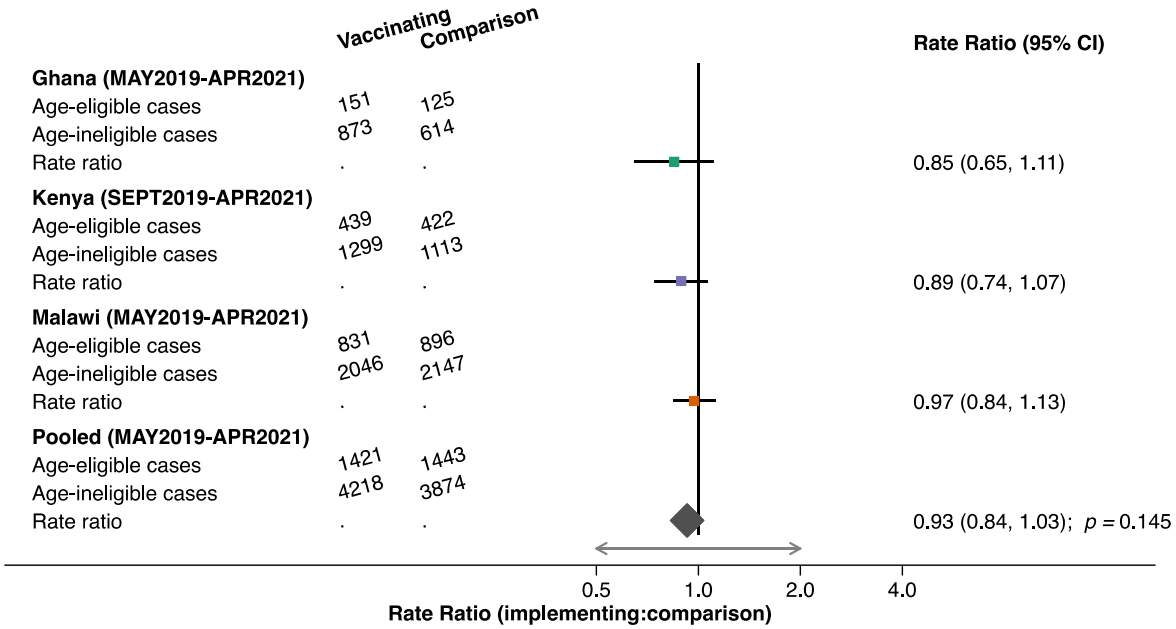


Figure A4. Mortality excluding accidents and trauma (impact population): Rate Ratios for the association between the introduction of RTS,S/AS01 and death (excluding those due to accidents or trauma) in children age-eligible to have received dose 3.



ORIGINAL ARTICLE

Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention

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ABSTRACT

BACKGROUND

Malaria control remains a challenge in many parts of the Sahel and sub-Sahel regions of Africa.

METHODS

We conducted an individually randomized, controlled trial to assess whether seasonal vaccination with RTS,S/AS01$_E$ was noninferior to chemoprevention in preventing uncomplicated malaria and whether the two interventions combined were superior to either one alone in preventing uncomplicated malaria and severe malaria-related outcomes.

RESULTS

We randomly assigned 6861 children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (2287 children [chemoprevention-alone group]), RTS,S/AS01$_E$ (2288 children [vaccine-alone group]), or chemoprevention and RTS,S/AS01$_E$ (2286 children [combination group]). Of these, 1965, 1988, and 1967 children in the three groups, respectively, received the first dose of the assigned intervention and were followed for 3 years. Febrile seizure developed in 5 children the day after receipt of the vaccine, but the children recovered and had no sequelae. There were 305 events of uncomplicated clinical malaria per 1000 person-years at risk in the chemoprevention-alone group, 278 events per 1000 person-years in the vaccine-alone group, and 113 events per 1000 person-years in the combination group. The hazard ratio for the protective efficacy of RTS,S/AS01$_E$ as compared with chemoprevention was 0.92 (95% confidence interval [CI], 0.84 to 1.01), which excluded the prespecified noninferiority margin of 1.20. The protective efficacy of the combination as compared with chemoprevention alone was 62.8% (95% CI, 58.4 to 66.8) against clinical malaria, 70.5% (95% CI, 41.9 to 85.0) against hospital admission with severe malaria according to the World Health Organization definition, and 72.9% (95% CI, 2.9 to 92.4) against death from malaria. The protective efficacy of the combination as compared with the vaccine alone against these outcomes was 59.6% (95% CI, 54.7 to 64.0), 70.6% (95% CI, 42.3 to 85.0), and 75.3% (95% CI, 12.5 to 93.0), respectively.

CONCLUSIONS

Administration of RTS,S/AS01$_E$ was noninferior to chemoprevention in preventing uncomplicated malaria. The combination of these interventions resulted in a substantially lower incidence of uncomplicated malaria, severe malaria, and death from malaria than either intervention alone. (Funded by the Joint Global Health Trials and PATH; ClinicalTrials.gov number, NCT03143218.)

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In many parts of the Sahel and sub-Sahel regions of Africa, malaria transmission is high during a few months of the year.[1] Seasonal malaria chemoprevention, which involves monthly administration of sulfadoxine–pyrimethamine and amodiaquine to young children during the transmission season, is highly effective in preventing malaria.[2] However, despite widespread deployment of seasonal chemoprevention and access to effective diagnosis and treatment, the burden of malaria remains very high in many parts of the Sahel and sub-Sahel regions. Of the 10 African countries classified by the World Health Organization (WHO) as "high burden to high impact" and targeted for enhanced malaria control, 6 are within this region.[3]

In a multicountry, phase 3 trial involving young children,[4] the malaria vaccine RTS,S/AS01$_E$, a viruslike particle expressing the *Plasmodium falciparum* circumsporozoite protein and hepatitis B surface antigen, administered with the adjuvant AS01$_E$, reduced the incidence of malaria,[5] and it is currently being evaluated in a large pilot implementation program in Ghana, Kenya, and Malawi.[6] The protective efficacy of RTS,S/AS01$_E$ is higher during the first few months after vaccination[4,7,8] but then wanes, although not completely.[9] Therefore, we have suggested that RTS,S/AS01$_E$ could be used as a seasonal vaccine in areas in which malaria transmission is highly seasonal, with an annual booster dose administered to vaccine-primed children just before the peak of the transmission season.[10] In this article, we describe the results of a double-blind, randomized, controlled trial involving young children in Burkina Faso and Mali that investigated whether seasonal vaccination with the RTS,S/AS01$_E$ malaria vaccine after priming was noninferior to chemoprevention in preventing clinical malaria and whether a combination of the RTS,S/AS01$_E$ vaccine and chemoprevention was superior to either intervention alone.

Methods

Trial Oversight

The trial protocol[11] (available with the full text of this article at NEJM.org) was approved by the ethics committees of the London School of Hygiene and Tropical Medicine; the Ministry of Health of Burkina Faso; the University of Sciences, Techniques, and Technologies of Bamako; and the national regulatory authorities of Burkina Faso and Mali. A data and safety monitoring board reviewed serious adverse events, approved the statistical analysis plan, and archived the locked databases before unblinding. A steering committee provided scientific advice and monitored the progress of the trial. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and all applicable local regulations. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. GlaxoSmithKline (GSK) Biologicals donated the RTS,S/AS01$_E$ and Havrix vaccines. Dispersible sulfadoxine–pyrimethamine and amodiaquine and matching placebos were donated by Guilin Pharmaceutical.

Trial Sites and Population

The trial was conducted in Bougouni district and neighboring areas in Mali and in Houndé district in Burkina Faso.[12] Information regarding the trial sites is provided in the Supplementary Methods section and Figure S1 in the Supplementary Appendix, available at NEJM.org.

Enrollment and Randomization

All households with children who would be 5 to 17 months of age on April 1, 2017, within the trial areas were enumerated from February through March 2017. Inclusion and exclusion criteria are listed in the Supplementary Appendix. After written informed consent had been obtained from parents or guardians, an independent statistician randomly assigned eligible children to receive chemoprevention (chemoprevention-alone group), the RTS,S/AS01$_E$ vaccine (vaccine-alone group), or chemoprevention plus RTS,S/AS01$_E$ (combination group). The randomization list used permuted blocks after sorting according to age, sex, area of residence, and previous receipt of chemoprevention. Tablet computers with the randomization list were accessible only to the chief pharmacists. All other investigators and trial staff were unaware of treatment assignments until the locked database for analysis had been archived with the data and safety monitoring board in June 2020. All participating children were given an identity card containing their photograph and a quick response (QR) code that included the child's trial identification number, name, and date of birth. At the time of vaccination or administration of chemoprevention, these cards were scanned to

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2
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ensure that the correct intervention was administered.

INTERVENTIONS

All the participating children were given a long-lasting insecticide-treated bed net at the time of enrollment. Children in the vaccine-alone group and the combination group received three doses of RTS,S/AS01$_E$ in April, May, and June 2017, followed by a fourth and fifth dose in June 2018 and June 2019 (Fig. S2). Syringes containing vaccines were prepared by a chief pharmacist and masked with tape to conceal the contents from the administrator, caretakers, and children. The pharmacist and the vaccine administrators had no further role in the trial.

Children in the chemoprevention-alone group and the combination group received four courses of sulfadoxine–pyrimethamine and amodiaquine at monthly intervals each year; children in the vaccine-alone group received four courses of sulfadoxine–pyrimethamine and amodiaquine placebos on that same schedule. Children 12 months of age or older in the chemoprevention-alone group and the combination group received 500 mg of sulfadoxine, 25 mg of pyrimethamine, and 150 mg of amodiaquine on day 1, and an additional 150-mg dose of amodiaquine on days 2 and 3; infants received 250 mg of sulfadoxine, 12.5 mg of pyrimethamine, and 75 mg of amodiaquine on day 1 and 75 mg of amodiaquine on days 2 and 3. The trial drugs were prepared by a pharmacist, who had no further role in the trial, and were placed in resealable envelopes labeled with the QR code. Administration of each dose of sulfadoxine–pyrimethamine and amodiaquine or placebo was directly observed by trial staff at distribution points in trial villages. Children in the chemoprevention-alone group also received three doses of inactivated rabies vaccine (Rabipur)[13] in 2017 and a dose of hepatitis A vaccine (Havrix)[14] in 2018 and 2019.

OUTCOMES

The primary outcome was uncomplicated clinical malaria, defined as a measured temperature of at least 37.5°C or a history of fever within the previous 48 hours and *P. falciparum* parasitemia (parasite density ≥5000 per cubic millimeter) in children who presented to a trial health facility. Prespecified secondary outcomes were hospital admission with malaria, death from malaria, and malaria parasitemia or anemia at the end of the malaria transmission season (see the Supplementary Methods section of the Supplementary Appendix).

SURVEILLANCE

Trial staff based at trial health facilities tested children with suspected malaria with the use of a rapid diagnostic test. Children who were positive were treated with artemether–lumefantrine, and a blood film was obtained for subsequent microscopic examination. Blood films were read by two independent microscopists according to a standardized algorithm.[15] Discrepant readings were resolved by a third reader. The quality of the blood film readings in each country was confirmed by an external reference laboratory (see the Supplementary Methods section in the Supplementary Appendix and Table S1 and Fig. S3).

Each week, 24 randomly selected children in each country were visited at home (8 children per trial group), and a blood film was obtained. Children were also evaluated during a cross-sectional survey conducted 1 month after the last course of chemoprevention at the end of each malaria transmission season to measure hemoglobin level and to obtain a blood film. At the end of the 2018 and the 2019 transmission seasons, 200 randomly selected school-age children who were 6 to 12 years of age (and therefore too old to receive chemoprevention), resided in the trial areas, and were in good health were tested for malaria by means of microscopic examination. If a child was identified as having clinical malaria at a home visit or in a cross-sectional survey, the child was treated with artemether–lumefantrine.

To determine the curative efficacy of the chemoprevention regimen, further informed consent was obtained, and children with asymptomatic malaria parasitemia at the time of the final cross-sectional survey were treated with the same doses of sulfadoxine–pyrimethamine and amodiaquine as those used for the chemoprevention intervention. Blood films were obtained for microscopic analysis on days 1, 2, 4, 7, 14, and 28 after treatment.

Serious adverse events were reported within 72 hours after identification. Deaths that occurred outside a health care facility were assessed by means of verbal autopsy.[16] Assignment of the causes of hospital admissions or deaths that occurred inside or outside the hospital was performed by two physicians who were unaware of the trial-

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group assignments. A third independent physician reviewed cases for which there was a disagreement, and a consensus was reached.

STATISTICAL ANALYSIS

The rationale for the trial's sample size is described in the statistical analysis plan, available with the protocol. For the noninferiority comparison, we determined that 2000 children per group would provide 80% power to exclude, at the 2.5% significance level, a difference in the hazard ratio for clinical malaria between the vaccine-alone group and the chemoprevention-alone group of 20% (favoring vaccine alone) over the 3-year trial period. For the superiority comparisons, assuming that the difference in the hazard ratio between the combination group and the vaccine-alone group or the chemoprevention-alone group would be 30% (favoring the combination), we calculated that this sample size would provide close to 100% power to exclude a minimum difference in the hazard ratios of 0% and would give the trial 90% power to exclude a minimum difference in the hazard ratios of 15%.

The primary analysis was performed in the modified intention-to-treat population, which included all eligible children whose parents or guardians provided consent and who received a first dose of trial vaccine or placebo in April 2017. The per-protocol population for each trial year included all children who received all doses of the vaccine and attended all four chemoprevention visits in that year. Secondary outcomes were assessed only in the modified intention-to-treat population. Person-time at risk was calculated from the date of first vaccination until the date of death, the date of permanent emigration, the date consent was withdrawn, the date last seen for children lost to follow-up or who temporarily traveled out of the trial area, or the end of the trial (March 31, 2020).

The hazard ratio for the primary outcome was estimated with the use of Cox regression models, adjusted for trial center, with a robust standard error to account for potential clustering of recurrent episodes of malaria. Protective efficacy (the percent difference in the total number of events over the trial period) was estimated as (1 − hazard ratio) × 100. Effect modification according to trial center and year, prespecified in the statistical analysis plan, was assessed with the use of the Wald test for the interaction term without adjustment for multiple comparisons. Two-sided 90%, 95%, and 99% confidence intervals for the hazard ratio for the comparison of RTS,S/AS01$_E$ alone with chemoprevention alone were calculated and compared with the prespecified noninferiority margin of 1.20. To preserve the type I error rate at 5%, a closed testing procedure was used: the Wald test of the null hypothesis of equal hazard ratios comparing all three groups was performed. If the null hypothesis was rejected at the 5% significance level, pairwise comparisons were performed, also with a 5% significance level. Incidence rate differences and prevalence ratios were calculated with the use of published methods.[17,18] An analysis was conducted to explore patterns of missingness in the outcome data and to assess sensitivity to missing outcome data (Table S8). Full details of the conduct of the trial are provided in the protocol.

RESULTS

VACCINE COVERAGE

From April through May 2017, a total of 5920 children received the first dose of the trial vaccine or placebo (1965 in the chemoprevention-alone group, 1988 in the vaccine-alone group, and 1967 in the combination group), and the data from these children were used in the calculation of the hazard ratios. On March 31, 2020, a total of 1716 children (87.3%) in the chemoprevention-alone group, 1734 (87.2%) in the vaccine-alone group, and 1740 (88.5%) in the combination group had completed follow-up (Fig. 1). Country-specific information, including the reasons for and timing of losses to follow-up, is provided in Figures S4 through S7. The baseline characteristics and the use of insecticide-treated bed nets were well balanced between groups (Tables S2 through S4). Children who did not receive a first dose of vaccine or vaccine placebo were of similar ages and sexes and had similar (though slightly lower) coverage of other childhood vaccines as children who were vaccinated (Table S5). In the first year of the trial, 93.4% of children received all three doses of vaccine; among children who were still in follow-up, 95.1% received a booster dose in year 2 and 94.7% received a booster dose in year 3 (Table S6). All four chemoprevention visits were attended by 82.8% of the children in year 1, 84.1% in year 2, and 87.7% in year 3 (Table S7).

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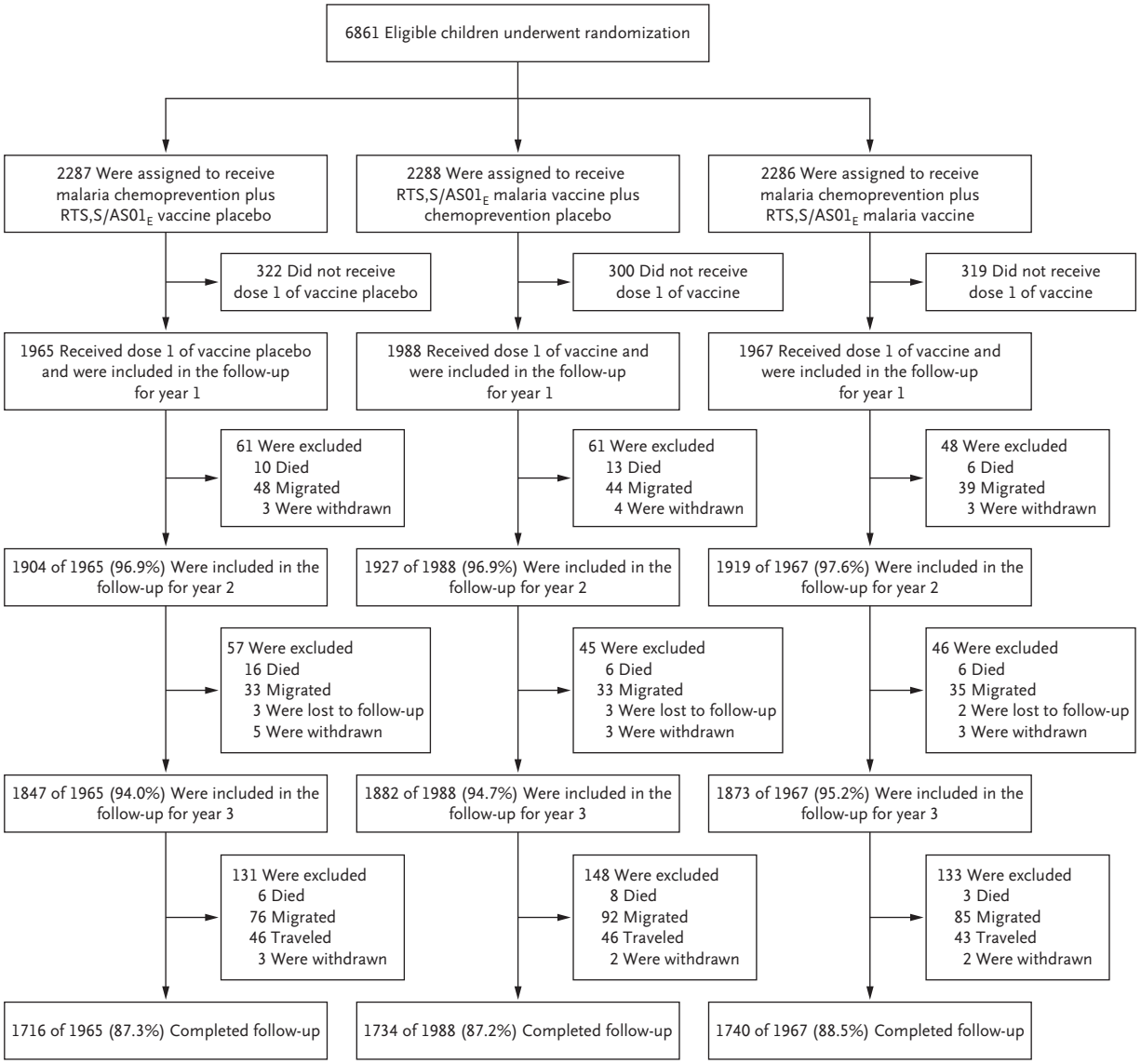

Figure 1. Randomization and Follow-up.

Children in the vaccine-alone and combination groups who did not attend the first intervention visit (vaccine dose 1) were considered to have not participated in the trial. Of the children who attended the first visit in 2017, a total of 1790 of 1965 (91.1%) in the chemoprevention-alone group, 1840 of 1988 (92.6%) in the vaccine-alone group, and 1815 of 1967 (92.3%) in the combination group attended the first visit to receive chemoprevention or chemoprevention placebo. Children who did not have an outcome of interest that was observed through passive case detection but who remained in the trial (i.e., did not die or migrate and were not withdrawn during the trial period) were considered to be included in the trial follow-up in each year. The number of children remaining in follow-up at the end of the trial was confirmed by an exit census of all children in March 2020. Table S8 in the Supplementary Appendix shows the characteristics of children whose data were censored during the trial period as compared with those who remained in the trial. Children who traveled were considered to be those who temporarily traveled away from the trial area at the time of the exit census in March 2020 but had not permanently migrated; for these children, the last documented contact date was used to calculate person-time at risk.

EFFICACY

There were 3825 events of clinical malaria among the children. In the modified intention-to-treat analysis, the incidence of clinical malaria was 278.2 events per 1000 person-years at risk in the vaccine-alone group and 304.8 events per 1000 person-years in the chemoprevention-alone group (hazard ratio, 0.92) (Table 1). The 90%,

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Table 1. Incidence of Uncomplicated Clinical Malaria (Modified Intention-to-Treat Population).*

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/1000 person-yr at risk*		
Burkina Faso and Mali					
Chemoprevention alone	5449.9	1661	304.8 (290.5 to 319.8)	Reference	
Vaccine alone	5535.7	1540	278.2 (264.6 to 292.4)	7.9 (–1.0 to 16.0)	Reference
Combination	5508.0	624	113.3 (104.7 to 122.5)	62.8 (58.4 to 66.8)	59.6 (54.7 to 64.0)
Burkina Faso					
Chemoprevention alone	2602.9	1028	394.9 (371.5 to 419.8)	Reference	
Vaccine alone	2550.9	998	391.2 (367.7 to 416.3)	1.1 (–10.1 to 11.1)	Reference
Combination	2602.3	401	154.1 (139.7 to 169.9)	61.1 (55.4 to 66.1)	60.7 (55.0 to 65.7)
Mali					
Chemoprevention alone	2847.0	633	222.3 (205.7 to 240.4)	Reference	
Vaccine alone	2984.8	542	181.6 (166.9 to 197.5)	18.6 (3.4 to 31.3)	Reference
Combination	2905.7	223	76.7 (67.3 to 87.5)	65.6 (57.9 to 71.9)	57.8 (47.9 to 65.8)
Year 1					
Chemoprevention alone	1794.3	309	172.2 (154.0 to 192.5)	Reference	
Vaccine alone	1816.8	318	175.0 (156.8 to 195.4)	–1.7 (–21.4 to 14.8)	Reference
Combination	1802.3	88	48.8 (39.6 to 60.2)	71.7 (63.8 to 77.8)	72.1 (64.4 to 78.2)
Year 2					
Chemoprevention alone	1868.5	705	377.3 (350.5 to 406.2)	Reference	
Vaccine alone	1903.4	647	339.9 (314.7 to 367.1)	10.1 (–1.9 to 20.6)	Reference
Combination	1894.4	264	139.4 (123.5 to 157.2)	63.2 (56.8 to 68.6)	59.1 (51.9 to 65.1)
Year 3					
Chemoprevention alone	1787.1	647	362.0 (335.2 to 391.0)	Reference	
Vaccine alone	1815.5	575	316.7 (291.9 to 343.7)	12.7 (0.9 to 23.1)	Reference
Combination	1811.3	272	150.2 (133.3 to 169.1)	58.6 (51.5 to 64.6)	52.6 (44.2 to 59.7)

* The modified intention-to-treat population included all eligible children whose parents or guardians provided consent and who received a first dose of trial vaccine or vaccine placebo. Children received chemoprevention (chemoprevention-alone group), RTS,S/AS01$_E$ (vaccine-alone group), or chemoprevention and RTS,S/AS01$_E$ (combination group). The protective efficacy was calculated as (1 – hazard ratio) × 100. CI denotes confidence interval.

Figure 2 (facing page). Primary Outcome.

Children received chemoprevention alone, the RTS,S/AS01$_E$ vaccine alone, or a combination of chemoprevention and RTS,S/AS01$_E$. Panel A shows the incidence of uncomplicated clinical malaria (the primary outcome) in each of the three groups. The I bars indicate 95% confidence intervals. Panel B shows the Nelson–Aalen cumulative hazard estimates for each group and the number of children remaining at risk at the end of each trial year. Panel C shows pairwise hazard ratios for uncomplicated clinical malaria. The I bars show 90%, 95%, and 99% confidence intervals: the blue bars represent the 90% confidence intervals (narrowest confidence intervals), the purple bars the 95% confidence intervals, and the red bars the 99% confidence intervals (widest confidence intervals). The dotted line shows the prespecified noninferiority margin of 1.20 for the comparison of vaccine alone with chemoprevention alone.

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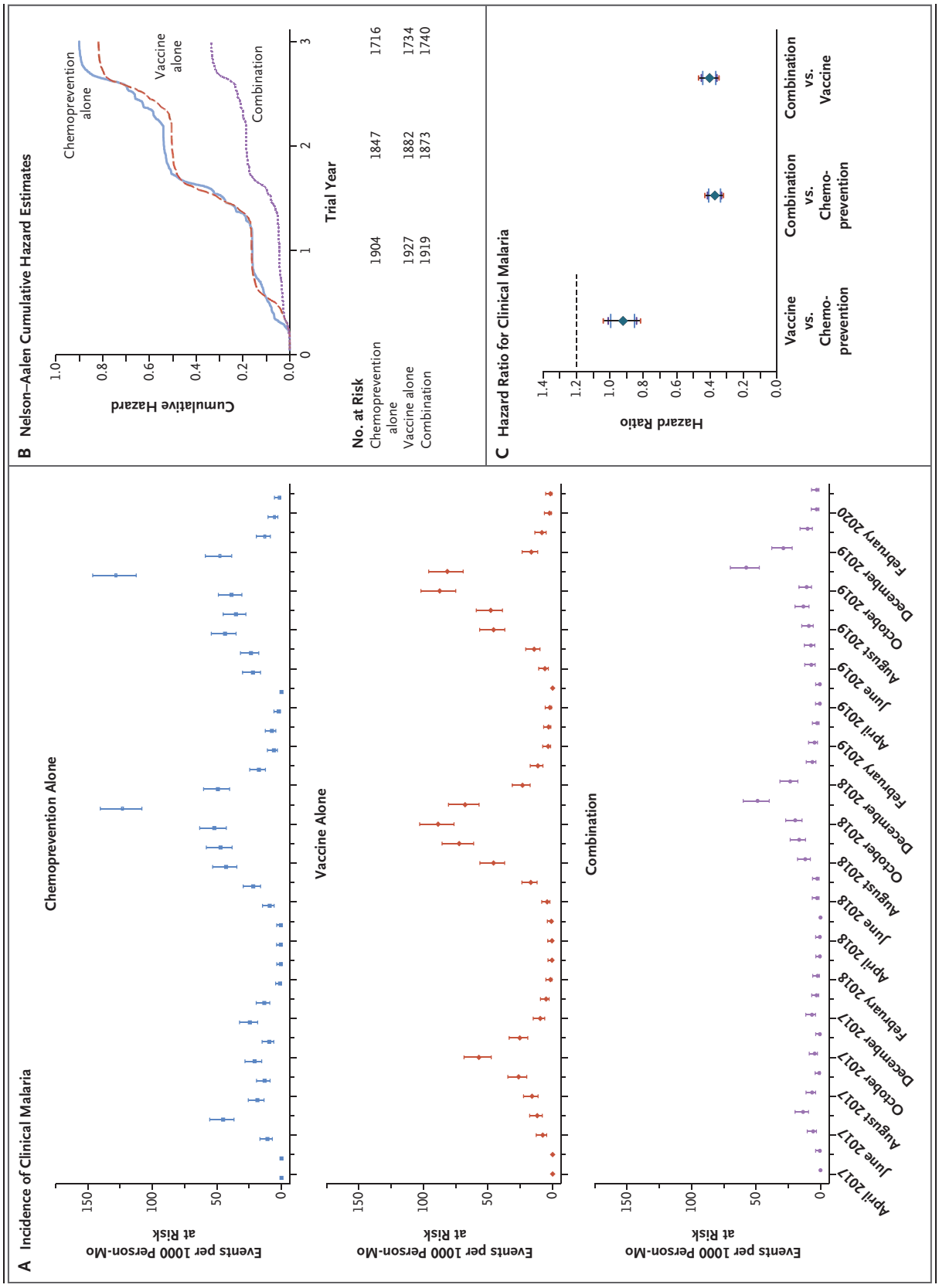

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95%, and 99% confidence intervals for the hazard ratios all excluded the prespecified noninferiority margin of 1.20 (99% confidence interval [CI], 0.82 to 1.04) (Fig. 2).

The incidence of clinical malaria in the combination group was 113 events per 1000 person-years at risk, indicating a protective efficacy of 62.8% (95% CI, 58.4 to 66.8) as compared with chemoprevention alone and an efficacy of 59.6% (95% CI, 54.7 to 64.0) as compared with vaccine alone. The protective efficacy was similar in the two countries but differed over time, being highest in the first year of the trial and slightly lower in years 2 and 3 (Table 1 and Fig. 2B). Results of per-protocol analyses were similar to those of the modified intention-to-treat analyses (Table S9), and the protective efficacy against secondary outcomes (clinical malaria with any parasite density or malaria diagnosed with the use of a rapid diagnostic test) was similar to that against the primary outcome. The incidence of non-falciparum malaria was lower in the two groups that received chemoprevention than in the vaccine-alone group (Table S10).

As compared with chemoprevention alone or vaccine alone, the combined intervention provided a high level of protection against the following prespecified secondary outcomes: hospitalization for malaria, hospitalization meeting WHO criteria for severe malaria, severe malarial anemia, and blood transfusion (Table 2). The protective efficacy of the combination as compared with chemoprevention alone was 62.8% (95% CI, 58.4 to 66.8) against clinical malaria, 70.5% (95% CI, 41.9 to 85.0) against hospital admission with severe malaria, and 72.9% (95% CI, 2.91 to 92.4) against death from malaria. The protective efficacy of the combination as compared with the vaccine alone against these outcomes was 59.6% (95% CI, 54.7 to 64.0), 70.6% (95% CI, 42.3 to 85.0), and 75.3% (95% CI, 12.5 to 93.0), respectively.

The incidences of death from any cause, excluding external causes and surgery, and deaths attributable to malaria were also markedly lower in the combination group than in either single-intervention group. As compared with chemoprevention alone, the combination intervention resulted in an incidence of clinical malaria that was lower by 190.8 events per 1000 person-years at risk (Table S11). In addition, there were 4.8 fewer events of WHO-defined severe malaria, 3.8 fewer hospital admissions for severe malarial anemia, 2.8 fewer blood transfusions, and 1.5 fewer deaths from malaria per 1000 person-years at risk (Table S12).

The prevalence of malaria parasitemia at weekly surveys was consistently approximately 50% lower in the combination group than in the chemoprevention-alone or vaccine-alone groups (Table 3). At the end of each malaria transmission season, the prevalence of *P. falciparum* parasitemia and anemia (hemoglobin level, <7 g per deciliter) was lower in the combination group than in the two other groups (Table 3). The prevalence of *P. falciparum* gametocytemia was also consistently lower in the combination group than in the chemoprevention-alone or vaccine-alone groups (Table S13). Among school-age children living in the trial areas who did not receive a trial intervention, the prevalence of parasitemia was high in each year (>60% in Burkina Faso and >17% in Mali) (Table 3). Among children with asymptomatic parasitemia, the curative efficacy of sulfadoxine–pyrimethamine and amodiaquine after 28 days was 99.1% (95% CI, 93.9 to 99.9) in Burkina Faso and 95.2% (95% CI, 82.7 to 98.8) in Mali (Table S14).

SAFETY

Febrile seizures developed in five children, all of whom had received RTS,S/AS01$_E$, the day after vaccination (three children in the vaccine-alone group and in two in the combination group). Three events occurred after a priming dose, and two occurred after a booster dose. These children recovered and had no sequelae. There were no other serious adverse events that were identified by the investigator as being related to vaccination. Eight cases of clinically suspected meningitis (four in the chemoprevention-alone group, three in the vaccine-alone group, and one in the combination group) were investigated with the use of lumbar puncture, but none showed proven meningitis. The distributions of the causes of hospital admissions and the causes of death are shown in Tables S15 through S17. There was no evidence of higher mortality or a greater number of hospital admissions among girls who received RTS,S/AS01$_E$ than among boys who received RTS,S/AS01$_E$ (Tables S18 and S19).

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Table 2. Incidence of Secondary Severe Outcomes According to Trial Group (Modified Intention-to-Treat Population).*

Outcome and Group	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/1000 person-yr at risk*		
Hospitalizations				
Any reason, excluding external causes and surgery				
Chemoprevention alone	60	11.0 (8.6 to 14.2)	Reference	
Vaccine alone	73	13.2 (10.5 to 16.6)	–22.3 (–74.4 to 14.3)	Reference
Combination	49	8.9 (6.7 to 11.8)	18.7 (–19.4 to 44.7)	33.5 (3.0 to 54.5)
All cases of malaria				
Chemoprevention alone	49	9.0 (6.8 to 11.9)	Reference	
Vaccine alone	54	9.8 (7.5 to 12.7)	–11.0 (–65.8 to 25.7)	Reference
Combination	28	5.1 (3.5 to 7.4)	43.2 (7.7 to 65.0)	48.8 (17.1 to 68.4)
Severe malaria†				
Chemoprevention alone	37	6.8 (4.9 to 9.4)	Reference	
Vaccine alone	37	6.7 (4.8 to 9.2)	–0.4 (–60.2 to 37.1)	Reference
Combination	11	2.0 (1.1 to 3.6)	70.5 (41.9 to 85.0)	70.6 (42.3 to 85.0)
Cerebral malaria†				
Chemoprevention alone	0	0	Reference	
Vaccine alone	4	0.7 (0.3 to 1.9)	—	Reference
Combination	1	0.2 (0.0 to 1.3)	—	74.6 (–128.0 to 97.2)
Severe malarial anemia†				
Chemoprevention alone	31	5.7 (4.0 to 8.1)	Reference	
Vaccine alone	25	4.5 (3.1 to 6.7)	18.4 (–39.3 to 52.2)	Reference
Combination	10	1.8 (1.0 to 3.4)	67.9 (34.1 to 84.3)	60.6 (18.3 to 81.0)
Blood transfusion				
Chemoprevention alone	23	4.2 (2.8 to 6.4)	Reference	
Vaccine alone	21	3.8 (2.5 to 5.8)	8.3 (–67.6 to 49.8)	Reference
Combination	8	1.5 (0.7 to 2.9)	65.4 (22.9 to 84.5)	62.3 (14.1 to 83.4)
Deaths				
All, including external causes and surgery				
Chemoprevention alone	32	5.9 (4.2 to 8.3)	Reference	
Vaccine alone	27	4.9 (3.3 to 7.1)	15.9 (–40.3 to 49.6)	Reference
Combination	15	2.7 (1.6 to 4.5)	53.4 (14.0 to 74.8)	44.6 (–4.1 to 70.5)
All, excluding external causes and surgery				
Chemoprevention alone	25	4.6 (3.1 to 6.8)	Reference	
Vaccine alone	22	4.0 (2.6 to 6.0)	12.1 (–55.7 to 50.4)	Reference
Combination	12	2.2 (1.2 to 3.8)	52.3 (5.0 to 76.0)	45.7 (–9.6 to 73.1)
Malaria				
Chemoprevention alone	11	2.0 (1.1 to 3.6)	Reference	
Vaccine alone	12	2.2 (1.2 to 3.8)	–9.5 (–148.3 to 51.7)	Reference
Combination	3	0.5 (0.2 to 1.7)	72.9 (2.9 to 92.4)	75.3 (12.5 to 93.0)

* Confidence intervals for the hazard ratios for secondary outcomes were not adjusted for multiplicity, and inferences drawn from these intervals may not be reproducible.
† Cases of severe malaria, cerebral malaria, and severe malarial anemia were classified according to World Health Organization definitions.

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SAGE meeting October 2021 9
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Table 3. Prevalence of Outcomes at Weekly Surveys and at Surveys Conducted at the End of Each Malaria Transmission Season.*

Variable	Children	Prevalence Ratio, Vaccine Alone or Combination vs. Chemoprevention (95% CI)	Prevalence Ratio, Combination vs. Vaccine Alone (95% CI)
	no./total no. (%)		
***Plasmodium falciparum* infection at weekly surveys**			
2017			
Chemoprevention	17/637 (2.7)	Reference	
Vaccine alone	36/627 (5.7)	2.20 (1.26–3.85)	Reference
Combination	8/648 (1.2)	0.47 (0.21–1.08)	0.21 (0.10–0.46)
2018			
Chemoprevention	46/666 (6.9)	Reference	
Vaccine alone	39/677 (5.8)	0.81 (0.55–1.21)	Reference
Combination	23/685 (3.4)	0.48 (0.30–0.78)	0.59 (0.36–0.97)
2019			
Chemoprevention	26/491 (5.3)	Reference	
Vaccine alone	34/505 (6.7)	1.25 (0.77–2.04)	Reference
Combination	11/518 (2.1)	0.39 (0.19–0.77)	0.31 (0.16–0.60)
***P. falciparum* infection at end-of-season surveys**			
2017			
Chemoprevention	29/1708 (1.7)	Reference	
Vaccine alone	100/1741 (5.7)	3.46 (2.30–5.19)	Reference
Combination	13/1718 (0.8)	0.45 (0.24–0.87)	0.13 (0.07–0.23)
2018			
Chemoprevention	225/1651 (13.6)	Reference	
Vaccine alone	210/1717 (12.2)	0.92 (0.78–1.08)	Reference
Combination	111/1695 (6.6)	0.48 (0.39–0.59)	0.52 (0.42–0.65)
2019			
Chemoprevention	219/1619 (13.5)	Reference	
Vaccine alone	213/1649 (12.9)	0.98 (0.83–1.17)	Reference
Combination	92/1641 (5.6)	0.42 (0.33–0.53)	0.43 (0.34–0.54)
Hemoglobin level <7 g/dl at end-of-season surveys			
2017			
Chemoprevention	21/1710 (1.2)	Reference	
Vaccine alone	28/1742 (1.6)	1.33 (0.76–2.33)	Reference
Combination	18/1719 (1.0)	0.86 (0.46–1.61)	0.65 (0.36–1.17)
2018			
Chemoprevention	38/1655 (2.3)	Reference	
Vaccine alone	40/1717 (2.3)	1.03 (0.67–1.59)	Reference
Combination	12/1695 (0.7)	0.31 (0.16–0.59)	0.30 (0.16–0.57)

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Table 3. (Continued.)

Variable	Children	Prevalence Ratio, Vaccine Alone or Combination vs. Chemoprevention (95% CI)	Prevalence Ratio, Combination vs. Vaccine Alone (95% CI)
	no./total no. (%)		
2019			
Chemoprevention	8/1619 (0.5)	Reference	
Vaccine alone	9/1650 (0.5)	1.11 (0.43–2.86)	Reference
Combination	4/1642 (0.2)	0.49 (0.15–1.63)	0.45 (0.14–1.45)
***P. falciparum* parasitemia in school-age children**			
2018			
Burkina Faso			
Any parasite density	123/200 (61.5)		
Parasite density ≥5000/mm^3	20/200 (10.0)		
Mali			
Any parasite density	34/200 (17.0)		
Parasite density ≥5000/mm^3	9/200 (4.5)		
2019			
Burkina Faso			
Any parasite density	123/200 (61.5)		
Parasite density ≥5000/mm^3	19/200 (9.5)		
Mali			
Any parasite density	45/200 (22.5)		
Parasite density ≥5000/mm^3	18/200 (9.0)		

* Samples for blood slides were obtained from a randomly selected subgroup of children each week throughout the trial period for the weekly surveys. Surveys were also performed every year at the end of each malaria transmission season; samples were obtained for blood slides from all children 1 month after receipt of the last course of chemoprevention or placebo. Confidence intervals for the prevalence ratios were not adjusted for multiplicity, and inferences drawn from these intervals may not be reproducible.

DISCUSSION

The results of this trial show that seasonal vaccination with the RTS,S/AS01$_E$ malaria vaccine was noninferior to four annual courses of chemoprevention with sulfadoxine–pyrimethamine and amodiaquine in protecting against uncomplicated clinical malaria over a period of 3 years. A combination of RTS,S/AS01$_E$ and chemoprevention was superior to RTS,S/AS01$_E$ and to chemoprevention alone with respect to reducing the incidence of uncomplicated clinical malaria, hospital admissions with severe malaria, and deaths from malaria. There was some evidence that efficacy of the combination intervention against clinical malaria was higher in the first year of the trial than in the subsequent 2 years, but substantial efficacy was seen in each year of the trial.

Chemoprevention alone was more protective than RTS,S/AS01$_E$ alone during the 4 months when it was administered, but RTS,S/AS01$_E$ alone provided protection outside this period, and was thus not inferior over the whole year. The addition of a fifth course of chemoprevention might have improved efficacy in both the chemoprevention-alone and combination groups[19] and might have reduced the incidence of malaria in the combination group to very low levels, despite the high level of malaria transmission in the trial areas, particularly in Burkina Faso.

The RTS,S/AS01$_E$ vaccine priming and booster regimen was not associated with any new con-

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cerning pattern of side effects. Febrile seizures developed in five children who received RTS,S/AS01$_E$, a finding consistent with previous trials of RTS,S/AS01$_E$,[4] but all children recovered and had no sequelae. No cases of meningitis were detected, and no imbalance in death according to sex was seen among children who received RTS,S/AS01$_E$ (meningitis and death were previously reported as safety concerns among children who received this vaccine).[4,20]

Among children who had undergone randomization, 14% in the vaccine-alone and combination groups did not attend the first visit and were considered to have not participated in the trial. This could have introduced a bias in favor of RTS,S/AS01$_E$ because no comparable restriction was applied to children in the chemoprevention-alone group. However, results of the per-protocol analysis and an analysis that was restricted to children who attended the first scheduled visit to receive chemoprevention or placebo were similar to those of the analysis in the modified intention-to-treat population. Strengths of the trial were the large size, high statistical power, high retention rate, the careful assessment of the causes of hospital admissions and deaths, and the consistency of the efficacy estimates against different outcomes and between the two countries.

The drugs currently used for chemoprevention (sulfadoxine–pyrimethamine and amodiaquine) remain effective in the trial areas, as shown by the results of our in vivo study involving asymptomatic children. However, if resistance to these drugs increases without an available alternative chemoprevention regimen, seasonal vaccination with RTS,S/AS01$_E$ could provide a potential alternative. The combination of seasonal chemoprevention (which when used alone has a high level of efficacy against uncomplicated and severe malaria[2]) with seasonal vaccination with RTS,S/AS01$_E$ provides a promising approach to the prevention of malaria in the large areas of Africa with seasonal malaria and where malaria is currently poorly controlled. Further research will be required to determine how best to deliver the combination of chemoprevention and seasonal malaria vaccination in areas of high malaria burden in the Sahel and sub-Sahel regions. In addition, there may be other epidemiologic situations in which a combination of chemoprevention and vaccination could improve on current methods of malaria control.

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APPENDIX

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