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

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-

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 chemoprevention 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 $(1-\text{hazard ratio}) \times 100$. 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).

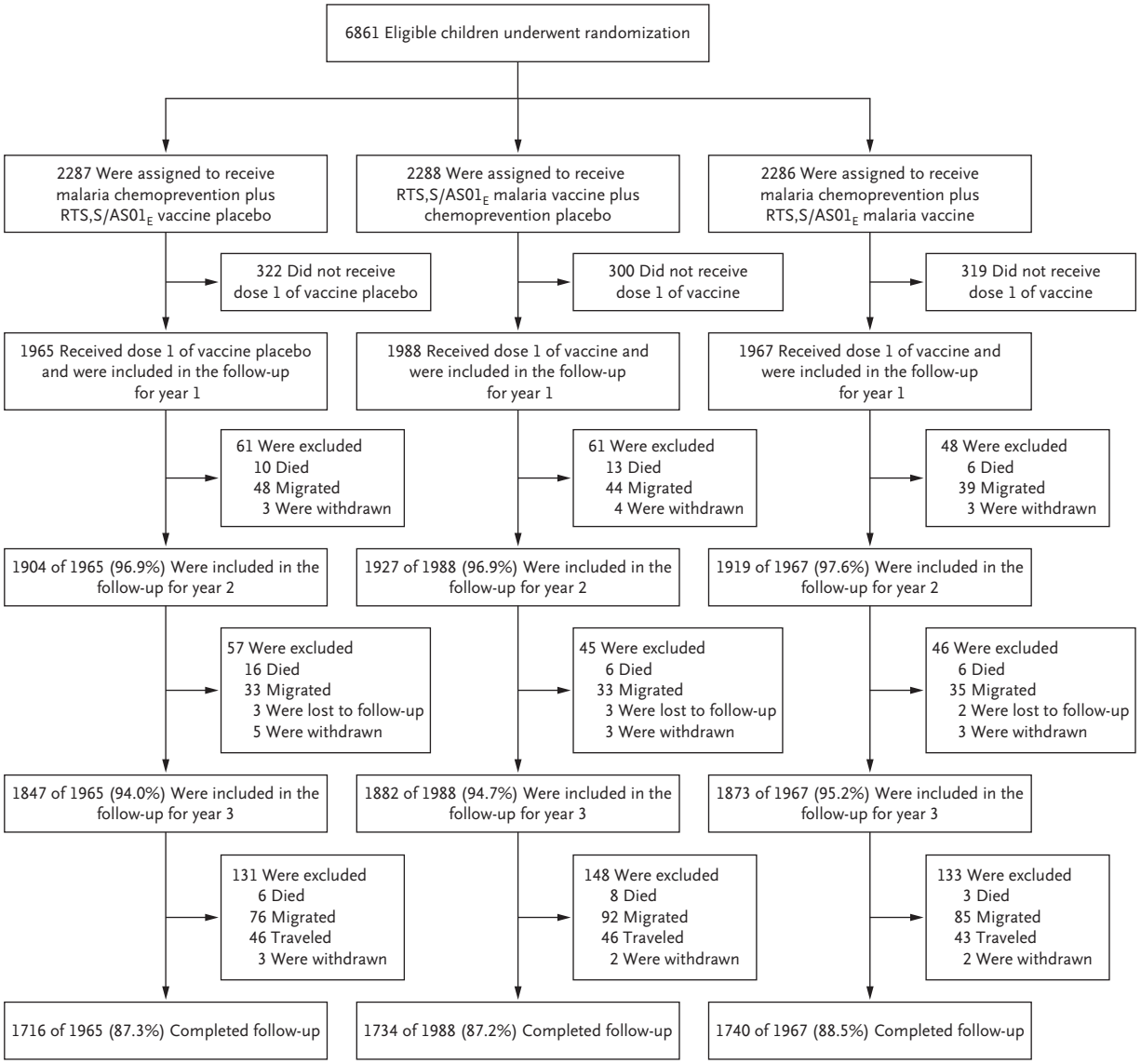


Figure 1. Randomization and Follow-up.

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%,

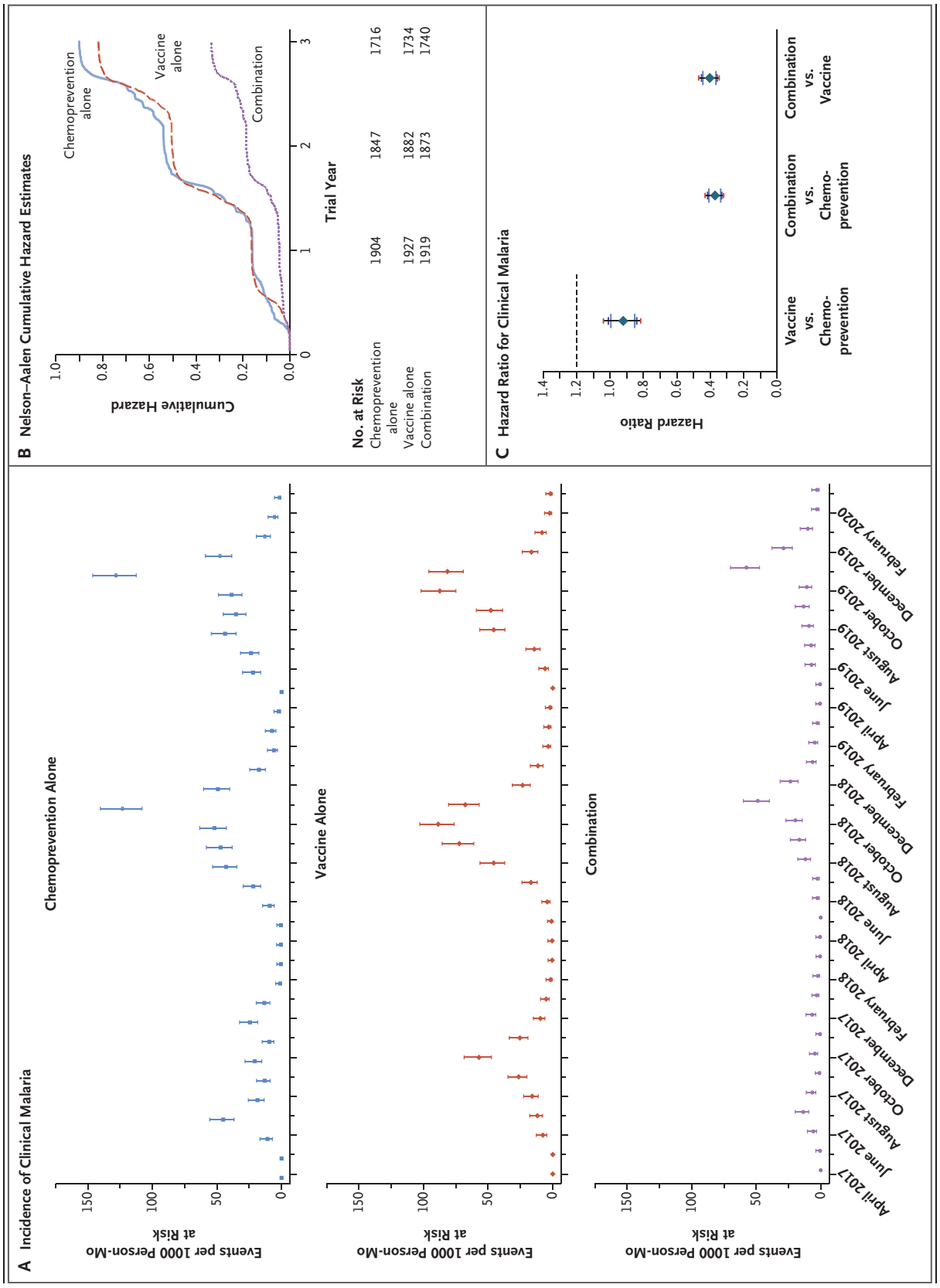
Table 1. Incidence of Uncomplicated Clinical Malaria (Modified Intention-to-Treat Population).*

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.



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).

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.

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)

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-

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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