

## First Results of Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Children

The RTS,S Clinical Trials Partnership\*

### ABSTRACT

#### BACKGROUND

An ongoing phase 3 study of the efficacy, safety, and immunogenicity of candidate malaria vaccine RTS,S/AS01 is being conducted in seven African countries.

#### METHODS

From March 2009 through January 2011, we enrolled 15,460 children in two age categories — 6 to 12 weeks of age and 5 to 17 months of age — for vaccination with either RTS,S/AS01 or a non-malaria comparator vaccine. The primary end point of the analysis was vaccine efficacy against clinical malaria during the 12 months after vaccination in the first 6000 children 5 to 17 months of age at enrollment who received all three doses of vaccine according to protocol. After 250 children had an episode of severe malaria, we evaluated vaccine efficacy against severe malaria in both age categories.

#### RESULTS

In the 14 months after the first dose of vaccine, the incidence of first episodes of clinical malaria in the first 6000 children in the older age category was 0.32 episodes per person-year in the RTS,S/AS01 group and 0.55 episodes per person-year in the control group, for an efficacy of 50.4% (95% confidence interval [CI], 45.8 to 54.6) in the intention-to-treat population and 55.8% (97.5% CI, 50.6 to 60.4) in the per-protocol population. Vaccine efficacy against severe malaria was 45.1% (95% CI, 23.8 to 60.5) in the intention-to-treat population and 47.3% (95% CI, 22.4 to 64.2) in the per-protocol population. Vaccine efficacy against severe malaria in the combined age categories was 34.8% (95% CI, 16.2 to 49.2) in the per-protocol population during an average follow-up of 11 months. Serious adverse events occurred with a similar frequency in the two study groups. Among children in the older age category, the rate of generalized convulsive seizures after RTS,S/AS01 vaccination was 1.04 per 1000 doses (95% CI, 0.62 to 1.64).

#### CONCLUSIONS

The RTS,S/AS01 vaccine provided protection against both clinical and severe malaria in African children. (Funded by GlaxoSmithKline Biologicals and the PATH Malaria Vaccine Initiative; RTS,S ClinicalTrials.gov number, NCT00866619.)

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EACH YEAR, MALARIA OCCURS IN APPROXIMATELY 225 million persons worldwide, and 781,000 persons, mostly African children, die from the disease.<sup>1</sup> During the past decade, the scale-up of malaria-control interventions has resulted in considerable reductions in morbidity and mortality associated with malaria in parts of Africa.<sup>2,3</sup> However, malaria continues to pose a major public health threat. A malaria vaccine, deployed in combination with current malaria-control tools, could play an important role in future control and eventual elimination of malaria in Africa.<sup>4</sup>

The RTS,S vaccine that targets the circumsporozoite protein and is given with an adjuvant system (AS01 or AS02) has consistently shown protection against *Plasmodium falciparum* malaria in children and infants in phase 2 trials.<sup>5-10</sup> The vaccine had an acceptable side-effect profile and was immunogenic in children who were 6 weeks of age or older. In addition, the vaccine could be administered safely with other childhood vaccines<sup>8,11</sup> and provided protection against severe malaria.<sup>5</sup> Here, we report the initial results of an ongoing phase 3 trial being conducted at 11 centers in 7 African countries (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

## METHODS

### STUDY DESIGN

Detailed methods are presented in the Supplementary Appendix and have been reported previously.<sup>12-15</sup> This randomized, controlled, double-blind trial was designed to evaluate vaccine efficacy, safety, reactogenicity, and immunogenicity in children up to 32 months after the administration of the first dose of vaccine. The trial included two age categories: children 6 to 12 weeks of age and those 5 to 17 months of age at enrollment. The trial included three study groups in each age category: children who received all three doses of the RTS,S/AS01 vaccine administered at 1-month intervals and who were scheduled to receive a booster dose 18 months after the third dose, children who received the RTS,S/AS01 primary vaccination series without a booster, and a control group who received a non-malaria comparator vaccine. This first analysis combines the first two groups (referred to as the RTS,S/AS01 group) and compares this group with the control group (Fig. 2 in the Supplementary Appendix). Children in the

younger age category received the RTS,S/AS01 vaccine along with routine childhood vaccinations beginning at 6 weeks of age.

The coprimary end points of the trial — vaccine efficacy against clinical malaria after 12 months of follow-up in each age category — have been completed for the first 6000 children enrolled in the older age category. Vaccine efficacy against severe malaria will be reported after 12 months of follow-up of the first 6000 children enrolled in each age category. Accordingly, vaccine efficacy against both clinical and severe malaria in the older age category is presented here, and findings regarding efficacy will be presented for the younger age category in approximately 1 year, after the first 6000 children in that age category have completed 12 months of follow-up. A secondary analysis of vaccine efficacy against severe malaria in the pooled age categories was planned to take place when at least one severe malaria episode had occurred in at least 250 children. This milestone was reached on May 31, 2011. Vaccine efficacy against severe disease in the pooled age categories is restricted to data obtained up to this date. Data for children who received a booster dose of vaccine before May 31, 2011, were censored at the time of booster vaccination.

The trial protocol, which is available at NEJM.org, was approved by the ethical review board and national regulatory authority at each study center and partner institution. Written informed consent was obtained from the children's parents or guardians (Table 1 in the Supplementary Appendix). The trial was undertaken in accordance with the provisions of the Good Clinical Practice Guidelines.<sup>16</sup>

### RANDOMIZATION AND VACCINATION

From March 2009 through January 2011, we randomly assigned 15,460 children to one of the three original study groups in a 1:1:1 ratio. Comparator vaccines were rabies vaccine (VeroRab, Sanofi-Pasteur) for children 5 to 17 months of age at enrollment and meningococcal serogroup C conjugate vaccine (Menjugate, Novartis) for children 6 to 12 weeks of age at enrollment. All vaccines were administered intramuscularly.

### SURVEILLANCE FOR CLINICAL AND SEVERE MALARIA

Passive surveillance for malaria was undertaken from the time of the administration of the first dose of vaccine until the end of the study. Participants were encouraged to seek care at a health

facility within the study area for any illness, and transportation was facilitated. All participants who presented to a study facility with a reported or measured fever during the previous 24 hours were evaluated for malaria (for details, see the Supplementary Appendix).

The primary efficacy end point for this analysis was the incidence of clinical malaria, which was defined as an illness in a child who was brought to a study facility with a temperature of 37.5°C or more and *P. falciparum* asexual parasitemia (>5000 parasites per cubic millimeter) or a case of malaria meeting the primary case definition of severe malaria.<sup>12</sup> Different parasite thresholds were used for secondary case definitions (Tables 1 and 2, and Table 2 in the Supplementary Appendix). Participants who were hospitalized were evaluated for severe malaria on the basis of a protocol-defined algorithm (Table 3 in the Supplementary Appendix).<sup>12</sup>

#### SAFETY SURVEILLANCE

Data regarding serious adverse events were collected throughout the trial by passive surveillance. Seizures that occurred within 7 days after vaccination were analyzed according to Brighton Collaboration guidelines.<sup>17</sup> Verbal autopsies were conducted on deaths that occurred outside study facilities.<sup>18</sup> Information was collected on all unsolicited reports of adverse events that occurred within 30 days after vaccination and on reactivity within 7 days after vaccination among the first 200 children in the older age category at each study center (Table 4 in the Supplementary Appendix).

#### IMMUNOGENICITY

Anti-circumsporozoite antibody titers were measured by means of enzyme-linked immunosorbent assay<sup>19</sup> in the first 200 children in the older age category at each study center at enrollment and 1 month after the administration of the third dose of a study vaccine. The threshold for a positive titer was 0.5 EU per milliliter.

#### LABORATORY AND RADIOLOGIC PROCEDURES

Laboratory and radiologic procedures are described in the Supplementary Appendix and have been reported previously.<sup>13</sup>

#### STUDY OVERSIGHT

The trial was sponsored by GlaxoSmithKline Biologicals (GSK), the vaccine developer and manu-

facturer, and funded by both GSK and the Program for Appropriate Technology in Health (PATH) Malaria Vaccine Initiative, which received a grant from the Bill and Melinda Gates Foundation. All study centers received study grants from the Malaria Vaccine Initiative, which also provided funding for authors' travel and accommodations related to this trial. All the authors reviewed all manuscript drafts, approved the final version of the manuscript, and made the decision to submit it for publication. The Clinical Trials Partnership Committee and Writing Group vouch for the completeness and accuracy of the data presented and for the fidelity of this report to the trial protocol.

#### STATISTICAL ANALYSIS

Statistical methods have been described previously.<sup>15</sup> We used Cox regression models (1 minus the hazard ratio) to evaluate vaccine efficacy against the first or only episode of clinical malaria in the older age category, using the study center as a stratification factor that allowed for differential baseline hazards. The proportionality of hazards was evaluated by Schoenfeld residuals and models, including time-varying covariates. Secondary analyses included evaluations of other clinical case definitions and multiple episodes of clinical malaria by means of negative binomial regression. Vaccine efficacy against severe malaria, which was defined as 1 minus the risk ratio, is expressed as a percent and is presented with Fisher's exact P values. All end points are presented with 95% confidence intervals except for the primary efficacy end point, which is presented with 97.5% confidence intervals.

Primary analyses of vaccine efficacy were based on the per-protocol population, which included all participants who received three doses of a study vaccine and who contributed to efficacy surveillance, starting 14 days after the administration of the third dose of a study vaccine. The intention-to-treat population included all participants who received at least one dose of a study vaccine.

Data were censored for the first 6000 children in the older age category 14 months after the administration of the first dose of vaccine or at the date of emigration, withdrawal of consent, or death. For analysis of the pooled age categories, the time at risk ended on May 31, 2011, when a booster dose was given, or at the date of withdrawal of consent or death. Estimates of vaccine efficacy according to study site and according to

**Table 1. Efficacy of the RTS,S/AS01 Vaccine against Clinical Malaria in Children Enrolled at 5 to 17 Months of Age.**

| Clinical Malaria  | RTS,S/AS01 Vaccine |           |            | Control Vaccine |           |            | Protective Efficacy Adjusted for Covariates* |         |
|---|--------------------|-----------|------------|-----------------|-----------|------------|--|---------|
|   | No. of Events      | Person-Yr | Event Rate | No. of Events   | Person-Yr | Event Rate | % (CI)†                                      | P Value |
| <b>Per-protocol population (12 mo after third dose of vaccine)</b>            |                    |           |            |                 |           |            |  |         |
| First or only episode   |                    |           |            |                 |           |            |  |         |
| >5000 parasites/mm <sup>3</sup> and temperature ≥37.5°C (coprimary end point) | 932                | 2144      | 0.435      | 752             | 903       | 0.833      | 55.8 (50.6–60.4)                             | <0.001  |
| >0 parasites/mm <sup>3</sup> and measured or reported fever                   | 1210               | 1963      | 0.616      | 883             | 798       | 1.107      | 54.1 (49.9–57.9)                             | <0.001  |
| >500 parasites/mm <sup>3</sup> and temperature ≥37.5°C                        | 1030               | 2088      | 0.493      | 789             | 874       | 0.903      | 53.9 (49.3–58.0)                             | <0.001  |
| >20,000 parasites/mm <sup>3</sup> and temperature ≥37.5°C                     | 838                | 2196      | 0.382      | 686             | 947       | 0.724      | 55.1 (50.3–59.5)                             | <0.001  |
| All episodes  |                    |           |            |                 |           |            |  |         |
| >5000 parasites/mm <sup>3</sup> and temperature ≥37.5°C                       | 1834               | 2495      | 0.735      | 1854            | 1263      | 1.468      | 55.1 (50.5–59.3)                             | <0.001  |
| <b>Intention-to-treat population (14 mo after first dose of vaccine)</b>      |                    |           |            |                 |           |            |  |         |
| First or only episode   |                    |           |            |                 |           |            |  |         |
| >5000 parasites/mm <sup>3</sup> and temperature ≥37.5°C                       | 1155               | 3633      | 0.318      | 879             | 1588      | 0.554      | 50.4 (45.8–54.6)                             | <0.001  |
| All episodes  |                    |           |            |                 |           |            |  |         |
| >5000 parasites/mm <sup>3</sup> and temperature ≥37.5°C                       | 2343               | 4243      | 0.552      | 2289            | 2110      | 1.085      | 53.9 (49.6–57.8)                             | <0.001  |

\* In the adjusted analyses, data were stratified according to study site with adjustment for age at the time of administration of the first dose of vaccine and the distance to the nearest outpatient health facility.

† All end points are presented with 95% confidence intervals except for the primary efficacy end point, which is presented with 97.5% confidence intervals. The primary efficacy end point is defined as vaccine efficacy against a first or only episode of clinical malaria, according to the primary case definition: an illness in a child brought to a study facility with a temperature of 37.5°C or more and *Plasmodium falciparum* asexual parasitemia (>5000 parasites per cubic millimeter) or a case of malaria meeting the primary case definition of severe malaria.

**Table 2. Efficacy of the RTS,S/AS01 Vaccine against Severe Malaria in Children Enrolled at 5 to 17 Months of Age and in Pooled Age Categories.\***

| Severe Malaria   | RTS,S/AS01 Vaccine |              |                    |                 | Control Vaccine |                    |                  |        | Protective Efficacy<br>P Value |
|--|--------------------|--------------|--------------------|-----------------|-----------------|--------------------|------------------|--------|--------------------------------|
|  | No. of Children    | No. Affected | Affected Rate<br>% | No. of Children | No. Affected    | Affected Rate<br>% | % (95% CI)       |        |                                |
| <b>Older age category (5–17 mo)</b>  |                    |              |                    |                 |                 |                    |                  |        |                                |
| Per-protocol analysis (12 mo after third dose of vaccine)                            |                    |              |                    |                 |                 |                    |                  |        |                                |
| Primary case definition  | 2830               | 57           | 2.0                | 1466            | 56              | 3.8                | 47.3 (22.4–64.2) | <0.001 |                                |
| Secondary case definition  | 2830               | 74           | 2.6                | 1466            | 72              | 4.9                | 46.8 (25.3–62.0) | <0.001 |                                |
| Intention-to-treat analysis (14 mo after first dose of vaccine)                      |                    |              |                    |                 |                 |                    |                  |        |                                |
| Primary case definition  | 3997               | 81           | 2.0                | 2003            | 74              | 3.7                | 45.1 (23.8–60.5) | <0.001 |                                |
| Secondary case definition  | 3997               | 102          | 2.6                | 2003            | 92              | 4.6                | 44.4 (25.5–58.5) | <0.001 |                                |
| <b>Pooled age categories (6 wk–17 mo)</b>  |                    |              |                    |                 |                 |                    |                  |        |                                |
| Per-protocol analysis (mean of 11 mo after third dose of vaccine, up to 22 mo)       |                    |              |                    |                 |                 |                    |                  |        |                                |
| Primary case definition  | 8597               | 149          | 1.7                | 4364            | 116             | 2.7                | 34.8 (16.2–49.2) | <0.001 |                                |
| Secondary case definition  | 8597               | 177          | 2.1                | 4364            | 140             | 3.2                | 35.8 (19.3–48.9) | <0.001 |                                |
| Intention-to-treat analysis (mean of 14 mo after first dose of vaccine, up to 24 mo) |                    |              |                    |                 |                 |                    |                  |        |                                |
| Primary case definition  | 10,307             | 198          | 1.9                | 5153            | 144             | 2.8                | 31.3 (14.2–44.8) | <0.001 |                                |
| Secondary case definition  | 10,307             | 233          | 2.3                | 5153            | 173             | 3.4                | 32.7 (17.5–44.9) | <0.001 |                                |

\* The primary case definition of severe malaria is *Plasmodium falciparum* asexual parasitemia (>5000 parasites per cubic millimeter) with one or more markers of disease severity and without a diagnosis of a coexisting illness. The secondary case definition of severe malaria is *P. falciparum* asexual parasitemia with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of 2 or less (on a scale of 0 to 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycemia, acidosis, elevated lactate level, or hemoglobin level of less than 5 g per deciliter. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis on analysis of cerebrospinal fluid, bacteremia, or gastroenteritis with severe dehydration.

the incidence of clinical or severe malaria in the younger age category are not yet available, owing to insufficient statistical power and follow-up time, but will be analyzed at a later time.

Adverse events were coded from clinician-assigned diagnoses for serious adverse events using the preferred terms of the *Medical Dictionary for Regulatory Activities*.<sup>20</sup> All adverse events are presented according to age category in the intention-to-treat population. Diagnoses for serious adverse events are based on all available clinical evidence and are not bound by stringent laboratory or diagnostic criteria. Therefore, they should not be used to infer vaccine efficacy. A formal analysis of vaccine efficacy against coexisting illnesses is planned for the end of the study.

To preserve blinding, analyses were conducted by external statisticians using SAS software, version 9.2 (SAS Institute).

## RESULTS

### STUDY POPULATION

The first 6000 children 5 to 17 months of age at enrollment were included in the primary analysis of vaccine efficacy during the 12 months after the administration of the third dose of vaccine. Of these children, 4296 (71.6%) were included in the per-protocol analysis (Fig. 1). (The number of children who participated according to study center is shown in Table 5 in the Supplementary Appendix.) A survey undertaken 14 months after the administration of the first dose of a study vaccine showed that approximately 75% of children in the two study groups were using bed nets (Table 6 in the Supplementary Appendix). At one center, enrollment was delayed, and no children from that center were among the first 6000 enrolled. At another center, study vaccines were exposed to temperatures outside the recommended storage range, leading to the exclusion of 870 children from the per-protocol analysis. The first 200 participants from each center contributed to the analysis of reactogenicity and immunogenicity.

In total, 15,460 participants were enrolled, including 6537 infants 6 to 12 weeks of age and 8923 children 5 to 17 months of age at the time of the first vaccination (Fig. 2). The mean follow-up times were 9 months in the younger age category and 18 months in the older age category after the administration of the first dose of a study vaccine (Table 7 in the Supplementary Appendix). Baseline demographic characteristics were similar

in the two study groups (Table 8 in the Supplementary Appendix).

### VACCINE EFFICACY AGAINST CLINICAL AND SEVERE MALARIA IN THE OLDER AGE CATEGORY

During 12 months of follow-up in the first 6000 children in the older age category, the incidence of the first or only episode of clinical malaria meeting the primary case definition was 0.44 per person-year in the RTS,S/AS01 group and 0.83 per person-year in the control group, resulting in a vaccine efficacy of 55.8% (97.5% confidence interval [CI], 50.6 to 60.4) (Fig. 3). Evaluation of the proportionality of the hazard assumption showed that vaccine efficacy was not constant over time ( $P < 0.001$  by Schoenfeld residuals) (Table 9 in the Supplementary Appendix), with vaccine efficacy higher at the beginning than at the end of the follow-up period. Vaccine efficacy against all clinical malaria episodes was 55.1% (95% CI, 50.5 to 59.3), and estimates were consistent across all case definitions and in both adjusted and intention-to-treat analyses (Table 1).

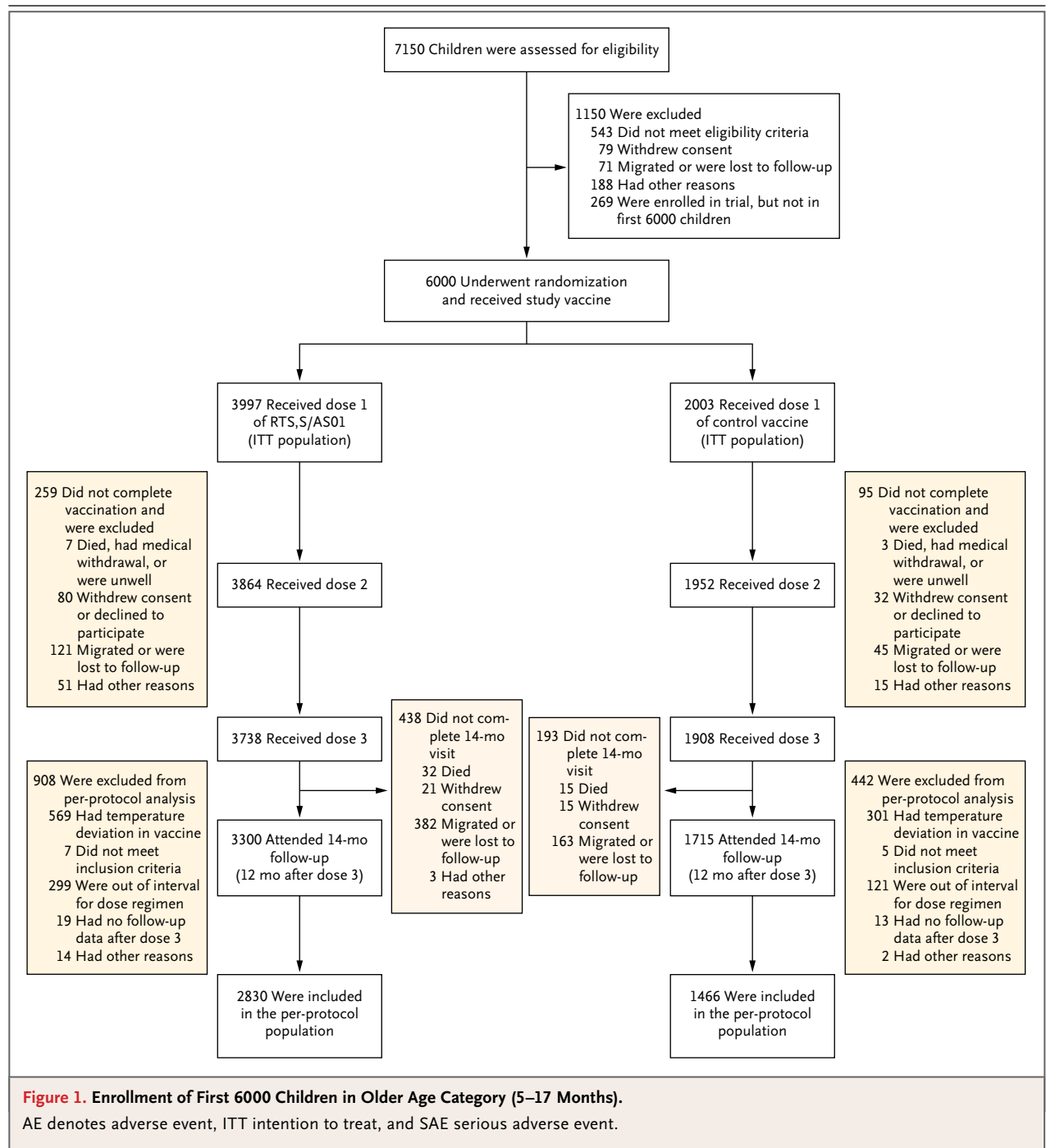
At least one episode of severe malaria that met the primary case definition occurred in 57 of 2830 children (2.0%) in the RTS,S/AS01 group and in 56 of 1466 children (3.8%) in the control group, for a vaccine efficacy of 47.3% (95% CI, 22.4 to 64.2) (Table 2).

### VACCINE EFFICACY AGAINST SEVERE MALARIA IN THE POOLED AGE CATEGORIES

Among children in the combined age categories, at least one episode of severe malaria that met the primary case definition occurred in 149 of 8597 children (1.7%) in the RTS,S/AS01 group and in 116 of 4364 children (2.7%) in the control group (Table 2). The average durations of follow-up were 16 months after the administration of the third dose of a study vaccine (range, 0 to 22 months) in the older age category and 7 months (range, 0 to 15 months) in the younger age category. Vaccine efficacy against severe malaria in the pooled age categories was 34.8% (95% CI, 16.2 to 49.2). Vaccine efficacy was similar for the secondary case definition and in the intention-to-treat population. (The clinical features of children with severe malaria are provided in Table 10 in the Supplementary Appendix.)

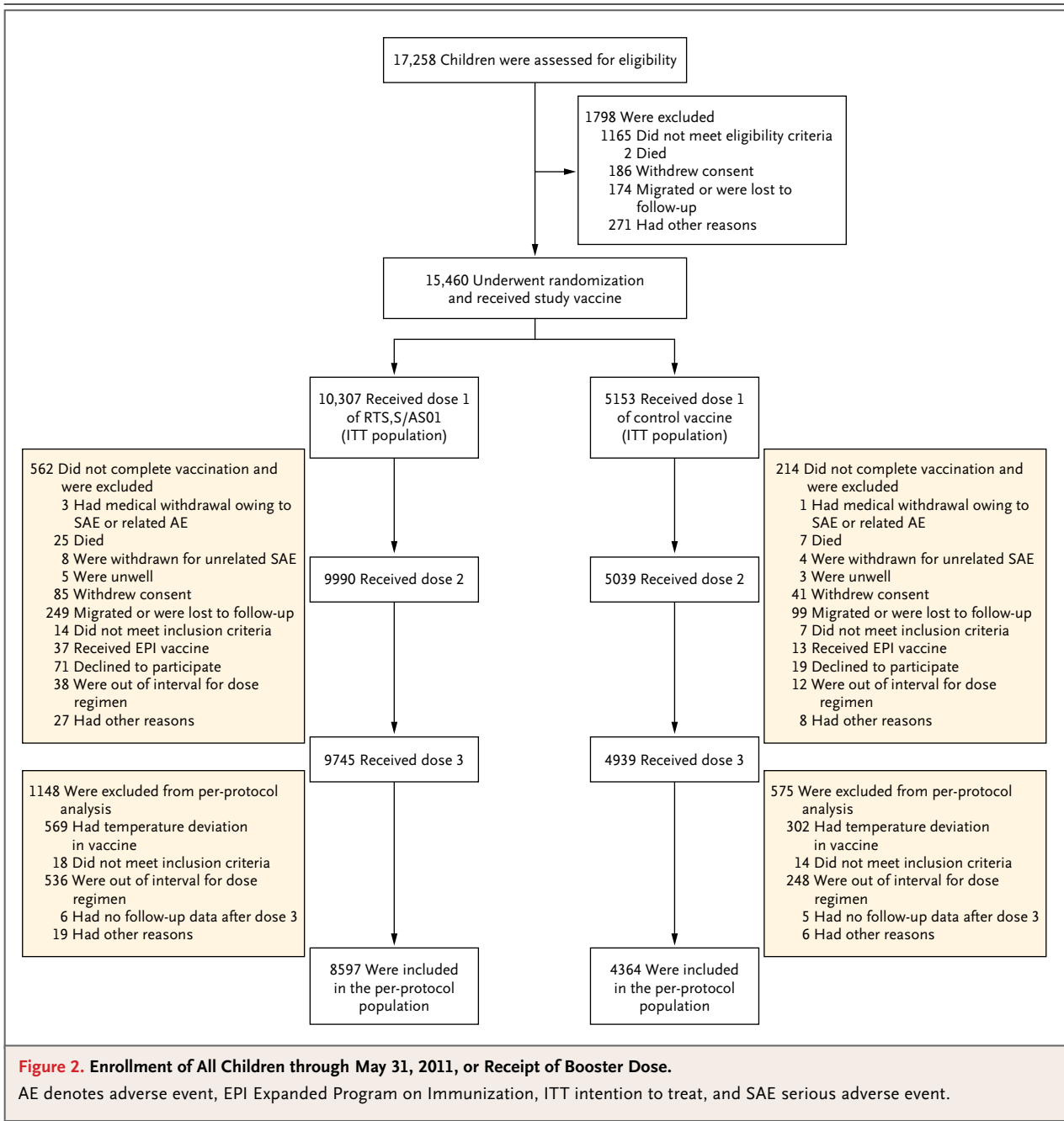
### SERIOUS ADVERSE EVENTS

In the older age category, serious adverse events were reported in 1048 of 5949 children (17.6%;



95% CI, 16.7 to 18.6) in the RTS,S/AS01 group and in 642 of 2974 children (21.6%; 95% CI, 20.1 to 23.1) in the control group (Table 3). In the younger age category, the corresponding rates were 569 of 4358 children (13.1%; 95% CI, 12.1 to 14.1) in the RTS,S/AS01 group and in 293 of 2179 children (13.4%; 95% CI, 12.0 to 15.0) in the control group (Table 3).

Similar proportions of children died in each study group. In the older age category, 56 of 5949 children (0.9%; 95% CI, 0.7 to 1.2) died in the RTS,S/AS01 group and 28 of 2974 children (0.9%; 95% CI, 0.6 to 1.4) in the control group; in the younger age category, 49 of 4358 children (1.1%; 95% CI, 0.8 to 1.5) died in the RTS,S/AS01 group and 18 of 2179 children (0.8%; 95% CI, 0.5 to 1.3)



in the control group. Of the 151 children who died, 78 (52%) died in the hospital after a thorough medical assessment was made; 9% of deaths occurred at a health facility before completion of a full medical assessment, and 39% occurred in the community. Causes of death were similar in the two groups (Table 11 in the Supplementary Appendix). Ten children died with a diagnosis of malaria, which was confirmed on blood smear in 7 children.

At least one serious adverse event that was considered to be related to a study vaccine occurred in 11 children in the older age category: 10 of 5949 children in the RTS,S/AS01 group reported 12 events (7 seizures, 3 episodes of pyrexia, 1 episode of myositis, and 1 injection-site reaction) and 1 of 2974 children in the control group reported 1 event (seizure). In the younger age category, serious adverse events that were considered to be re-



lated to a study vaccine occurred in 6 children: 3 of 4358 children in the RTS,S/AS01 group reported 3 events (1 injection-site reaction, 1 episode of pyrexia, and 1 episode of febrile convulsion), and 3 of 2179 children in the control group reported 3 events (2 episodes of pyrexia and 1 episode of anaphylaxis). All children who had seizures that were deemed to be related to a study vaccine recovered from the acute event; epilepsy subsequently developed in 1 child.

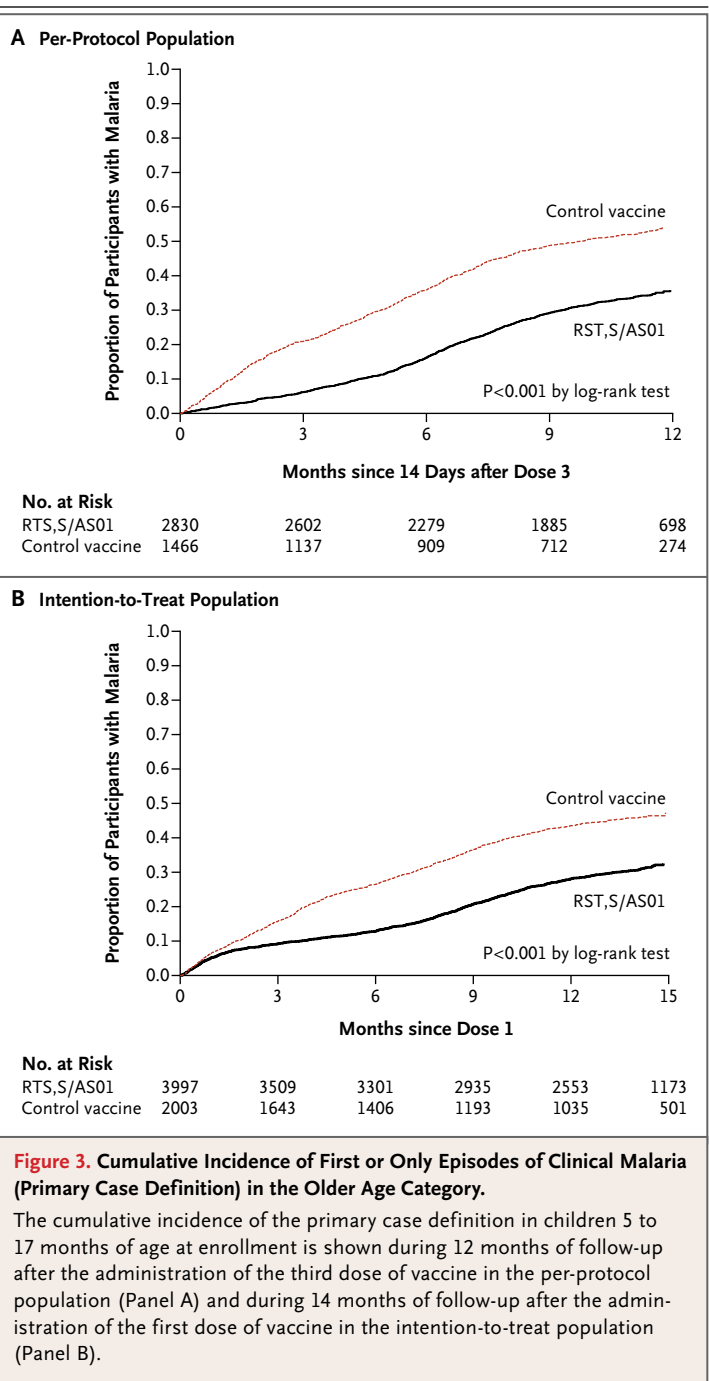
Meningitis was reported more frequently in the RTS,S/AS01 group than in the control group, with 11 of 5949 children versus 1 of 2974 children in the older age category and 8 of 4358 children versus 1 of 2179 children in the younger age category, for a relative risk of 5.5 (95% CI, 0.7 to 42.6) in the older age category and 4.0 (95% CI, 0.5, 32.0) in the younger age category. Laboratory diagnosis of meningitis, indicated by culture or elevated white-cell count in cerebrospinal fluid, was made in half these cases. There was no apparent temporal relationship to vaccination or clustering according to center.

#### SEIZURE WITHIN 7 DAYS AFTER VACCINATION

In the older age category, the incidence of generalized convulsive seizure within 7 days after vaccination (according to the Brighton Collaboration diagnostic certainty level of 1 to 3) was 1.04 per 1000 doses in the RTS,S/AS01 group (95% CI, 0.62 to 1.64) and 0.57 per 1000 doses in the control group receiving rabies vaccine (95% CI, 0.19 to 1.34), for a risk ratio of 1.8 (95% CI, 0.6 to 4.9). All seizures occurred in children with a history of fever; 23 occurred within 7 days after vaccination, and of those, 12 of 18 seizures occurred within 3 days after vaccination in the RTS,S/AS01 group and 2 of 5 seizures in the control group. In the younger age category, the incidence of generalized convulsive seizures within 7 days after vaccination was 0.16 per 1000 doses in the RTS,S/AS01 group (95% CI, 0.02 to 0.57) and 0.47 per 1000 doses in the control group receiving meningococcal vaccine (95% CI, 0.10 to 1.37), for a risk ratio of 0.3 (95% CI, 0.1 to 2.0).

#### ADVERSE EVENTS

Unsolicited reports of adverse events that occurred within 30 days after each vaccination were reported with similar frequency in the two study groups (Table 12 in the Supplementary Appendix). (The frequencies of solicited reports of



symptoms in the intention-to-treat population are shown in Table 13 and Figure 3 in the Supplementary Appendix.) The most frequently reported symptoms were pain and fever. Overall, RTS,S/AS01 vaccine was more reactogenic than was rabies vaccine, but grade 3 symptoms occurred infrequently.

**Table 3. Serious Adverse Events after the First Dose of a Study Vaccine in the Intention-to-Treat Population, According to Age Category.\***

| Serious Adverse Event   | 5–17 Mo                        |                  |                            |                  | 6–12 Wk                        |                  |                                   |                  |
|---|--------------------------------|------------------|----------------------------|------------------|--------------------------------|------------------|-----------------------------------|------------------|
|   | RTS,S/AS01 Vaccine<br>(N=5949) |                  | Rabies Vaccine<br>(N=2974) |                  | RTS,S/AS01 Vaccine<br>(N=4358) |                  | Meningococcal Vaccine<br>(N=2179) |                  |
|   | no. of<br>children             | %<br>(95% CI)    | no. of<br>children         | %<br>(95% CI)    | no. of<br>children             | %<br>(95% CI)    | no. of<br>children                | %<br>(95% CI)    |
| <b>All children</b>   |                                |                  |                            |                  |                                |                  |                                   |                  |
| At least one serious adverse event                                  | 1048                           | 17.6 (16.7–18.6) | 642                        | 21.6 (20.1–23.1) | 569                            | 13.1 (12.1–14.1) | 293                               | 13.4 (12.0–15.0) |
| At least one serious adverse event excluding malaria                | 990                            | 16.6 (15.7–17.6) | 600                        | 20.2 (18.7–21.7) | 554                            | 12.7 (11.7–13.7) | 286                               | 13.1 (11.7–14.6) |
| At least one fatal serious adverse event†                           | 56                             | 0.9 (0.7–1.2)    | 28                         | 0.9 (0.6–1.4)    | 49                             | 1.1 (0.8–1.5)    | 18                                | 0.8 (0.5–1.3)    |
| At least one serious adverse event related to vaccine               | 10                             | 0.2 (0.1–0.3)    | 1                          | 0.0 (0.0–0.2)    | 3                              | 0.1 (0.0–0.2)    | 3                                 | 0.1 (0.0–0.4)    |
| At least one serious adverse event within 30 days after vaccination | 310                            | 5.2 (4.7–5.8)    | 181                        | 6.1 (5.3–7.0)    | 191                            | 4.4 (3.8–5.0)    | 96                                | 4.4 (3.6–5.4)    |
| <b>Incidence in ≥0.5% of children‡</b>                              |                                |                  |                            |                  |                                |                  |                                   |                  |
| Anemia  | 182                            | 3.1 (2.6–3.5)    | 149                        | 5.0 (4.3–5.9)    | 58                             | 1.3 (1.0–1.7)    | 39                                | 1.8 (1.3–2.4)    |
| Bronchiolitis   | 35                             | 0.6 (0.4–0.8)    | 18                         | 0.6 (0.4–1.0)    | 26                             | 0.6 (0.4–0.9)    | 17                                | 0.8 (0.5–1.2)    |
| Bronchitis  | 24                             | 0.4 (0.3–0.6)    | 17                         | 0.6 (0.3–0.9)    | NA                             | NA               | NA                                | NA               |
| Bronchopneumonia  | 54                             | 0.9 (0.7–1.2)    | 37                         | 1.2 (0.9–1.7)    | 28                             | 0.6 (0.4–0.9)    | 16                                | 0.7 (0.4–1.2)    |
| Gastroenteritis   | 263                            | 4.4 (3.9–5.0)    | 160                        | 5.4 (4.6–6.3)    | 194                            | 4.5 (3.9–5.1)    | 93                                | 4.3 (3.5–5.2)    |
| HIV infection   | 37                             | 0.6 (0.4–0.9)    | 19                         | 0.6 (0.4–1.0)    | 23                             | 0.5 (0.3–0.8)    | 6                                 | 0.3 (0.1–0.6)    |
| Malaria   | 383                            | 6.4 (5.8–7.1)    | 297                        | 10.0 (8.9–11.1)  | 116                            | 2.7 (2.2–3.2)    | 74                                | 3.4 (2.7–4.2)    |
| Otitis media  | 25                             | 0.4 (0.3–0.6)    | 17                         | 0.6 (0.3–0.9)    | NA                             | NA               | NA                                | NA               |
| Pneumonia   | 337                            | 5.7 (5.1–6.3)    | 176                        | 5.9 (5.1–6.8)    | 224                            | 5.1 (4.5–5.8)    | 102                               | 4.7 (3.8–5.7)    |
| Salmonella sepsis   | 41                             | 0.7 (0.5–0.9)    | 23                         | 0.8 (0.5–1.2)    | 16                             | 0.4 (0.2–0.6)    | 10                                | 0.5 (0.2–0.8)    |
| Sepsis  | 48                             | 0.8 (0.6–1.1)    | 35                         | 1.2 (0.8–1.6)    | 23                             | 0.5 (0.3–0.8)    | 8                                 | 0.4 (0.2–0.7)    |
| Upper respiratory tract infection                                   | 55                             | 0.9 (0.7–1.2)    | 37                         | 1.2 (0.9–1.7)    | 21                             | 0.5 (0.3–0.7)    | 11                                | 0.5 (0.3–0.9)    |
| Urinary tract infection   | 36                             | 0.6 (0.4–0.8)    | 21                         | 0.7 (0.4–1.1)    | NA                             | NA               | NA                                | NA               |
| Hypoglycemia  | 12                             | 0.2 (0.1–0.4)    | 18                         | 0.6 (0.4–1.0)    | NA                             | NA               | NA                                | NA               |
| Kwashiorkor   | 12                             | 0.2 (0.1–0.4)    | 16                         | 0.5 (0.3–0.9)    | NA                             | NA               | NA                                | NA               |
| Malnutrition  | 49                             | 0.8 (0.6–1.1)    | 19                         | 0.6 (0.4–1.0)    | NA                             | NA               | NA                                | NA               |
| Convulsion  | 55                             | 0.9 (0.7–1.2)    | 37                         | 1.2 (0.9–1.7)    | 24                             | 0.6 (0.4–0.8)    | 15                                | 0.7 (0.4–1.1)    |
| Febrile convulsion  | 211                            | 3.5 (3.1–4.0)    | 106                        | 3.6 (2.9–4.3)    | 48                             | 1.1 (0.8–1.5)    | 25                                | 1.1 (0.7–1.7)    |

\* The average follow-up was 18 months (up to 24 months) in the older age category (5 to 17 months) and 9 months (up to 17 months) in the younger age category (6 to 12 weeks). HIV denotes human immunodeficiency virus, and NA not applicable (because the incidence was less than 0.5%).

† More than one fatal serious adverse event could be attributed to a single child if there was more than one underlying cause of death (e.g., meningitis and sepsis).

‡ Events are listed according to the preferred terms in the *Medical Dictionary for Regulatory Activities*.

### IMMUNOGENICITY

The geometric mean titer of anti-circumsporozoite antibody at enrollment was low in the two study groups and remained low in the control

group (Table 14 and Fig. 4 in the Supplementary Appendix). One month after the administration of the third dose of a study vaccine, 99.9% of children in the RTS,S/AS01 group were positive

for anti-circumsporozoite antibodies, with a geometric mean titer of 621 EU per milliliter (95% CI, 592 to 652).

## DISCUSSION

The RTS,S/AS01 candidate malaria vaccine reduced clinical episodes of malaria and severe malaria by approximately half during the 12 months after vaccination in children 5 to 17 months of age. These findings are robust, with narrow confidence limits and similar results in the per-protocol and intention-to-treat populations and in the adjusted and unadjusted analyses. These efficacy results are consistent with those from phase 2 trials.<sup>5,6</sup>

The level of protection provided by the RTS,S/AS01 vaccine to the 6000 children 5 to 17 months of age was lower at the end of the 12-month surveillance period than shortly after vaccination. The body of data from phase 2 studies of RTS,S/AS01 suggests a persistence in vaccine efficacy. However, varying study designs and statistical methods have led to different interpretations of the dynamics of efficacy over time, with some studies suggesting persistent protection and others suggesting waning protection.<sup>7,21-25</sup> Decreasing protection over time could reflect waning immunity, acquisition of natural immunity in the control group, or heterogeneity of exposure.<sup>26</sup> Further follow-up and evaluation of the effect of a booster dose will provide a better understanding of the relative contribution of these factors.

Vaccine efficacy against severe malaria in the pooled age categories showed a lower estimate than was seen in the first 6000 children in the older age category who were followed for 12 months (Table 2). Although the confidence limits on these estimates overlap, we have considered reasons that might explain the differing estimates. Immunity against severe malaria may have waned beyond the 12-month follow-up period in the older age category. Alternatively, vaccine efficacy may have been lower in the younger age category for a number of possible reasons. However, the latter supposition is not supported by phase 2 data, which have shown similar efficacy against clinical malaria in younger and older children.<sup>6,7</sup> The questions raised by these different efficacy estimates should be answered by continuation of follow-up of children in the trial.

In 1 year, we will report vaccine efficacy against clinical and severe malaria in the younger age category, and at study end, we will report the duration of efficacy in each age category.

Despite the relatively high vaccine efficacy against severe malaria, we did not observe a reduction in the rate of death from malaria or from any cause in the RTS,S/AS01 group. Malaria-specific mortality was very low in the trial, representing only 10 of the 151 reported deaths (6.6%). Seven of these deaths were confirmed to have been caused by malaria on blood smears. Since the rate of death from malaria was low, we would not expect to be able to detect a reduction in the rate of death from any cause unless RTS,S/AS01 also provided protection against coexisting illnesses and the associated deaths. We attribute the very low malaria-specific mortality in this trial to the high level of access to high-quality care provided at study facilities. The low malaria-specific mortality is unlikely to be due to misclassification of moderate malaria as severe malaria. Children who were classified as having severe malaria had objective clinical markers of severe disease, and nearly half had two or more markers. Approximately 3% of children with clinical malaria and 35% of those who were hospitalized with malaria were classified as having severe malaria, consistent with reported estimates.<sup>27</sup> At the end of the study, a formal analysis of vaccine efficacy against death will be conducted.

In the older age category, RTS,S/AS01 was more reactogenic than rabies vaccine in terms both of systemic and local effects. However, few reactions were severe. Generalized convulsive seizures in the 7 days after RTS,S/AS01 vaccination occurred at a rate of approximately 1 per 1000 vaccine doses, a higher rate than that seen with the comparator rabies vaccine. All cases were associated with a history of fever, and all children recovered from the acute event. The increase in the rate of meningitis in the RTS,S/AS01 group is being monitored. Additional data from ongoing follow-up will clarify the relationship with the study intervention. However, the lack of a temporal association with vaccination and low biologic plausibility suggest that these events are unlikely to be related to the vaccine.

The trial was conducted with rigorous standardization among centers and provided a high standard of clinical care.<sup>12</sup> Participants from one

center were excluded from the per-protocol analyses because vaccines at that center were exposed to temperatures outside the recommended range. However, participants at this center were included in the intention-to-treat analyses, with similar results to those in the per-protocol analyses.

Our initial results show that the RTS,S/AS01 vaccine reduced malaria by half in children 5 to 17 months of age during the 12 months after vaccination and that the vaccine has the poten-

tial to have an important effect on the burden of malaria in young African children. Additional information on vaccine efficacy among young infants and the duration of protection will be critical to determining how this vaccine could be used most effectively to control malaria.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

#### APPENDIX

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