Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial

RTS,S Clinical Trials Partnership*

Summary

Background The efficacy and safety of the RTS,S/AS01 candidate malaria vaccine during 18 months of follow-up have been published previously. Herein, we report the final results from the same trial, including the efficacy of a booster dose.

Methods From March 27, 2009, until Jan 31, 2011, children (age 5–17 months) and young infants (age 6–12 weeks) were enrolled at 11 centres in seven countries in sub-Saharan Africa. Participants were randomly assigned (1:1:1) at first vaccination by block randomisation with minimisation by centre to receive three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20 (R3R group); three doses of RTS,S/AS01 and a dose of comparator vaccine at month 20 (R3C group); or a comparator vaccine at months 0, 1, 2, and 20 (C3C [control group]). Participants were followed up until Jan 31, 2014. Cases of clinical and severe malaria were captured through passive case detection. Serious adverse events (SAEs) were recorded. Analyses were by modified intention to treat and per protocol. The coprimary endpoints were the occurrence of malaria over 12 months after dose 3 in each age category. In this final analysis, we present data for the efficacy of the booster on the occurrence of malaria. Vaccine efficacy (VE) against clinical malaria was analysed by negative binomial regression and against severe malaria by relative risk reduction. This trial is registered with ClinicalTrials.gov, number NCT00866619.*

Findings 8922 children and 6537 young infants were included in the modified intention-to-treat analyses. Children were followed up for a median of 48 months (IQR 39–50) and young infants for 38 months (34–41) after dose 1. From month 0 until study end, compared with 9585 episodes of clinical malaria that met the primary case definition in children in the C3C group, 6616 episodes occurred in the R3R group (VE 36·3%, 95% CI 31·8–40·5) and 7396 occurred in the R3C group (28·3%, 23·3–32·9); compared with 171 children who experienced at least one episode of severe malaria in the C3C group, 116 children experienced at least one episode of severe malaria in the R3R group (32·2%, 13·7 to 46·9) and 169 in the R3C group (1·1%, –23·0 to 20·5). In young infants, compared with 6170 episodes of clinical malaria that met the primary case definition in the C3C group, 4993 episodes occurred in the R3R group (VE 25·9%, 95% CI 19·9–31·5) and 5444 occurred in the R3C group (18·3%, 11·7–24·4); and compared with 116 infants who experienced at least one episode of severe malaria in the C3C group, 96 infants experienced at least one episode of severe malaria in the R3R group (28·3%, 17·3–39·4) and 104 in the R3C group (13·7%, 8·3–21·7). In children, 1774 cases of clinical malaria were averted per 1000 children (95% CI 1387–2186) in the R3R group and 1363 per 1000 children (995–1797) in the R3C group. The numbers of cases averted per 1000 young infants were 983 (95% CI 592–1337) in the R3R group and 558 (158–926) in the R3C group. The frequency of SAEs overall was balanced between groups. However, meningitis was reported as a SAE in 22 children: 11 in the R3R group, ten in the R3C group, and one in the C3C group. The incidence of generalised convulsive seizures within 7 days of RTS,S/AS01 booster was 2·2 per 1000 doses in young infants and 2·5 per 1000 doses in children.

Interpretation RTS,S/AS01 prevented a substantial number of cases of clinical malaria over a 3–4 year period in young infants and children when administered with or without a booster dose. Efficacy was enhanced by the administration of a booster dose in both age categories. Thus, the vaccine has the potential to make a substantial contribution to malaria control when used in combination with other effective control measures, especially in areas of high transmission.

Funding GlaxoSmithKline Biologicals SA and the PATH Malaria Vaccine Initiative.

Introduction Substantial progress has been made in malaria control during the past decade, but the burden of malaria in Africa remains high.1 A malaria vaccine could be an important complement to existing control measures and could help reduce morbidity and mortality in children.

RTS,S/AS01 is a recombinant protein candidate malaria vaccine that targets the circumsporozoite protein of Plasmodium falciparum, expressed by the malaria parasite at the pre-erythrocytic stage, in which part of the circumsporozoite sequence is coexpressed with fused and free hepatitis B surface antigen2 and formulated with the AS01 adjuvant. Previous studies have established the ability of RTS,S/AS01 to provide protective immunity.3 4

We undertook a phase 3, double-blind (observer-blind), individually randomised, controlled trial to
assess the efficacy and safety of RTS,S/AS01. Study results up to 18 months of follow-up have been reported previously. The coprimary endpoints of efficacy to clinical malaria over the first 12 months after dose 3 were 55.8% (97.5% CI 50.6–60.4) in children aged 5–17 months and 31.3% (23.6–38.3) in infants aged 6–12 weeks. Protection against clinical and severe malaria was noted in both children and young infants during the first 12 months after vaccination, but protection waned over time in both age categories. Herein, we report the efficacy, immunogenicity, and safety of RTS,S/AS01 and the number of cases averted by the use of the vaccine in children and young infants followed up to the end of the trial, including findings in those who received a booster dose of vaccine.

Methods
Study design and participants
We undertook this phase 3, double-blind, observer-blind, individually randomised controlled trial between March 27, 2009, and Jan 31, 2014, at 11 centres in seven countries in sub-Saharan Africa that are situated in areas with different intensities of malaria transmission (appendix p 18). Trial methods have been reported previously, and are described in the appendix (pp4–13). We initially designed this trial to assess vaccine efficacy (VE), safety, and immunogenicity during 32 months of follow-up, but the protocol was amended before month 32, on Dec 1, 2010, to extend the follow-up period to Dec 31, 2013 (median follow-up 48 months for children and 38 months for young infants). Parents or legally authorised representatives of all participants provided written or thumb printed and witnessed informed consent at enrolment to the primary study and to the extension. Access to an insecticide-treated bednet was optimised for all screened children. Net use and condition were assessed during protocol-specified home visits done at month 13, month 31, and 1 month before study end.

The trial protocol was approved by the ethical review board at each study centre and partner institution and by the national regulatory authority in each country (appendix p 44–45) and the trial was undertaken in accordance with the provisions of the Good Clinical Practice Guidelines.

Randomisation and masking
From March 27, 2009, until Jan 31, 2011, infants aged 6–12 weeks and children aged 5–17 months were recruited and randomly assigned (1:1:1) by block randomisation with different intensities of malaria transmission, and the numbers of cases averted by the use of the vaccine in children and young infants followed up to the end of the trial, including findings in those who received a booster dose of vaccine.

Added value of this study
This study provided additional information on the safety and long-term efficacy of RTS,S/AS01 in a large population of children across different malaria transmission settings. Additionally, the study showed how booster vaccination extended the period of protection provided by the vaccine.

Implications of all available evidence
The RTS,S malaria vaccine candidate has consistently shown protection against clinical malaria episodes in different age groups across different transmission settings. Vaccine efficacy has been shown with or without concurrent Expanded Program on Immunization vaccination. The vaccine has consistently shown a good safety profile, although a meningitis safety signal reported among older children will need further follow-up. The results of the present study show the potential public health benefit of the RTS,S vaccine as an additional means for malaria control whilst the next generation of malaria vaccines are being developed.
10,267 children assessed for eligibility*

8922 children randomly assigned†

2976 assigned to RTS,S/AS01 with booster and received dose 1 (modified ITT population)‡

2806 received doses 1, 2, and 3

362 did not receive booster dose

31 withdrew consent

2 medical withdrawal

220 migrated or were lost to follow-up

45 refused

2 unwell

23 other

2444 received dose 4 (booster)

613 did not attend visit 34

52 died

364 migrated or were lost to follow-up

108 withdrew consent

82 refused

7 other

2362 attended visit 34 (32 months after dose 3)

706 not enrolled in extension phase

1 inclusion criteria not met

52 died

390 migrated or were lost to follow-up

261 withdrew consent or refused

2 other

2270 enrolled in extension phase

206 did not attend visit 38

9 died

13 withdrew consent

22 refused

135 migrated or were lost to follow-up

27 other

2064 attended visit 38 (end of extension phase)

530 excluded from per-protocol population

296 temperature deviation

11 did not meet inclusion criteria

197 out of interval of doses

17 no follow-up data after dose 3

11 other

2276 included in per-protocol population

1345 failed screening

835 did not meet eligibility criteria

116 withdrew consent

112 migrated or were lost to follow-up

302 other

2972 assigned to RTS,S/AS01 without booster and received dose 1 (modified ITT population)‡

2793 received doses 1, 2, and 3

179 did not complete primary vaccination

25 withdrew consent

2 medical withdrawal

81 migrated or were lost to follow-up

31 refused

2 unwell

35 other

2974 assigned to control vaccine and received dose 1 (modified ITT population)‡

2848 received doses 1, 2, and 3

2618 received dose 4 (control vaccine)

362 did not receive booster dose

31 withdrew consent

4 medical withdrawal

220 migrated or were lost to follow-up

45 refused

2 unwell

23 other

2472 attended visit 34 (32 months after dose 3)

530 did not attend visit 34

41 died

348 migrated or were lost to follow-up

108 withdrew consent

84 refused

8 other

2276 included in per-protocol population

2064 attended visit 38 (end of extension phase)

530 excluded from per-protocol population

296 temperature deviation

11 did not meet inclusion criteria

197 out of interval of doses

17 no follow-up data after dose 3

11 other

2276 included in per-protocol population

29/4 assigned to control vaccine and received dose 1 (modified ITT population)‡

2848 received doses 1, 2, and 3

2468 received dose 4 (control vaccine)

2392 attended visit 34 (32 months after dose 3)

590 did not attend visit 34

41 died

348 migrated or were lost to follow-up

108 withdrew consent

84 refused

8 other

2329 enrolled in extension phase

2085 attended visit 38 (end of extension phase)

512 excluded from per-protocol population

304 temperature deviation

10 did not meet inclusion criteria

171 out of interval of doses

20 no follow-up data after dose 3

7 other

2306 included in per-protocol population

2038 attended visit 38 (end of extension phase)
7200 infants assessed for eligibility*

6537 infants randomly assigned

2180 assigned to RTS,S/AS01 with booster and received dose 1 (modified ITT population)†

2072 received doses 1, 2, and 3

108 did not complete primary vaccination
  15 withdrew consent
  7 died
  3 medical withdrawal
  43 migrated or were lost to follow-up
  9 refused
  1 unwell
  30 other

248 did not receive booster dose
  48 withdrew consent
  28 died
  3 medical withdrawal
  144 migrated or were lost to follow-up
  28 refused
  1 unwell
  6 other

1824 received dose 4 (booster)

454 did not attend visit 34
  49 died
  276 migrated or were lost to follow-up
  75 withdrew consent
  46 refused
  8 other

1726 attended visit 34 (32 months after dose 3)

1679 enrolled in extension phase

124 did not attend visit 38
  3 died
  4 withdrew consent
  11 refused
  106 migrated or were lost to follow-up

1555 attended visit 38 (end of extension phase)

1985 included in per-protocol population

663 failed screening
  419 did not meet eligibility criteria
    3 died
    99 withdrew consent
    70 migrated or were lost to follow-up
    72 other

106 did not complete primary vaccination
  8 withdrew consent
  11 died
  4 medical withdrawal
  41 migrated or were lost to follow-up
  17 refused
  25 other

2179 assigned to RTS,S/AS01 without booster and received dose 1 (modified ITT population)†

2072 received doses 1, 2, and 3

106 did not complete primary vaccination
  8 withdrew consent
  11 died
  4 medical withdrawal
  41 migrated or were lost to follow-up
  17 refused
  25 other

235 did not receive booster dose
  21 withdrew consent
  27 died
  1 medical withdrawal
  152 migrated or were lost to follow-up
  23 refused
  3 unwell
  3 other

1837 received dose 4 (control vaccine)

467 did not attend visit 34
  51 died
  281 migrated or were lost to follow-up
  65 withdrew consent
  37 refused
  13 other

1731 attended visit 34 (32 months after dose 3)

496 not enrolled in extension phase
  17 inclusion criteria not met
  51 died
  286 migrated or were lost to follow-up
  136 withdrew consent or refused
  6 other

1682 enrolled in extension phase

149 did not attend visit 38
  3 died
  2 withdrew consent
  15 refused
  125 migrated or were lost to follow-up
  1 serious adverse event
  3 other

1553 attended visit 38 (end of extension phase)

67 excluded from per-protocol population
  4 did not meet inclusion criteria
  45 out of interval of doses
  9 no follow-up data after dose 3
  9 other

2005 included in per-protocol population

89 did not complete primary vaccination
  11 withdrew consent
  4 died
  4 medical withdrawal
  39 migrated or were lost to follow-up
  8 refused
  1 unwell
  22 other

1985 included in per-protocol population

2007 excluded from per-protocol population
  5 did not meet inclusion criteria
  64 out of interval of doses
  3 no follow-up data after dose 3
  11 other

2090 received doses 1, 2, and 3

263 did not receive booster dose
  11 withdrew consent
  26 died
  1 medical withdrawal
  185 migrated or were lost to follow-up
  31 refused
  1 unwell
  8 other

1827 received dose 4 (control vaccine)

454 did not attend visit 34
  41 died
  304 migrated or were lost to follow-up
  54 withdrew consent
  50 refused
  5 other

1727 attended visit 34 (32 months after dose 3)

500 not enrolled in extension phase
  17 inclusion criteria not met
  41 died
  294 migrated or were lost to follow-up
  1 serious adverse event
  143 withdrew consent or refused
  4 other

1679 enrolled in extension phase

130 did not attend visit 38
  1 died
  1 withdrew consent
  13 refused
  114 migrated or were lost to follow-up
  1 serious adverse event

1549 attended visit 38 (end of extension phase)

83 excluded from per-protocol population
  5 did not meet inclusion criteria
  64 out of interval of doses
  3 no follow-up data after dose 3
  11 other

1500 included in per-protocol population

2178 assigned to RTS,S/AS01 without booster and received dose 1 (modified ITT population)†
young infants (C3C [control group]; appendix p 19). Young infants received the study vaccine at the same time as the Expanded Program on Immunization vaccines.

Procedures
Participants did not receive malaria treatment before vaccination. The treatment of malaria during the study was done in accordance with national guidelines. Malaria was detected by passive surveillance. The primary case definition for clinical malaria was an illness accompanied by an axillary temperature of at least 37.5°C and a concentration of less than 50 g/L. Anaemia was defined as a haemoglobin concentration (≥5.0 mmol/L), or haemoglobin acidosis (base excess ≤–10.0 mmol/L), raised lactate concentration (≥5.0 mmol/L), or haemoglobin concentration of less than 50 g/L. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

Fatal malaria was defined as a fatal case meeting the criteria for severe malaria according to a predefined algorithm (appendix p 46). The secondary case definition for clinical malaria was an illness accompanied by an axillary temperature of at least 37.5°C or reported fever within the past 24 h and P. falciparum asexual parasitaemia at a density of more than 0 parasites per mm³. The primary case definition for severe malaria was P. falciparum asexual parasitaemia at a density of more than 5000 parasites per mm³ with one or more markers of severe disease and without diagnosis of a coexisting illness (appendix p 47). The secondary case definition for severe malaria was P. falciparum asexual parasitaemia at a density of more than 5000 parasites per mm³ with one or more markers of severe disease, including cases in which a coexisting illness was present or could not be ruled out. Markers of severe disease were prostration, respiratory distress (defined as lower chest wall indrawing or abnormally deep breathing), a Blantyre coma score of 2 or less (on a scale of 0–5, with higher scores suggesting a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia (glucose less than 2.2 mmol/L), acidosis (base excess ≤–10.0 mmol/L), raised lactate concentration (≥5.0 mmol/L), or haemoglobin concentration of less than 50 g/L. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration.

The case histories of all participants with reported meningitis or other CNS infections or inflammation were reviewed by two independent experts and designated as confirmed meningitis, not meningitis, or undetermined (appendix pp 7–8). Anti-circumsporozoite antibodies were measured by ELISA in the first 200 participants in each age category at each study site at enrolment; 1 and 18 months after the third dose of vaccine; 1, 12, and 24 months after the booster dose; and at the last study visit. The threshold for a positive titre was 0.5 EU/mL. Other laboratory and radiological procedures are described in the appendix (pp 9–10).

Outcomes
Analysis of the original coprimary endpoints of the occurrence of malaria up to 12 months after dose 3 and other secondary outcomes have been published previously. In this final analysis, we present data for the efficacy of the booster on the occurrence of malaria and other disease endpoints that allow the assessment of the public health effect of the vaccine, such as VE against anaemia, blood transfusion, hospital admission, mortality, and other serious illnesses.

Statistical analysis
All results presented are for the modified intention-to-treat (ITT) population, unless otherwise recorded as per protocol. The modified ITT population included all participants who received at least one dose of vaccine. The per-protocol population included all participants who received three doses of vaccine according to protocol and contributed to the efficacy surveillance starting 14 days after the third dose. Efficacy against all episodes of malaria was analysed by negative binomial regression with follow-up time as offset, allowing for interdependence.
between episodes within the same participant. Overall estimates were adjusted for study site as a fixed effect, whereas site estimates were unadjusted for covariates. Inter-site variation was assessed by site interaction terms. VE over time was assessed by calculating VE during consecutive time periods, months 0–20, months 21–32, and month 33 to study end. The incremental efficacy of the RTS,S/AS01 booster dose was calculated for the time period after month 20, when the booster dose was administered, and was calculated as 1 minus the incident rate ratio between the R3R and R3C groups. VE against severe endpoints (i.e., severe malaria, malaria hospital admission, fatal malaria, all-cause hospital admission, all-cause mortality, incident severe anaemia, and blood transfusion) was estimated as a relative risk reduction with Fisher’s exact p values. The number of cases averted over

### Table 1: Efficacy against clinical malaria (primary case definition) of a primary schedule with or without a booster dose and incremental efficacy of the booster dose

<table>
<thead>
<tr>
<th>Age Category</th>
<th>C3C Group</th>
<th>R3C Group</th>
<th>R3R Group</th>
<th>Point Estimate of VE Unadjusted for Covariates</th>
<th>Incremental Efficacy Unadjusted for Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>T</td>
<td>n/T</td>
<td>N</td>
</tr>
<tr>
<td>5–17 months age category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 0 to study end</td>
<td>2974</td>
<td>9585</td>
<td>9994·9</td>
<td>0·96</td>
<td>2972</td>
</tr>
<tr>
<td>Months 0–20</td>
<td>2974</td>
<td>6768</td>
<td>7088·5</td>
<td>0·95</td>
<td>2972</td>
</tr>
<tr>
<td>Months 0–20*</td>
<td>2974</td>
<td>4305</td>
<td>4484·4</td>
<td>0·96</td>
<td>5949</td>
</tr>
<tr>
<td>Months 21–32</td>
<td>2700</td>
<td>2442</td>
<td>2609·9</td>
<td>0·94</td>
<td>2717</td>
</tr>
<tr>
<td>Months 33 to study end</td>
<td>2309</td>
<td>2817</td>
<td>2912·0</td>
<td>0·97</td>
<td>2267</td>
</tr>
<tr>
<td>Month 21 to study end</td>
<td>2701</td>
<td>5259</td>
<td>5516·3</td>
<td>0·95</td>
<td>2719</td>
</tr>
<tr>
<td>6–12 weeks age category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 0 to study end</td>
<td>2179</td>
<td>6170</td>
<td>6147·3</td>
<td>1·00</td>
<td>2178</td>
</tr>
<tr>
<td>Months 0–20</td>
<td>2179</td>
<td>4916</td>
<td>5162·4</td>
<td>0·95</td>
<td>2178</td>
</tr>
<tr>
<td>Months 0–20*</td>
<td>2179</td>
<td>2751</td>
<td>3273·6</td>
<td>0·84</td>
<td>4358</td>
</tr>
<tr>
<td>Months 21–32</td>
<td>1976</td>
<td>2156</td>
<td>1889·3</td>
<td>1·14</td>
<td>1995</td>
</tr>
<tr>
<td>Months 33 to study end</td>
<td>1657</td>
<td>1254</td>
<td>986·1</td>
<td>1·27</td>
<td>1668</td>
</tr>
<tr>
<td>Month 21 to study end</td>
<td>1976</td>
<td>3410</td>
<td>2874·2</td>
<td>1·19</td>
<td>1996</td>
</tr>
</tbody>
</table>

Analyses were by modified intention to treat. p values were calculated using negative binomial regression. C3C=control group. N=number of participants. n=number of episodes meeting the case definition. n/T=incidence. R3C=RTS,S/AS01 primary schedule without booster. R3R=RTS,S/AS01 primary schedule with booster. T=person-years at risk. VE=vaccine efficacy (negative binomial model).

*Data from a previous analysis that compared R3R plus R3C with C3C.
time was calculated as the sum of 3-monthly differences in the estimated number of cases between the control and the RTS,S/AS01 groups (R3R and R3C combined up to the booster dose) and expressed per 1000 participants vaccinated. 14 days after an episode were subtracted from the time of booster dose and R3R and R3C separately after the booster dose) and expressed per 1000 participants vaccinated. 14 days after an episode were subtracted from the time of booster dose and R3R and R3C separately after the booster dose)

This trial is registered with ClinicalTrials.gov, number NCT00866619.

Role of the funding source
GSK Biologicals SA were involved in study design, and coordinated data collection, data analysis, data interpretation, and writing of the report. The PATH Malaria Vaccine Initiative (MVI) contributed to study design and data interpretation, but were not involved in data collection, data analysis, or writing of the report. The RTS,S Clinical Trials Partnership had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
8922 children and 6537 young infants were enrolled and included in the modified ITT analyses; of these, 6918 (78%) children and 5997 (92%) young infants were enrolled and included in the per-protocol analyses (figures 1 and 2).
The median follow-up after dose 1 in the 6–12 weeks age group was 37–8 months (IQR 34–41–1) in R3R, 37.7 months (34.1–41.1) in R3C, and 37–8 months (34.1–41.1) in C3C (median overall 37.7 months, IQR 34.1–41.1; modified ITT). The median follow-up after dose 1 in the 5–17 months age group was 48.1 months (IQR 36.7–50–1) in R3R, 48.1 months (37.9–50–1) in R3C, and 48.4 months (41.3–50–1) in C3C (median overall 48.2 months, IQR 39.4–50–1; modified ITT). Baseline characteristics were similar in the three study groups in each age category and between the modified ITT and per-protocol populations, but differed between sites (appendix p 20). Insecticide-treated bednet use was consistently high, although it varied between study sites (appendix p 25). Malaria incidence in young infants in the C3C group during the first 12 months of follow-up ranged across sites from 0.03 to 4.27 episodes per infant per year (per protocol; appendix p 48). Artemisinin combination therapy was the first-line antimalarial and was given to treat 99% of malaria cases (42,353 of 42,977 episodes in children and 29,012 of 29,257 episodes in infants; appendix p 25). 158 of 8922 (1.8%, 95% CI 1.5–2.1) children and 148 of 6537 (2.3%, 1.9–2.7) young infants died during follow-up (month 0 to study end; appendix pp 49, 59).

In the modified ITT population, from month 0 until study end, compared with 9585 episodes of clinical malaria that met the primary case definition in children in the C3C group, 6616 episodes occurred in children in the R3R group (VE 39–0%, 95% CI 34–43–3) and 6597 in the R3C group (26–2%, 20–8–31–2; appendix p 67). Efficacy was similar in children vaccinated when 5–11 months of age or 12–17 months of age (appendix p 71). Efficacy varied by site with or without booster vaccination, but these differences were not significant (p

<table>
<thead>
<tr>
<th>C3C group</th>
<th>R3C group</th>
<th>R3R group</th>
<th>Point estimate of VE unadjusted for covariates R3C vs C3C</th>
<th>Point estimate of VE unadjusted for covariates R3R vs C3C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>n</td>
<td>Proportion affected*</td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>5–17 months age category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 0 to study end</td>
<td>2179</td>
<td>116</td>
<td>0.05</td>
<td>2178</td>
</tr>
<tr>
<td>Month 0–32</td>
<td>2179</td>
<td>101</td>
<td>0.05</td>
<td>2178</td>
</tr>
<tr>
<td>Month 0–20</td>
<td>2179</td>
<td>66</td>
<td>0.03</td>
<td>4358</td>
</tr>
<tr>
<td>Month 21–32</td>
<td>1976</td>
<td>43</td>
<td>0.02</td>
<td>1995</td>
</tr>
<tr>
<td>Month 33 to study end</td>
<td>1657</td>
<td>16</td>
<td>0.01</td>
<td>1658</td>
</tr>
<tr>
<td>Month 21 to study end</td>
<td>1976</td>
<td>58</td>
<td>0.03</td>
<td>1996</td>
</tr>
</tbody>
</table>

Table 2: Efficacy against severe malaria (primary case definition) of a primary schedule with or without a booster dose
end, compared with 62 children in the C3C group, 64 in the R3R group (VE 47·8%, 95% CI 11·6 to 69·9) and 34 in the R3C group (VE –4·0%, 95% CI –50·0 to 27·8) had at least one blood transfusion (table 3). The number of cases of clinical and severe malaria averted varied substantially by study site; the highest numbers of cases of clinical malaria averted were noted in areas of high malaria incidence, such as Siaya, Kenya, and Nanoro, Burkina Faso (figure 4A).

### Table 3: Number of cases averted per 1000 participants in children or young infants immunised with a primary vaccination schedule with or without a booster dose

<table>
<thead>
<tr>
<th>Clinical malaria (secondary case definition)</th>
<th>5–17 months age category</th>
<th>6–12 weeks age category</th>
</tr>
</thead>
<tbody>
<tr>
<td>R3C group</td>
<td>R3R group</td>
<td>R3C group</td>
</tr>
<tr>
<td>Months 0–20</td>
<td>96 (807 to 1133)†</td>
<td>...</td>
</tr>
<tr>
<td>Months 0–32</td>
<td>1221 (973 to 1483)</td>
<td>1475 (1234 to 1733)</td>
</tr>
<tr>
<td>Month 0 to study end†</td>
<td>1363 (995 to 1797)</td>
<td>174 (1387 to 2386)</td>
</tr>
</tbody>
</table>

| Malaria hospital admission                  |                          |                         |                          |
| Month 0–20                                 | 42 (28 to 59)†           | ...                     | 8 (–9 to 25)†            | ...                     |
| Month 0–32                                 | 33 (13 to 53)            | 44 (26 to 64)           | 5 (–17 to 27)           | 14 (–10 to 35)         |
| Month 0 to study end†                       | 26 (4 to 51)             | 40 (19 to 64)           | 14 (–13 to 39)          | 18 (–8 to 42)          |

| Severe malaria (secondary case definition)  |                          |                         |                          |
| Month 0–20†                                 | 19 (8 to 32)             | ...                     | 5 (–8 to 18)             | ...                     |
| Month 0–32†                                 | 12 (2 to 27)             | 20 (7 to 34)            | 5 (–12 to 24)           | 9 (–8 to 28)           |
| Month 0 to study end†                       | 8 (–9 to 26)             | 19 (4 to 35)            | 8 (–13 to 28)           | 12 (–6 to 32)          |

| Fatal malaria                               |                          |                         |                          |
| Month 0–20†                                 | 0 (–2 to 3)              | ...                     | –1 (–3 to 2)            | ...                     |
| Month 0–32†                                 | –1 (–4 to 3)             | 1 (–2 to 4)             | –1 (–5 to 2)           | –2 (–5 to 2)           |
| Month 0 to study end†                       | –2 (–7 to 2)             | 1 (–3 to 5)             | –3 (–7 to 1)           | –2 (–6 to 2)           |

| All-cause hospital admission                |                          |                         |                          |
| Month 0–20†                                 | 57 (29 to 88)†           | ...                     | 22 (–16 to 60)          | ...                     |
| Month 0–32                                 | 53 (16 to 92)             | 64 (29 to 103)         | 15 (–32 to 70)          | 38 (–9 to 89)         |
| Month 0 to study end                        | 41 (0 to 84)             | 59 (28 to 103)         | 24 (–27 to 82)          | 36 (–17 to 90)        |

| All-cause mortality                         |                          |                         |                          |
| Month 0–20†                                 | –1 (–7 to 4)             | ...                     | –5 (–12 to 3)           | ...                     |
| Month 0–32†                                 | –3 (–10 to 3)            | 0 (–7 to 6)             | –5 (–13 to 3)          | –6 (–14 to 3)         |
| Month 0 to study end                        | –5 (–12 to 3)            | –1 (–9 to 6)            | –5 (–14 to 4)          | –6 (–15 to 3)         |

| Incident severe anaemia                     |                          |                         |                          |
| Month 0–20†                                 | 8 (1 to 15)              | ...                     | 0 (–8 to 11)            | ...                     |
| Month 0–32†                                 | 9 (0 to 19)              | 10 (1 to 20)            | 0 (–13 to 15)          | 3 (–9 to 16)           |
| Month 0 to study end                        | 9 (–3 to 21)             | 11 (1 to 24)            | –1 (–16 to 15)         | 3 (–11 to 17)         |

| Blood transfusion                           |                          |                         |                          |
| Month 0–20†                                 | 13 (4 to 21)             | ...                     | 1 (–10 to 13)           | ...                     |
| Month 0–32†                                 | 13 (10 to 24)            | 15 (3 to 27)            | 2 (–10 to 20)          | 5 (–9 to 23)           |
| Month 0 to study end                        | 13 (–1 to 28)            | 15 (3 to 31)            | 1 (–18 to 19)          | 4 (–12 to 23)         |

Data are number of cases averted per 1000 participants (95% CI). Analyses were by modified intention to treat. R3C=RTS,S/AS01 primary schedule without booster. R3R=RTS,S/AS01 primary schedule with booster. *This definition was used for this analysis because, during routine clinical practice, these children would normally receive a full course of anti-malarial treatment. †The schedule without a booster (R3C) and the schedule with a booster (R3R) were pooled for this analysis because, during routine clinical practice, these children would normally receive a full course of anti-malarial treatment.

Significant efficacy against prevalent parasitaemia was noted in the R3R group compared with the C3C group at the cross-sectional assessments at month 32 (p=0·0001), month 44 (p=0·019), and study end (early p=0·018 and late p=0·044), and in the R3C group at month 32 (p=0·0001), but not at study end (appendix p 78). No significant VE was noted against incident bacteraemia, pneumonia, all-cause mortality, or malaria mortality (appendix pp 74–76) and there was no effect on indices of malnutrition with or without a booster dose (appendix p 80).

From month 0 until study end, 1774 cases of clinical malaria per 1000 children (95% CI 1387–2186; range across sites 205–6565) were averted in the R3R group and 1363 per 1000 children (95% CI 995–1797; range 215–4443) in the R3C group (table 3; figure 4; appendix p 83). The numbers of cases averted per 1000 children in the R3R group and R3C group, respectively, were 19 (95% CI 4·5 to 35) and eight (–9·5 to 26) for severe malaria, 40 (19·5 to 64) and 26 (4·5 to 51) for malaria hospital admission, 59 (18·0 to 103) and 40 (0·4 to 84) for all-cause hospital admission, 11 (1·24) and nine (–3·3 to 21) for severe anaemia, and 15 (1·31) and 13 (–1·3 to 28) for...
Analyses were by modified intention to treat. Data are ordered by increasing malaria incidence at each study site. Cases 5–17 months age category

Figure 4: Cases of clinical and severe malaria averted at each site during 48 months of follow-up in the 5–17 months age category

In the modified ITT population, from month 0 to study end, compared with 116 young infants in the C3C group, 96 young infants in the R3R group (VE 17·3%, 95% CI –9·4 to 37·5) and 104 in the R3C group (10·3%, –17·9 to 31·8) experienced at least one episode of severe malaria that met the primary case definition (table 2). Compared with 35 young infants in the C3C group, 24 young infants in the R3R group (VE 31·5%, 95% CI –18·5 to 61·0) and 31 in the R3C group (11·1%, –10·1 to 28·3) had at least one episode of incident severe malaria anaemia (appendix pp 88). Compared with 188 young infants in the C3C group, 142 young infants in the R3R group (VE 24·5%, 95% CI 5·6 to 39·7) and 167 in the R3C group (11·1%, –10·1 to 28·3) were admitted to hospital at least once for malaria (appendix p 88). No protection was noted against all-cause hospital admission, bacteraemia, pneumonia, all-cause mortality, or malaria mortality (appendix p 88–90). VE did not differ between the control and RTS,S/AS01 vaccine with or without a booster groups in terms of prevalent parasitaemia or indices of malnutrition (appendix p 92–93).

Between month 0 and study end, the number of cases averted per 1000 young infants in the R3R and R3C study groups, respectively, were 983 (95% CI 592–1337; range across sites –30 to 3406) and 558 (95% CI 158–926; range –172 to 2178) for clinical malaria, 12 (–6 to 32) and eight (–13 to 28) for severe malaria, 18 (–8 to 42) and 14 (–13 to 39) for malaria hospital admissions, and 36 (–17 to 90) and 24 (–27 to 82) for all-cause hospital admissions (figure 6; table 3; appendix p 94).

Anti-circumsporozoite antibody responses are shown in the appendix (p 36). 1 month after the booster dose with RTS,S/AS01, the geometric mean titre in children in the R3R group was 318·2 EU/mL (95% CI 295·1–343·0) compared with 34·2 EU/mL (30·5–38·3) in the R3C group (per-protocol population; appendix p 95). The comparable data in young infants were 169·9 EU/mL (95% CI 153·8–187·7) and 6·2 EU/mL (5·4–7·0), respectively (per-protocol population; appendix p 96).

Antibody concentrations fell after the increase induced by the booster dose and 12 months later were 52·4 EU/mL (95% CI 47·8–57·6) in the R3R group and 19·3 EU/mL (17·2–21·8) in the R3C group and children and 15·9 EU/mL (13·8–18·3) in the R3R group and 3·7 EU/mL (3·3–4·2) in the R3C group in young infants (appendix pp 36, 95–96). Anti-circumsporozoite antibodies were categorised by tertile. Infants who were RTS,S/AS01 vaccine recipients and whose antibody response was in the top tertile 1 month after primary vaccination series had a 36·9% (95% CI 17·3–51·8; p=0·0009) reduction in risk of subsequent malaria episodes compared with those in the lowest tertile. No significant risk reduction was noted in children in the highest tertile compared with those in the lowest tertile (3·6% reduction, 95% CI –25·6 to 26·0; p=0·79; appendix pp 37–39).

The RTS,S/AS01 booster dose was more reactogenic than the comparator vaccine in both children and young infants in the uncorrected ITT population, with 80% more children in the R3R group (VE 26·7%, 95% CI 20·5–32·4) and 5072 in the C3C group compared with 4532 in the R3C group (18·2%, 11·4–24·5; appendix p 84).

Estimates of VE across sites ranged from –14·6% to 50·4% in the R3R group and from –2·8% to 33·6% in the R3C group (figure 5). Efficacy waned over time, but, compared with the C3C group, was still present in the R3R group during the last study period (VE month 33 to study end 10·5%, 95% CI 0·2 to 19·7), but not in the R3C group (4·4%, –6·7 to 14·3; table 1; appendix p 34). The incremental efficacy against clinical malaria provided by the booster dose during the 12 months after booster vaccination was 22·3% (95% CI 14·0–29·8; table 1; appendix p 35).
infants, with a higher frequency of both systemic and local reactions within 7 days of vaccination in the R3R group than in the R3C or C3C groups (appendix p 97–98). However, grade 3 reactions were rare, except for grade 3 fevers (>39°C), which occurred in 34 of 641 children (5.3%, 95% CI 3.7–7.3) and nine of 608 infants (1.5%, 0.7–2.8) after a booster dose of RTS,S/AS01 (appendix pp 41–97). The incidence of generalised convulsive seizures within 7 days of a booster dose in children was 2.5 per 1000 doses in the R3R group, 1.2 per 1000 doses in the R3C group, and 0.4 per 1000 doses in the C3C group (appendix p 99).

The incidence of SAEs overall and of unsolicited AEs within 30 days of booster vaccination were similar in all three study groups (appendix pp 49, 59). Meningitis was reported as a SAE in 22 children: 11 in the R3R group, ten in the R3C group, and one in the C3C group (appendix pp 49, 59). Five of these 22 cases were reported after booster vaccination: two in the R3R group and three in the R3C group. A bacterial cause was identified in ten cases (five meningococcal, three Haemophilus influenzae, one pneumococcal, and one tuberculosis), all in children in the R3R or R3C groups. Meningitis was reported as a SAE in 18 young infants; no imbalance in cases of meningitis was noted in the younger age group (five cases in the R3R group, seven in the R3C group, and six in the C3C group). Meningitis cases were not temporally related to vaccination (appendix p 42). Most study sites reported one to three cases of meningitis, but 15 cases were reported from Lilongwe, Malawi, and five from Kombewa, Kenya. All cases of meningitis and other infections of the nervous system reported as a SAE were reviewed by two independent experts. In children, 33 episodes were reviewed by the experts, who classified 12 as confirmed cases of meningitis (six in R3R and six in R3C), 11 as not

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**Figure 5:** Vaccine efficacy against clinical and severe malaria by study site in the 6–12 weeks age category

VE against all episodes of clinical malaria (primary case definition) in (A) the R3C group and (B) the R3R group from month 0 to study end, and VE against severe malaria (primary case definition) in (C) the R3C group and (D) the R3R group from month 0 to study end. Study sites are ordered from lowest (Kilifi) to highest (Siaya) modified intention to treat. Bars are 95% CIs. The size of each square is proportional to the number of participants enrolled at each study site. The following numbers of infants aged 6–12 weeks were enrolled by site for all three groups (R3R, R3C, and C3C) together: 304 in Kilifi, 593 in Korogwe, 635 in Manhiça, 226 in Lambaréné, 802 in Siaya, 215 in (8 1 to 33 0).

**A Clinical malaria, R3C group**

<table>
<thead>
<tr>
<th>Site</th>
<th>VE (95% CI)</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kilifi, Kenya</td>
<td>23.1 (12.7 to 47.2)</td>
<td>-14.6 (-21.3 to 58.2)</td>
</tr>
<tr>
<td>Korogwe, Tanzania</td>
<td>23.1 (-41.5 to 50.2)</td>
<td>44.1 (-64.7 to 20.7)</td>
</tr>
<tr>
<td>Manhiça, Mozambique</td>
<td>33.6 (2.8 to 75.3)</td>
<td>7.4 (-41.4 to 57.0)</td>
</tr>
<tr>
<td>Lambaréné, Gabon</td>
<td>32.8 (-106.0 to 47.7)</td>
<td>43.9 (-121.6 to 71.8)</td>
</tr>
<tr>
<td>Bagamoyo, Tanzania</td>
<td>28.0 (-821.0 to 57.4)</td>
<td>50.4 (13.8 to 75.5)</td>
</tr>
<tr>
<td>Lilongwe, Malawi</td>
<td>28.6 (2.8 to 47.5)</td>
<td>38.4 (15.8 to 55.1)</td>
</tr>
<tr>
<td>Agogo, Ghana</td>
<td>10.2 (-11.1 to 36.3)</td>
<td>34.6 (17.9 to 45.6)</td>
</tr>
<tr>
<td>Kombewa, Kenya</td>
<td>21.7 (2.0 to 37.4)</td>
<td>19.8 (-0.5 to 35.9)</td>
</tr>
<tr>
<td>Kintampo, Ghana</td>
<td>4.1 (-12.6 to 21.8)</td>
<td>0.1 (-23.3 to 19.1)</td>
</tr>
<tr>
<td>Nanoro, Burkina Faso</td>
<td>11.4 (0.9 to 20.7)</td>
<td>17.4 (8.2 to 29.5)</td>
</tr>
<tr>
<td>Siaya, Kenya</td>
<td>21.5 (8.1 to 33.0)</td>
<td>30.6 (18.2 to 41.1)</td>
</tr>
<tr>
<td>Overall</td>
<td>21.3 (11.7 to 24.4)</td>
<td>25.9 (19.9 to 31.5)</td>
</tr>
</tbody>
</table>

**B Clinical malaria, R3R group**

<table>
<thead>
<tr>
<th>Site</th>
<th>VE (95% CI)</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kilifi, Kenya</td>
<td>-19.9 (-7902.1 to 89.7)</td>
<td>-9.4 (-8485.6 to 98.6)</td>
</tr>
<tr>
<td>Korogwe, Tanzania</td>
<td>-98.0 (-11579.6 to 89.7)</td>
<td>3.0 (-7515.4 to 98.8)</td>
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<tr>
<td>Manhiça, Mozambique</td>
<td>-26.2 (-535.9 to 72.8)</td>
<td>-24.4 (-527.0 to 73.2)</td>
</tr>
<tr>
<td>Lambaréné, Gabon</td>
<td>-74.4 (-1827.5 to 75.0)</td>
<td>15.0 (-1017.2 to 93.8)</td>
</tr>
<tr>
<td>Bagamoyo, Tanzania</td>
<td>85.5 (-12.9 to 99.7)</td>
<td>85.7 (-11.6 to 99.7)</td>
</tr>
<tr>
<td>Lilongwe, Malawi</td>
<td>26.2 (-101.4 to 74.2)</td>
<td>25.4 (-103.6 to 70.0)</td>
</tr>
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<td>Agogo, Ghana</td>
<td>-50.0 (-412.1 to 52.3)</td>
<td>-17.7 (-323.9 to 66.1)</td>
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<tr>
<td>Kombewa, Kenya</td>
<td>52.0 (9.9 to 78.0)</td>
<td>20.4 (-49.3 to 58.1)</td>
</tr>
<tr>
<td>Kintampo, Ghana</td>
<td>-9.1 (-115.6 to 52.8)</td>
<td>1.8 (-108.8 to 54.0)</td>
</tr>
<tr>
<td>Nanoro, Burkina Faso</td>
<td>8.3 (-126.9 to 63.4)</td>
<td>57.8 (-28.8 to 88.3)</td>
</tr>
<tr>
<td>Siaya, Kenya</td>
<td>-12.9 (-89.3 to 33.4)</td>
<td>3.6 (-64.7 to 43.5)</td>
</tr>
<tr>
<td>Overall</td>
<td>20.3 (17.9 to 32.8)</td>
<td>17.3 (-9.4 to 37.5)</td>
</tr>
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</table>
Discussion

The decrease in efficacy of RTS,S/AS01 against clinical and severe malaria over time since vaccination, which was reported previously,9 continued during the extended follow-up period in both children and infants who did not receive a booster dose of vaccine. Nevertheless, VE against clinical malaria during the full follow-up period in the absence of a booster dose were about 28% in children and 18% in young infants, which resulted in a substantial reduction in the number of cases of clinical malaria. Protection against clinical malaria was prolonged in both children and young infants by a booster dose, which increased the number of cases prevented across sites in both children and young infants. The proportional increase in efficacy against clinical malaria associated with booster vaccination was similar in children and young infants, but efficacy after the booster dose remained lower in those who received their primary vaccination when aged 6–12 weeks rather than at the age of 5–17 months. No significant efficacy against severe malaria was noted during the study period in young infants or children who did not receive a booster dose of vaccine. This finding contrasts with our earlier report of a significant reduction in severe malaria in children in the older age category who were followed up until the time of booster vaccination.9,9 This anomaly can be explained by the higher risk of severe malaria from month 21 until the end of the trial in children who did not receive a booster dose compared with children in the control group, whereas this was not noted in children who received a booster dose of vaccine. This increased risk occurred predominantly in sites with a higher level of malaria transmission. Why children who received the RTS,S/AS01 primary vaccination series but who did not receive a booster dose were at increased risk of severe malaria during the latter part of the study is uncertain. This finding might have occurred by chance; the number of cases was low and a similar pattern was not noted for cases of uncomplicated malaria. However, vaccination, by providing protection against malaria infection, might have reduced the natural acquisition of immunity obtained through repeated infections, making these children more susceptible when the vaccine effect waned. This possibility needs to be explored in further studies, and ongoing surveillance of study participants is taking place at three centres. The increased risk for severe malaria in the older age category was reduced by the administration of a booster dose of RTS,S/AS01. This finding suggests that if a decision is made to implement RTS,S/AS01 in an age category similar to that of the older children recruited to this trial, then consideration should be given to inclusion of a booster dose, especially in higher transmission areas, and the possible effect of administration of further booster doses will need to be explored.

Vaccination with RTS,S/AS01 significantly reduced overall hospital admissions, admissions because of malaria, severe anaemia, and the need for blood transfusion in children, with these protective effects being more marked in those who received a booster dose. The numbers of cases averted of these endpoints were lower in infants vaccinated at age 6–12 weeks. No significant effect on overall mortality, malaria mortality, pneumonia, or sepsis was noted in either age category. The latter finding is surprising because malaria seems to be an important risk factor for invasive bacterial infections.6 Failure to detect an effect of RTS,S/AS01 on these secondary outcomes, including mortality, might have been caused in part by the high level of clinical care provided during the trial, including high coverage with
Administration of a booster dose of RTS,S/AS01 led to an increase in anti-circumsporozoite geometric mean titres in both young infants and children, as noted previously in adults immunised with an earlier formulation of the vaccine (RTS,S/AS02), but the anti-circumsporozoite geometric mean titres after the booster remained lower than concentrations after the primary course and the booster effect was only transitory. Changes in anti-circumsporozoite concentration over time paralleled changes in efficacy against clinical malaria. No previously unvaccinated children vaccinated with a single dose of RTS,S/AS01 at the same age as the children who received the booster dose were included in the trial, so we cannot conclude definitively that children who received the booster dose had acquired immunological memory. However, limited data from a previous study suggest that the antibody response to a booster dose in children who had been primed with RTS,S/AS01 was greater than that reported in participants who had received a single dose without priming, and that some immunological memory had been induced with the prime series of RTS,S/AS01 vaccination. Further studies are needed to define the mechanism of memory induced with RTS,S/AS01 and whether there are ways in which this could be improved.

SAEs were reported in about a quarter of children in the trial, with a similar incidence in all study groups, but only 0–3% were judged to be vaccine related (appendix pp 49, 59). However, the significant imbalance in cases of meningitis in children vaccinated at the age of 5–17 months between the RTS,S/AS01 and control groups, reported previously, remained. Five new cases of meningitis were recorded from month 21 until the end of the trial in children in the RTS,S/AS01 groups, but none occurred in the control group; two of the five new cases occurred in children who had received the booster dose of RTS,S/AS01 and three in children who had received the control meningococcal serogroup C vaccine. The imbalance in cases of meningitis was not noted in young infants. This imbalance in cases of meningitis in children could be a chance finding because comparisons were made across groups for many different diagnostic classifications of SAEs, most of the cases were clustered in two sites, and there was no temporal relation to vaccination. If children who received RTS,S/AS01 do have an increased risk of meningitis, the mechanism that could have brought this about is difficult to understand. If RTS,S/AS01 is licensed, post-registration studies will be done to establish the significance of this finding. The incidence of fever in the 1 week after vaccination was higher in both infants and children who received a booster dose of RTS,S/AS01 vaccine than in those who received the control vaccine, as noted during the primary series of vaccination, and a small number of these febrile reactions were accompanied by generalised convulsive seizures.

Despite its large size and attention to detail, this trial has some weaknesses. The per-protocol population was high in young infants but lower in children because of a loss of data from one centre after administration of vaccine affected by a temperature deviation. At one centre (Bagamoyo, Tanzania), there was a concern about the quality of the work of two field workers assigned to undertake monthly home visits, but further investigation found no evidence that this had led to under-reporting of SAEs. Differences in the effect of RTS,S/AS01 were found between study sites, but because of the infrequency of assessment of some of the trial endpoints, including severe malaria, site-to-site comparisons should be made with caution. The detailed study analyses done at several timepoints generated many hundreds of comparisons and created the opportunity for some unexpected associations to emerge by chance. Finally, the high standard of care provided to all trial participants might have limited the ability of the trial to detect an effect on mortality or other severe outcomes.

An application for a Committee for Medicinal Products for Human Use (CHMP) scientific opinion on RTS,S/AS01 through the European Medicines Agency Article 58 procedure is under review. If a positive scientific opinion is obtained from the CHMP and the vaccine is prequalified by WHO, malaria-endemic countries will need to decide whether to license and use RTS,S/AS01 and, if so, what schedule to use. In anticipation of a positive opinion from the CHMP, WHO has established a Joint Technical Expert Group to monitor progress with the RTS,S/AS01 trials with the intention that this group will provide advice to a joint committee of WHO’s Malaria Policy Advisory Committee and the Strategic Advisory Group of Experts committees, which will formulate WHO’s recommendations on the use of RTS,S/AS01. The results provided in this phase 3 trial should help these groups in making their decisions and, if RTS,S/AS01 is licensed in African countries, help national malaria control programmes in deciding how best to use this vaccine, which, if used correctly, has the potential to prevent millions of cases of malaria.

Contributors
SAb, TA, STA, DA, JJA, KPA, WRB, PBe, UD’A, SGe, BG, MJH, IH, Skar, PGK, TL, DLu, AL, BL, MLz, MLI JL, EMa, EM, FM, PN, OO-A, AOlo, LO, WO, SO-A, JSa, BS, LS, MT, HT, and IV designed the study. OA, SAh, BPA, AAA, EA, SAd, TA, STA, SAh, PAl, PAK, AA, PAl JA, DA IA, KPA, NA, KA, EB, AB-P, TB, FBe, OB, PBu, HB, DC, CC, RC, JCow, KD, DD, CD, AE, JFF, SGe, [JC, SGo, CG, AH, MJH, SI, EJ, WK, ALK, Skaf, PK, Skar, KK, CK, SKS, FK, VM-E, AK, PGK, KFL, BL, MLe, EL, PL, JL, DCM, Ema, LM, MM, CMah, CMA, AMa, SMn, KAM, FM, MML, SMas, JAM, AMd, RM, BMM, AMo, BMI, TM, SMw, EMz, PN, RN, Joc, CO, SOd, BO, GO, RO, AOlo, Jom, MO, AO1, KO, LO, WO, NO, FO, JBO, SOu, HOB, SO-A, Jov, VP, TR, JSa, NS, DSA, TS, HS, Jsy, MCT, GT, TT, TGT, HT, BT, IV, EV, AW, ARY, and ZY collected data. AMo, JJA, DH, and MLI developed the analysis plan for the data. JJA, DH, and MLI vouch for the data and analysis. TA, STA,
PAI, PAK, UDA, DA, JJA, [Coh, SGe, BG, YG, MJH, DH, IH, PK, SKar, DK, PGK, DLa, AL, DLe, ML, JL, AMI, PN, BO, AOI, LO, WO, SO-A, JS, NS, BS, DSc, IS, HT, and JV interpreted data. Sah, JAC.B, MJH, DH, AL, ML, JL, PN, AOI, LO, DSc, MT, and JV wrote the manuscript. All authors reviewed manuscript drafts, approved the final version of the manuscript, decided to publish the manuscript, and agreed to be accountable for all aspects of the work.

RTS.S Clinical Trials Partnership members


Declaration of interests

PAI is an investigator received grants from the Catalan Government, the Spanish Government, Medicines for Malaria Venture, and the Bill & Melinda Gates Foundation. PAI has received personal fees from Medicines for Malaria Venture. DCM, CMAI, and LO’s institutes have received grants from MVI for other malaria studies. AMo has received personal fees from Spanish Government, Medicines for Malaria Venture, and the Bill & Melinda Gates Foundation, and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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References