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, 6616 episodes occurred in the R3R group (17·3%, 95% CI 13·8–21·4) and 104 in the R3C group (10·3%, 6·9–14·8). In children, 1774 cases of clinical malaria were averted per 1000 children (95% CI 1387–2186) 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.3,4,5 We undertook a phase 3, double-blind (observer-blind), individually randomised, controlled trial to...
Research in context

Evidence before this study

We did a systematic literature search between Dec 18, 2014, and Feb 20, 2015, of randomised controlled trials of RTS,S malaria vaccine on PubMed, the Cochrane Library, and other relevant data sources for the period 1984 to Jan 31, 2015. We searched PubMed using the Medical Subject Headings (MeSH) terms “RTS,S-AS01B vaccine” [All Fields] OR “RTS,S-AS01E vaccine” [All Fields] OR “RTS,S-AS02A vaccine” [All Fields] OR “RTS,S-AS02D vaccine” [All Fields] OR “RTS,S/AS01” [All Fields] OR “RTS,S/AS02” [All Fields] AND “clinical trial” [Publication Type] OR “clinical trials as topic” [MeSH Terms] OR “clinical trial” [All Fields] AND “humans” [MeSH Terms]. For the Cochrane Library and other data sources, we used the following key search terms: “RTS,S”, “malaria vaccines”, and “clinical trials”. The 60 manuscripts identified included five that reported the results of randomised controlled trials with long-term safety or efficacy follow-up or booster dose, two pooled analyses, and two systematic reviews.

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.

assess the efficacy and safety of RTS,S/AS01. Study results up to 18 months of follow-up have been reported previously.2–9 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.2–9 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.9 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;2–9 and are described in the appendix (pp 4–13). 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.10

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 minimisation by centre to one of three groups. One group received RTS,S/AS01 at months 0, 1, and 2, followed by a booster dose at month 20 (R3R group); a second group received RTS,S/AS01 at months 0, 1, and 2, followed by a booster dose at month 13, month 31, and 1 month before study end. 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.

Figure 1: Trial profile for participants aged 5–17 months

Participants’ flow in the study on those enrolled in the 5–17 months age category. ITT=intention to treat. *For 70 children, the screening data had not been reported before the database freeze of the previous analyses and these participants were not included in the CONSORT charts published previously. †During monitoring, one participant was found to have been enrolled twice at two different clinics under two different participant numbers. This participant was excluded from the per-protocol analyses. Because of the removal of one participant number from the database, the total number of participants enrolled into the study changed from 15 460 (8923 in the 5–17 months age group), as reported in previous analyses, to 15 459 participants (8922 in the 5–17 months age group) in the final analyses reported here. 12867 children in the with booster group, 2887 in the without booster group, and 2905 in the control group received doses 1 and 2.
7200 infants assessed for eligibility*
6537 infants randomly assigned
2180 assigned to RTS,S/AS01 with booster and received dose 1 (modified ITT 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
2072 received doses 1, 2, and 3
6537 infants randomly assigned
2178 assigned to RTS,S/AS01 without booster and received dose 1 (modified ITT population)†
2072 received doses 1, 2, and 3
663 failed screening
419 did not meet eligibility criteria
3 died
99 withdrew consent
70 migrated or were lost to follow-up
72 other
1824 received dose 4 (booster)
1837 received dose 4 (control vaccine)
2179 assigned to control vaccine and received dose 1 (modified ITT population)†
2090 received doses 1, 2, and 3
501 not enrolled in extension phase
1731 attended visit 34 (32 months after dose 3)
1682 enrolled in extension phase
124 did not attend visit 38
1985 included in per-protocol population
87 excluded from per-protocol population
3 did not meet inclusion criteria
9 no follow-up data after dose 3
12 other
500 not enrolled in extension phase
1679 enrolled in extension phase
1549 attended visit 38 (end of extension phase)
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 *P falciparum* asexual parasitaemia (>5000 parasites per mm³) or a case of malaria meeting the primary case definition of 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.

Fetal malaria was defined as a fatal case meeting the *International statistical classification of diseases and related health problems*, tenth edition, categories B50, B53, and B54. All-cause hospital admission was defined as a hospital admission accompanied by an axillary temperature of at least 37.5°C 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

Articles

Figure 2: Trial profile for participants aged 6–12 weeks
Participants’ flow in the study in those enrolled in the 6–12 weeks age category. ITT=intention to treat. aFor 118 infants, the screening had not been reported before the database freeze of the previous analyses and these participants were not included in the CONSORT charts published previously. b2115 children in the with booster group, 2119 in the without booster group, and 2134 in the control group received doses 1 and 2. cFor some participants, consent to the extension occurred before visit 34. One participant consented to the extension but died before visit 34. This participant is considered as enrolled into the extension and the reason for not undertaking visit 35 is recorded as died.
## 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>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>N n T n/T</td>
<td>N n T n/T</td>
<td>N n T n/T</td>
<td>R3C vs C3C (95% CI) p value</td>
<td>R3R vs C3C (95% CI) p value</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>2974 9585 9934.9 0.96</td>
<td>2972 7396 10037.3 0.74</td>
<td>2976 6616 9957.6 0.66</td>
<td>0.66</td>
</tr>
<tr>
<td>Months 0–32</td>
<td>2974 6768 7088.5 0.95</td>
<td>2972 4711 7180.0 0.66</td>
<td>2976 4078 7099.7 0.57</td>
<td>0.57</td>
</tr>
<tr>
<td>Months 0–20*</td>
<td>2974 4305 4484.4 0.96</td>
<td>5949 5106 9059.1 0.56</td>
<td>5949 5106 9059.1 0.56</td>
<td>0.56</td>
</tr>
<tr>
<td>Months 21–32</td>
<td>2700 2442 2609.9 0.94</td>
<td>2717 2076 2621.7 0.79</td>
<td>2679 1592 2610.0 0.61</td>
<td>0.61</td>
</tr>
<tr>
<td>Month 33 to study end</td>
<td>2309 2817 2912.0 0.97</td>
<td>2267 2685 2861.6 0.94</td>
<td>2236 2539 2862.2 0.89</td>
<td>0.89</td>
</tr>
<tr>
<td>Month 21 to study end</td>
<td>2701 5259 5516.3 0.95</td>
<td>2719 4761 5479.1 0.87</td>
<td>2681 4130 5458.9 0.76</td>
<td>0.76</td>
</tr>
</tbody>
</table>

| 6–12 weeks age category |
| Month 0 to study end | 2179 6170 6147.3 1.00 | 2178 5444 6174.3 0.88 | 2180 4993 6156.4 0.81 | 0.81 | 0.0001 | 25.9% (19.9 to 31.5) | <0.0001 | -- | -- |
| Months 0–32 | 2179 4916 5162.4 0.95 | 2178 4174 5190.7 0.80 | 2180 3842 5173.3 0.74 | 0.74 | 0.0001 | 27.8% (21.7 to 33.4) | <0.0001 | -- | -- |
| Months 0–20* | 2179 2751 3273.6 0.84 | 4358 4252 6583.6 0.65 | 4358 4252 6583.6 0.65 | 0.65 | 0.0001 | -- | -- | -- | -- |
| Months 21–32 | 1976 2156 1889.3 1.14 | 1995 2079 1893.0 1.10 | 1966 1671 1888.4 0.88 | 0.88 | 0.0001 | 28.1% (20.6 to 34.8) | <0.0001 | 22.3% (14.0 to 29.8) | <0.0001 |
| Month 33 to study end | 1657 1254 986.1 1.27 | 1668 1271 984.0 1.29 | 1654 1154 984.9 1.17 | 1.17 | 0.006 | 10.5% (0.2 to 19.7) | 0.046 | -- | -- |
| Month 21 to study end | 1976 3410 2874.2 1.19 | 1996 3349 2876.7 1.16 | 1966 2822 2871.5 0.98 | 0.98 | 0.076 | 23.5% (16.4 to 30.1) | <0.0001 | 17.5% (9.5 to 24.8) | <0.0001 |

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.

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 (ie, 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
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 14 days after an episode were subtracted from the estimated number of cases between the control and the vaccinated. 14 days after an episode were subtracted from the estimated number of cases between the control and the vaccinated. 14 days after an episode were subtracted from the estimated number of cases between the control and the vaccinated.

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 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 34.3–41.0) 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 25). 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 0.03–4.27 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 36.3%, 95% CI 31.8–40.5) and 7396 in the R3C group (28.3%, 23.3–32.9; table 1; appendix pp 28, 69). The per-protocol population was 8352 episodes in the C3C group compared with 5691 in the R3R group (VE 39.0%, 95% CI 34.3–43.3) 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 (pmaximump<0.09 and pmaximum=0.11, respectively; figure 3). Efficacy waned over time, and in the R3C group it was no longer detectable in the last study period (VE month 33 to study end 2.9%, 95% CI 6.4 to 11.4; table 1; appendix p 29). By contrast, VE persisted to study end in the R3R group (VE month 33 to study end 12.3%, 95% CI 3.6–20.1; table 1 and appendix p 29). The incremental efficacy provided by the booster dose during the 12 months after booster vaccination was 25.6% (95% CI 18.2–32.3; table 1 and appendix p 30).

In the modified ITT population, from month 0 until study end, compared with 171 children in the C3C group, 116 children in the R3R group (VE 32.2%, 95% CI 13.3 to 46.9) and 169 in the R3C group (1.1%, −23.0 to 20.5) experienced at least one episode of severe malaria that met the primary case definition (table 2; appendix p 69). Corresponding data in the per-protocol population were 135 children affected in the C3C group compared with 94 in the R3R group (VE 28.5%, 95% CI 6.3 to 45.7) and 141 in the R3C group (−5.8%, −35.0 to 17.0; appendix p 67). From month 0 until month 20, 156 children in the combined R3C plus R3 group experienced severe malaria compared with 118 in the C3C group (VE 33.9%, 95% CI 15.3–48.3); however, from month 21 to study

---

**Table 2: Efficacy against severe malaria (primary case definition) of a primary schedule with or without a booster dose**

<table>
<thead>
<tr>
<th>5-17 months age category</th>
<th>6-12 weeks age category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C3C group</strong></td>
<td><strong>R3C group</strong></td>
</tr>
<tr>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Month 0 to study end</td>
<td>2974</td>
</tr>
<tr>
<td>Months 0–32</td>
<td>2974</td>
</tr>
<tr>
<td>Months 0–201</td>
<td>2974</td>
</tr>
<tr>
<td>Months 21–32</td>
<td>2701</td>
</tr>
<tr>
<td>Month 33 to study end</td>
<td>2309</td>
</tr>
<tr>
<td>Month 21 to study end</td>
<td>2702</td>
</tr>
</tbody>
</table>
| **Analyses were by modified intention to treat.** **p values were calculated using a two-sided Fisher’s exact test.** **C3C=control group. N=number of participants. n=number of participants with at least one event in each group.** **R3C+RTS,S/AS01 primary schedule without booster. R3R+RTS,S/AS01 primary schedule with booster. VE=vaccine efficacy (1-relative risk for severe malaria).** **Proportion of participants who reported at least one event.** **†Data from a previous analysis that compared R3R plus R3C with C3C.**
From month 0 until study end, compared with 44 children in the C3C group, 23 children in the R3 group (VE 47·8%, 95% CI 11·6 to 69·9) and 34 in the R3C group (22·7%, 23·8 to 52·1) had at least one episode of incident severe malaria anaemia; and compared with 347 children in the C3C group, 227 children in the R3 group (34·6%, 22·5 to 44·9) and 286 in the R3C group (17·5%, 3·3 to 29·7) were admitted to hospital for malaria at least once (appendix p 74–76). Compared with 771 children in the C3C group, 644 children in the R3 group (VE 16·5%, 7·2 to 24·9) and 682 in the R3C group (17·5%, 3·3 to 29·7) were admitted to hospital at least once for any cause (appendix p 76). Between month 0 and study end, compared with 109 controls, 78 children in the R3R group (VE 47·8%, 95% CI 11·6 to 69·9) and 286 in the R3C group (17·5%, 3·3 to 29·7) had at least one blood transfusion (appendix p 76).

Significant efficacy against prevalent parasitaemia was noted in the R3 group compared with the C3 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 R3 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 R3 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 to 35) and nine (3·3 to 21) for severe malaria, 40 (19 to 64) and 26 (4 to 51) for malaria hospital admission, 59 (18 to 103) and 41 (0 to 84) for all-cause hospital admission, 11 (1 to 24) and nine (3·3 to 21) for severe anaemia, and 15 (1 to 31) and 13 (1 to 28) for blood transfusions (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>Month 0–20</th>
<th>Month 0–32</th>
<th>Month 0 to study end‡</th>
<th>Month 0–20*</th>
<th>Month 0–32*</th>
<th>Month 0 to study end†</th>
</tr>
</thead>
<tbody>
<tr>
<td>R3C group</td>
<td>R3R group</td>
<td>R3C group</td>
<td>R3R group</td>
<td>R3C group</td>
<td>R3R group</td>
</tr>
</tbody>
</table>

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 (R3R plus R3C) to calculate the number of cases averted. ‡Median of 48 months after the first dose for the 5–17 months age category and 39 months after the first dose for the 6–12 weeks 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, bacteremia, 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 (6–23) and 8 (−20 to 12) for severe malaria, 18 (2–88) and 18 (−7 to 55) 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 in 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 children (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 11·7; p=0·30) and 24·0% (95% CI 9·5–38·5; p=0·003) in the R3C group (18·2%, 11·4–24·5; appendix p 84).

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%, 0·7–2·8) after a booster dose of RTS,S/AS01 (appendix pp 41, 97–98).

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, and in young infants it was 2·2 per 1000 doses in the R3R group, 0·0 per 1000 doses in the R3C group, and 0·4 per 1000 doses in the C3C group (appendix p 99).

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, 681 in Nanoro, and 820 in Siaya. C3C=control group. R3C=RTS,S/AS01 primary schedule without booster. R3R=RTS,S/AS01 primary schedule with booster. VE=vaccine efficacy.

Articles

www.thelancet.com Published online April 24, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60721-8

11
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. 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...
insecticide-treated bednets and enhanced access to effective treatment of malaria and other disorders. RTS,S/AS01 might have reduced the numbers of cases averted of these endpoints even more in communities where access to a high level of clinical care is less readily accessible than was the case during the trial.

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, WBP, PB, UDA, SGe, BG, MJH, IH, SKar, PGK, TL, DLu, AL, BL, MLe, MLI, IJL, EMA, EM, FM, PN, OO-A, AOlo, LO, WO, SO-A, JSA, BS, IJ, LT, HT, and JV designed the study. JJA, DH, and MLi vouch for the data and analysis. TA, STA, 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,
Acknowledgments

The trial was sponsored by GlaxoSmithKline Biologicals SA and was funded by both GSK Biologicals SA and the PATH MVI. All centres received a grant from the MVI for running the trial. Author travel and accommodation related to this trial were financed by the MVI. GlaxoSmithKline Biologicals SA received a grant from the MVI to run the trial. The MVI received a grant from the Bill & Melinda Gates Foundation to run this trial and to compensate MVI authors for trial-related travel. GlaxoSmithKline Biologicals SA developed and manufactured the vaccine. The opinions and assertions herein are the views of The RTS,S Clinical Trials Partnership and not the Department of Defense or US Government. We thank A Gervais (University of Geneva, Geneva, Switzerland) and C Newton (University of Oxford, Oxford, UK) for reviewing the case histories of all participants with reported meningitis or other CNS infections or inflammation. The findings and conclusions in this report are those of The RTS,S Clinical Trials Partnership and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

References


Final results from a pivotal phase 3 malaria vaccine trial

In The Lancet, the RTS,S Clinical Trials Partnership report the most recent results from the pivotal phase 3 trial of RTS,S/AS01 malaria vaccine, the fourth major publication from this randomised controlled trial. The trial enrolled 15,459 infants and young children at 11 centres in seven sub-Saharan African countries: Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania. Two age groups were included: 6–12 weeks and 5–17 months at first dose. The schedule involved a primary series of three monthly doses, with a booster dose given 18 months later in one of the three trial groups. The partnership responsible for undertaking this trial, consisting of GlaxoSmithKline and PATH, are to be congratulated on the quality of the study. Industry involvement in malaria vaccine development has been crucial to the promising next-generation malaria vaccine work that is underway. The generous funding from the Bill & Melinda Gates Foundation to PATH for clinical trials of RTS,S/AS01 has been very important, as has the continued commitment of a large pharmaceutical company to this project despite the absence of a market for this product in high-income settings. GlaxoSmithKline and PATH worked with many of the leading scientists in sub-Saharan Africa in a clinical trial partnership model, through a committee in which many of the decisions were taken together with and by local investigators. The strengthening of clinical trial capacity in sub-Saharan Africa to support the trial has already left a strong legacy.

The new results show that the vaccine induces partial protection against clinical malaria in the older age group (5–17 months) at all 11 sites over the follow-up period of the trial, and shows benefit of the 18-month booster. In the intention-to-treat population, vaccine efficacy in older children who received three doses plus a booster on months 0, 1, 2, and 20 was 36.3% (95% CI 31.8–40.5) between month 0 and study end (median 48 months per child). This is a decline from 50.4% (intention-to-treat analysis, 95% CI 45.8–54.6) reported over the 14 months from the first dose. Efficacy against clinical and severe malaria endpoints in 6–12-week olds was lower, and no significant efficacy against severe malaria was noted in the 6–12 week age group, even with a booster, over the duration of the trial.

Two WHO advisory groups—the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC)—will formulate their recommendations to the WHO Director-General with regard to introduction of the RTS,S/AS01 vaccine into the vaccination schedule of children in Africa. These two groups will meet in open joint session if the European Medicines Agency provides a positive scientific opinion on its regulatory assessment, which is underway. The earliest month for the SAGE and MPAC recommendation is October, 2015, depending on timing of the European Medicines Agency’s decision.

One key question SAGE and MPAC will consider is the duration of protection of the vaccine. Without a booster dose of vaccine, the new results do not show overall efficacy against severe malaria in the 5–17 month age group, with cases prevented in the first 20 months of the trial shifted to older age groups. The new results show that, with a booster of the vaccine, the overall efficacy against severe malaria in 5–17-month-old children was 32.2% (95% CI 13.7–46.9), and efficacy was detected against both malaria hospital admission (34.6%, 22.5–44.9) and all-cause hospital admission (16.5%, 7.2–24.9). Unlike many illnesses of infancy, the risk of death from malaria continues through early childhood, even in the face of repeated infection, although the mortality rate drops from the age of 2 years in high-transmission settings.

For every new malaria intervention, discussions about potential increased disease incidence after the effect of
the intervention wanes have been intense at the time of initial policy decisions. Another key question, which does not need to be addressed in pre-licensure trials of vaccines, is whether the intervention will reduce childhood mortality. Malaria models predict that the RTS,S/AS01 vaccine will reduce mortality, but we will only know whether or not this is the case if larger datasets become available.

From the perspective of the immunisation programme, there are added challenges with the delivery of this vaccine through new immunisation contacts. The required booster will need to be administered in settings where the booster platform is weak and needs to be strengthened. If recommendations were to support use of the vaccine with booster in the 5–17 months age range, at least two new visits for immunisation and a new visit for the booster would be needed.

Malaria remains an ongoing public health crisis in many settings in sub-Saharan Africa. Every day, on average, about 1200 children die in sub-Saharan Africa from malaria. This figure is a substantial reduction from mortality estimates 15 years ago, and the decline has been associated with scale-up in longlasting insecticidal nets, access to effective artemisinin-combination treatments, and other WHO recommended control measures. Nevertheless, present mortality owing to malaria is unacceptable. Drug and insecticide resistance are major threats, and new malaria interventions are necessary.

The donor community would need to coordinate any financing for the RTS,S/AS01 vaccine carefully, should it reach that stage. In particular, funding must not be redirected away from meeting adequate access to artemisinin-combination treatments, rapid diagnostic tests, longlasting insecticidal nets, and other malaria control measures already in place in some settings, and financial resources might be better raised through the GAVI Alliance, if their board chooses to support such a role. GAVI has a strong track record for financing the delivery of new vaccines in sub-Saharan Africa. Finally, strong guidance is needed about the role of the vaccine in the context of existing malaria control measures, and about which malaria transmission intensity settings are best suited for vaccine use. The outcomes of regulatory and global policy assessments will no doubt be of interest to policy makers in malaria-endemic countries and multilateral financing agencies. WHO has a major responsibility to articulate evidence-based policy recommendations for use to support decision making in malaria-endemic countries.

*Vasee S Moorthy, Jean-Marie Okwo-Bele
Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva 1211, Switzerland
moorthyv@who.int

We declare no competing interests.

© 2015. World Health Organization. Published by Elsevier Ltd/Inc/BV. All rights reserved.


