# Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: a multicentre, double-blind, randomised, phase 3 trial

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## Summary

**Background** Recently, we found that a new malaria vaccine, R21/Matrix-M, had over 75% efficacy against clinical malaria with seasonal administration in a phase 2b trial in Burkina Faso. Here, we report on safety and efficacy of the vaccine in a phase 3 trial enrolling over 4800 children across four countries followed for up to 18 months at seasonal sites and 12 months at standard sites.

**Methods** We did a double-blind, randomised, phase 3 trial of the R21/Matrix-M malaria vaccine across five sites in four African countries with differing malaria transmission intensities and seasonality. Children (aged 5–36 months) were enrolled and randomly assigned (2:1) to receive 5 µg R21 plus 50 µg Matrix-M or a control vaccine (licensed rabies vaccine [Abhayrab]). Participants, their families, investigators, laboratory teams, and the local study team were masked to treatment. Vaccines were administered as three doses, 4 weeks apart, with a booster administered 12 months after the third dose. Half of the children were recruited at two sites with seasonal malaria transmission and the remainder at standard sites with perennial malaria transmission using age-based immunisation. The primary objective was protective efficacy of R21/Matrix-M from 14 days after third vaccination to 12 months after completion of the primary series at seasonal and standard sites separately as co-primary endpoints. Vaccine efficacy against multiple malaria episodes and severe malaria, as well as safety and immunogenicity, were also assessed. This trial is registered on ClinicalTrials.gov, NCT04704830, and is ongoing.

**Findings** From April 26, 2021, to Jan 12, 2022, 5477 children consented to be screened, of whom 1705 were randomly assigned to control vaccine and 3434 to R21/Matrix-M; 4878 participants received the first dose of vaccine. 3103 participants in the R21/Matrix-M group and 1541 participants in the control group were included in the modified per-protocol analysis (2412 [51·9%] male and 2232 [48·1%] female). R21/Matrix-M vaccine was well tolerated, with injection site pain (301 [18·6%] of 1615 participants) and fever (754 [46·7%] of 1615 participants) as the most frequent adverse events. Number of adverse events of special interest and serious adverse events did not significantly differ between the vaccine groups. There were no treatment-related deaths. 12-month vaccine efficacy was 75% (95% CI 71–79; p<0·0001) at the seasonal sites and 68% (61–74; p<0·0001) at the standard sites for time to first clinical malaria episode. Similarly, vaccine efficacy against multiple clinical malaria episodes was 75% (71–78; p<0·0001) at the seasonal sites and 67% (59–73; p<0·0001) at standard sites. A modest reduction in vaccine efficacy was observed over the first 12 months of follow-up, of similar size at seasonal and standard sites. A rate reduction of 868 (95% CI 762–974) cases per 1000 children-years at seasonal sites and 296 (231–362) at standard sites occurred over 12 months. Vaccine-induced antibodies against the conserved central Asn-Ala-Asn-Pro (NANP) repeat sequence of circumsporozoite protein correlated with vaccine efficacy. Higher NANP-specific antibody titres were observed in the 5–17 month age group compared with 18–36 month age group, and the younger age group had the highest 12-month vaccine efficacy on time to first clinical malaria episode at seasonal (79% [95% CI 73–84]; p<0·001) and standard (75% [65–83]; p<0·001) sites.

**Interpretation** R21/Matrix-M was well tolerated and offered high efficacy against clinical malaria in African children. This low-cost, high-efficacy vaccine is already licensed by several African countries, and recently received a WHO policy recommendation and prequalification, offering large-scale supply to help reduce the great burden of malaria in sub-Saharan Africa.

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## Research in context

### Evidence before this study

RTS,S/AS01 (Mosquirix; GlaxoSmithKline) is the first malaria vaccine recommended by WHO for use in children aged 5–17 months in moderate-to-high transmission settings. Deployment is planned to start in 2024 after the Malaria Vaccine Implementation Programme supported a suitable safety profile in three African countries. We searched PubMed from database inception to Sept 20, 2023, for published articles using the search terms "malaria vaccine" AND "clinical trial" AND "phase III" AND "efficacy". No language restrictions were applied. In a large phase 3 trial, RTS,S/AS01 malaria vaccine had a vaccine efficacy of 56% (95% CI 51–60) in children aged 5–17 months over 12 months after administration of the initial three doses. At 12 months after a booster dose, administered 18 months after the primary series, vaccine efficacy over 30 months was 44% (95% CI 40–48) and this efficacy waned over time. Over a median time of 48 months, vaccine efficacy was 36% (95% CI 32–41). Recent evidence from a trial of a seven-dose regimen of RTS,S/AS01 (three primary series doses with an annual booster for 4 years) showed improved vaccine efficacy of 73% (95% CI 64–80) over 1 year and 58% (53–62) over 5 years when administered seasonally in west Africa, with high coverage of seasonal malaria chemoprevention. 18 million doses of this vaccine are available for deployment over 3 years from 2023 to 2025.

### Added value of this study

This phase 3 licensure trial shows high vaccine efficacy over 1 year with a three-dose regimen of R21/Matrix-M in 4644 children aged 5–36 months with both seasonal (75% [95% CI 71–79]) and age-based perennial (standard; 68% [61–74]) vaccine administration regimens. In the 5–17 month age group, which has been the most studied to date, efficacy was 79% (95% CI 73–84) at seasonal sites and 75% (65–83) at standard sites, which was significantly higher than that in the 18–36 month age group. At seasonal sites, vaccine efficacy was well maintained to 18 months, with a single booster dose given 12 months after the primary series. Vaccine-induced antibody responses correlated with efficacy and were significantly higher in the younger age group. No safety concerns were identified with administration of R21/Matrix-M.

### Implications of all the available evidence

The findings of this trial support the findings of a smaller, single-country, phase 2b trial, which showed vaccine efficacy of more than 75% over 12 months with seasonal administration in children aged 5–17 months, which was maintained over 24 months. R21/Matrix-M offers a safe, high-efficacy vaccine for prevention of malaria in young African children. This efficacy is in an extended age group, up to 36 months of age, which is important given the malaria burden in children younger than 5 years old. The low dose of R21 antigen used (5 µg) facilitates large-scale manufacturing and a lower cost, with expected production of up to 200 million doses annually in the coming years. These key factors ensure all of the target population are reached and should contribute substantially towards malaria control and elimination. This vaccine has already been licensed for use in three West African countries and has now received a policy recommendation and prequalification from WHO.

## Introduction

In recent years, progress in reducing malaria has stalled, with more than 220 million cases and 620 000 deaths annually.[1] However, important developments have been made in the field of malaria vaccines, with the WHO recommendation and prequalification of RTS,S/AS01 for prevention of *Plasmodium falciparum* malaria in children living in regions with moderate to high malaria transmission.[1]

See Online for appendix

In the phase 3 trial of RTS,S/AS01,[2] a circumsporozoite protein-based vaccine, vaccine efficacy in children aged 5–17 months with a four-dose regimen was 56% over 1 year and 36% over 4 years. More recently, the Malaria Vaccine Implementation Programme reported a 30% reduction in severe malaria and a 21% reduction in hospital admissions with malaria parasitaemia.[3] However, the initial supply of this four-dose vaccine (18 million doses over 3 years)[4] is insufficient for coverage of all children born in regions with moderate-to-high malaria transmission (over 25 million children annually).[5]

R21 is a virus-like particle comprising the central repeats of Asn-Ala-Asn-Pro (NANP) and C-terminal sequence of circumsporozoite protein fused to the hepatitis B surface antigen (HBsAg). R21 differs from RTS,S as all, rather than 20%, of HBsAg molecules are fused to the NANP repeat and C-terminus of circumsporozoite protein (appendix p 12). R21 is administered with a saponin adjuvant, Matrix-M, is used at a low dose of 5 µg, and was designed to maximise durable antibodies to the central NANP repeat sequence of the circumsporozoite protein antigen.[6–9] These NANP antibody responses correlate with vaccine efficacy in phase 2 trials.[10,11] We previously reported 24 month efficacy of 75% and 77% for time to first episode and multiple episodes of clinical malaria, respectively, with four doses of R21/Matrix-M in children aged 5–17 months at enrolment in Nanoro, Burkina Faso, in a phase 2b study.[10,11]

80% of malaria deaths in the WHO African region are in children younger than 5 years.[1] In this multicentre, double-blind, randomised, phase 3 trial, we aimed to assess the safety and efficacy of R21/Matrix-M vaccine in the extended age range of 5–36 months of age at the first dose, rather than from 5–17 months.

## Methods

### Study design and participants

This double-blind, randomised, phase 3 trial was conducted at two seasonal sites (l'Unité de Recherche Clinique de Nanoro, Nanoro, Burkina Faso and the Malaria Research and Training Centre, Bamako and Bougouni, Mali) and three perennial standard (ie, where malaria transmission occurs throughout the year and where an age-based vaccine administration schedule was used) sites (l'Institut des Sciences et Techniques, Dande, Burkina Faso; the Kenya Medical Research Institute Centre for Geographical Medicine Research–Coastt, Kilifi, Kenya; and the Ifakara Health Institute, Bagamoyo, Tanzania). These centres were chosen to ensure that vaccine assessment took place in areas of high and low, and both perennial and seasonal, malaria transmission across sub-Saharan Africa.

The study planned to enrol 4800 participants across all sites, with 1200 per site, except for Kilifi and Bagamoyo with 600 per site, which were combined for adequate statistical power as East Africa in the main analysis of site-specific efficacy. The primary series of vaccinations consisted of three vaccinations, 4 weeks apart, followed by a booster vaccination approximately 12 months after the third vaccination. At the seasonal sites, the primary series of vaccinations were administered before the malaria season, with the booster vaccination administered 12 months later and before the subsequent malaria season. At the standard sites, the primary series was administered at any time of year, with the booster vaccination administered 12 months later.

Safety, immunogenicity, and vaccine efficacy are being assessed over 24 months, with the primary efficacy endpoint assessed at 12 months after the primary series of vaccinations. This involves collection of solicited adverse events across 7 days after vaccination and blood sampling at prespecified timepoints. Data were collected on indoor residual spraying, adequate insecticide-treated net use (categorised by the presence or absence of holes), and the number of rounds and doses of seasonal malaria chemoprevention taken by the participant during the malaria season in areas where this is recommended policy.

Lists of eligible children were identified from local surveillance databases and community sensitisation. Caregivers who expressed interest were invited to a screening visit. Before screening, parents or guardians of participants provided written or thumb-printed consent, which was verbally re-checked at every study visit. The following inclusion criteria were used: participants aged 5–36 months at the time of their first vaccination, signed and witnessed informed consent was obtained from the parent or guardian, the investigator believed that the parents or guardians can and will comply with the requirements of the protocol if the child is enrolled in the study, and the participant remained in the study area for the duration of the trial. Exclusion criteria included substantial comorbidities and receipt of another malaria vaccine. Full details of the eligibility criteria can be found in the protocol (appendix pp 87–174). There was a minimum 2-week interval between administration of the study vaccine and any Expanded Programme on Immunisation vaccine. The trial was approved by all the local ethics committees and regulatory authorities, as well as the ethics committees at the University of Oxford (Oxford, UK) and The London School of Hygiene & Tropical Medicine (London, UK), with supportive coordination by the African Vaccine Regulatory Forum. Further details are in the appendix (p 13).

### Randomisation and masking

Children aged 5–36 months who fulfilled the eligibility criteria were randomly assigned (2:1) to receive vaccinations with R21/Matrix-M or a licensed rabies vaccine (Abhayrab), respectively. For the booster vaccination at 12 months, participants received the same vaccine.

Randomisation was done using an electronic interactive web response system (DiagnoSearch Life, Thane, India). Randomisation was stratified by trial site (seasonal or standard), and potential confounders, including age (5–12 months, 13–24 months, or 25–36 months) and sex (male or female), using block randomisation with variable block sizes.

Malaria and control vaccines were prepared by the pharmacists using the same type of syringe, the same volume, and they were the same colour and consistency. The contents of the syringe were masked with an opaque label. The trial was double-blinded: participants, their families, all investigators, the laboratory teams, and the local study team were all masked to treatment.

### Procedures

Participants received R21 (Serum Institute of India) as a two-vial formulation: R21 was mixed immediately before administration with the saponin-based vaccine adjuvant Matrix-M (Novavax AB, Uppsala, Sweden). A dose of 5 µg R21 with 50 µg Matrix-M was used in the trial. A licensed rabies vaccine (Abhayrab; Indian Immunologicals, Hyderabad, India) was the control vaccine.

All vaccines were administered as a 0·5 mL dose intramuscularly into the thigh or deltoid muscle.

On the day of vaccination, if any participant had a fever of 37·5 degrees C or higher, vaccination was deferred and they were assessed clinically and appropriately managed. If a blood film was indicated and was positive for *Plasmodium* spp, the participant was treated for malaria in accordance with local guidelines before having a study vaccination.

Serious adverse events and adverse events of special interest are being collected for the duration of the trial in all participants. All unsolicited adverse events were collected across 28 days after each vaccination in all participants. Clinical judgement by masked site study clinicians was used to assess causality of adverse events and any association with vaccine.

Additional safety data were collected in the first 50% of participants enrolled at each trial site. These data included local and systemic solicited adverse events collected over 7 days after each vaccination and safety laboratory values measured at 28 days after third vaccination and booster vaccination, to look for clinically significant deviations from baseline.

Intensity of symptoms was evaluated using standardised methods (appendix pp 160–161) and all adverse events were monitored until resolution.

After the third vaccination, participants were visited by field workers approximately every 8 weeks until 12 months after the third vaccination. During these visits, the participants' caregivers were asked whether any medical event that might be a serious adverse event had occurred since the last visit and this information was recorded. If clinical assessment was required, the participant was referred to the trial site clinic or the nearest community health facility. A detailed schedule of visits is in the protocol (appendix pp 136–137).

Interim analyses were performed to facilitate data safety monitoring board reviews after completion of the primary series of three vaccinations. Further reviews were held after administration of the booster vaccinations. The data safety monitoring board were also provided with reports of serious adverse events when they occurred as well as monthly line listings.

Caregivers of participants were advised to attend their local community health facility for clinical review if their child had any illness or a temperature (≥37·5°C), or history of fever within the last 24 h, to enable assessment for malaria and blood film microscopy to detect *Plasmodium* spp. Two independent microscopists at each site, who were masked to the vaccination status of all participants, analysed each blood film, with a third microscopist adjudicating in cases of disagreement. The primary case definition of clinical malaria was the presence of an axillary temperature (≥37·5°C), or history of fever within the past 24 h, and *P falciparum* asexual parasite density of more than 5000 parasites per µL of blood using passive case detection. The secondary case definitions of clinical malaria were presence of an axillary temperature (≥37·5°C), or history of fever during the past 24 h, and *P falciparum* parasite density of more than 0 parasites per µL or *P falciparum* parasite density of more than 2500 parasites per µL.

IgG antibodies against a polypeptide of six repeats of the central NANP region sequence were measured in the first 50% of participants enrolled at each trial site by a validated ELISA using electrochemiluminescence as a detection technique (Meso Scale Discovery; Rockville, MD, USA). Samples were analysed before the first vaccination, at 28 days after third vaccination, 12 months after the third vaccination, and 28 days after the booster dose.

### Outcomes

The primary objective assessed protective efficacy of R21/Matrix-M from 14 days after third vaccination to 12 months after completion of the primary series at seasonal and standard sites separately as co-primary endpoints.

Safety and reactogenicity of R21/Matrix-M were also assessed according to either vaccination regimen (seasonal or standard) in the month after each vaccination.

Secondary objectives were efficacy of R21/Matrix-M at all sites combined, after booster vaccinations, against multiple malaria episodes, against severe malaria, incident severe anaemia, malaria-related hospital admission, and asymptomatic *P falciparum* infection. Cross-sectional asymptomatic *P falciparum* infection, defined as the presence of axillary temperature of less than 37·5°C, absence of history of fever within the last 24 h, and *P falciparum* parasite density of more than 0 parasites per µL, was analysed at 12 months (all sites) and 18 months (seasonal sites). Severe malaria case definitions were similar to the clinical malaria case definitions, with the addition of specified criteria of disease severity (definitions are detailed in the protocol; appendix pp 151–152).

Humoral immunogenicity of R21/Matrix-M was evaluated by measuring antibody titres to the central NANP repeat.

Further details of all outcomes can be found in the protocol and statistical analysis plan (appendix pp 59–85).

### Statistical analysis

The total sample size was determined by the objective of providing safety data for at least 3000 participants in the malaria vaccine (R21/Matrix-M) group: 3200 were enrolled alongside 1600 control participants. Half of these participants were recruited in the two seasonal sites and half in the three standard sites.

At the seasonal sites, the expected incidence rate was 0·58 cases per child per year among the 800 control participants which, with 12 months' follow-up, would give more than 95% power to exclude a lower limit of efficacy of 30% if the vaccine efficacy was at least 50%. At the standard sites, the expected incidence rate was 0·28 cases per child per year among the 800 control participants which, with 12 months' follow-up, would give 84% power to exclude a lower limit of efficacy of 30% if the vaccine efficacy was at least 50%.

Primary analyses of vaccine efficacy were based on 12 months of follow-up, and a modified per-protocol population, which included all participants who received three doses of the correct vaccine with an interval between the first and second doses of 3–6 weeks, and the interval between the second and third doses of 3–16 weeks. The longer interval between the second and third vaccine was due to a temporary pause at the Dande site, between November 2021 and January 2022, while clarifications took place with the national regulatory authority in Burkina Faso, causing a delay in administering the third

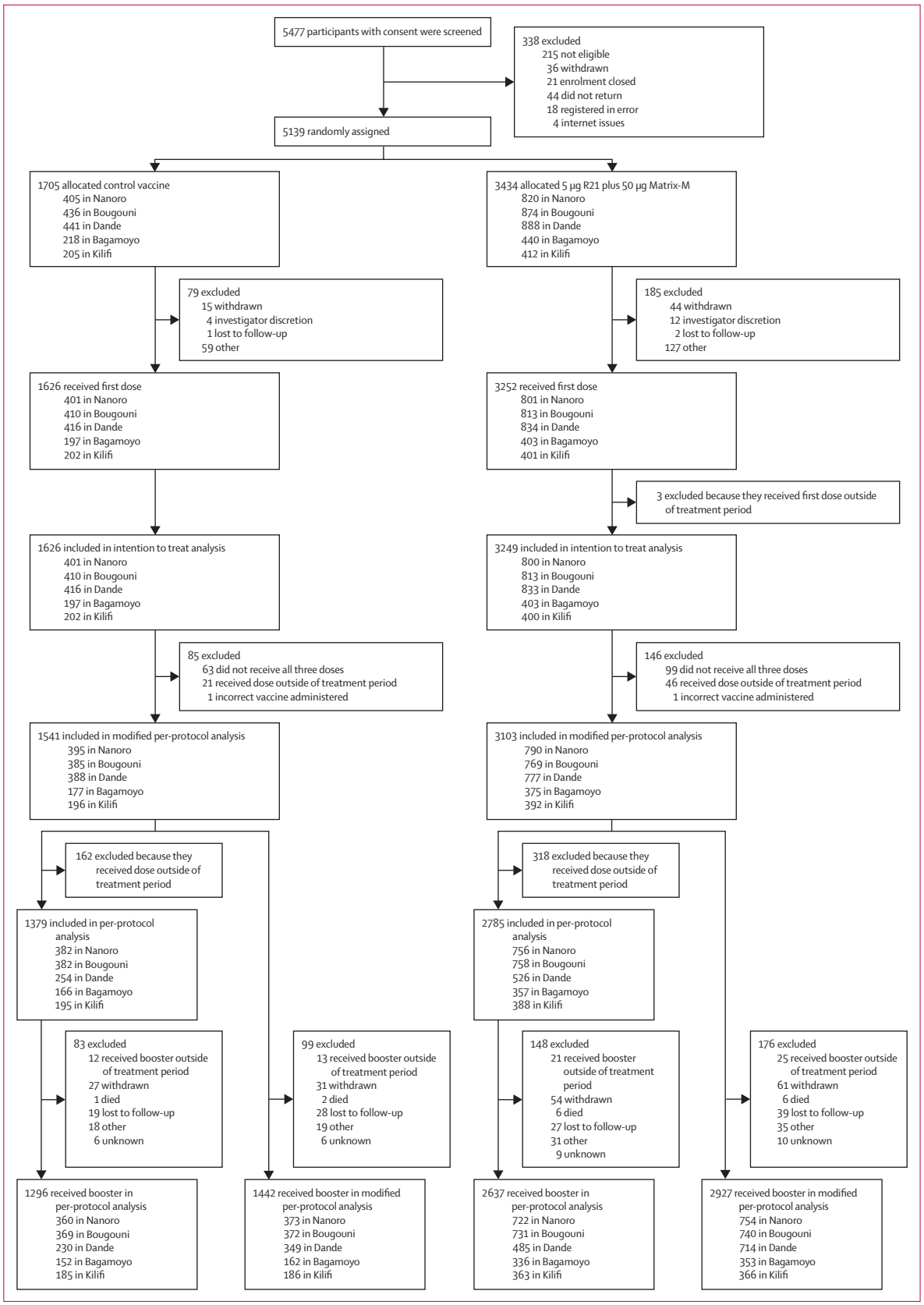


***Figure 1:*** **Trial profile**
Participants were aged 5–36 months at enrolment. Enrolment was the day of first vaccination. 4800 participants (±4%) was the target enrolment number. The first 50% of participants enrolled at each site underwent additional safety and immunogenicity monitoring.

dose. Analyses on a per-protocol and a modified intention-to-treat population are presented in the appendix (pp 17–49). The per-protocol population were as the modified per-protocol population except the third vaccine must have been received between 3–6 weeks after the second vaccine. The modified intention-to-treat population included all participants regardless of which vaccine they received, as long as they received at least one dose of a study vaccine in the first year of the study. At seasonal sites, follow-up reached 18 months (6 months after booster) for all participants, and analyses at both 18 months and from 13–18 months (6 months after booster) are presented.

For analyses of clinical malaria in the modified per-protocol and per-protocol populations, follow-up started 14 days after the third vaccination and finished at 12 months' follow-up, when the booster was given, or the date of study withdrawal, whichever occurred first. For the modified intention-to-treat analysis, follow-up started 14 days after the final primary series vaccination was received and finished with the same criteria applied to the modified per-protocol population. The primary analysis was time to first episode of clinical malaria and was analysed by Cox regression stratified by study site (seasonal or standard). A secondary analysis of rate of all (multiple) clinical malaria episodes was analysed by Cox regression, with a robust standard error to account for multiple episodes in the same child. Analyses adjusted for confounding factors of sex (male or female), age at randomisation (5–12 months, 13–24 months, and 25–36 months), number of rounds of seasonal malaria chemoprevention (1, 2, 3, and 4 or more), and bed net use (adequate or not) were carried out.

Vaccine efficacy was calculated as 1 minus the hazard ratio (HR). Kaplan-Meier graphs of time to first malaria episode and Nelson-Aalen plots of cumulative hazard of all malaria episodes were presented. Analyses stratified by study site and by age are presented.

Vaccine efficacy against severe malaria was estimated in the same way. Asymptomatic malaria infection at 12 months and 18 months were analysed using a log binomial model, including the randomised group as a covariate. This analysis was also done adjusting for the confounding factors previously described. To assess whether vaccine efficacy waned over the course of 12 months and according to seasonal or standard vaccine administration, a post-hoc efficacy analysis in 3-month periods at seasonal and standard sites was performed.

To maintain masking for the ongoing follow-up, analyses were performed by statisticians external to the clinical trial teams.

All statistical analyses were performed using Stata version 17. This study is registered on ClinicalTrials.gov, NCT04704830.

| | R21/Matrix-M (n=3103) | Control (n=1541) | Total (N=4644) |
|---|---|---|---|
| Sex | | | |
| Male | 1607/3103 (51·8%) | 805/1541 (52·2%) | 2412/4644 (51·9%) |
| Female | 1496/3103 (48·2%) | 736/1541 (47·8%) | 2232/4644 (48·1%) |
| Age, months | 19·1 (9·0) | 18·9 (9·0) | 19 (9·0) |
| Weight, kg | 9·7 (2·0) | 9·6 (2·1) | 9·7 (2·0) |
| Weight for age* | | | |
| Normal (WAZ>–2) | 2634/3102 (84·9%) | 1292/1538 (84·0%) | 3926/4640 (84·6%) |
| Underweight (WAZ–3 to –2) | 413/3102 (13·3%) | 202/1538 (13·1%) | 615/4640 (13·3%) |
| Severely underweight (WAZ<–3) | 55/3102 (1·7%) | 44/1538 (2·9%) | 99/4640 (2·1%) |
| Use of bed net at day 70* | | | |
| No adequate bed net | 92/3096 (2·9%) | 52/1535 (3·4%) | 144/4631 (3·1%) |
| Adequate bed net | 3006/3096 (97·1%) | 1483/1535 (96·6%) | 4489/4631 (96·9%) |
| Number of rounds of seasonal malaria chemoprevention in 2021 | | | |
| Not eligible for seasonal malaria chemoprevention | 767/3103 (24·7%) | 373/1541 (24·2%) | 1140/4644 (24·6%) |
| 0 | 68/3103 (2·2%) | 38/1541 (2·5%) | 106/4644 (2·3%) |
| 1 | 430/3103 (13·9%) | 201/1541 (13%) | 631/4644 (13·6%) |
| 2 | 357/3103 (11·5%) | 166/1541 (10·8%) | 523/4644 (11·3%) |
| 3 | 354/3103 (11·4%) | 214/1541 (13·9%) | 568/4644 (12·2%) |
| 4+ | 1127/3103 (36·3%) | 549/1541 (35·6%) | 1676/4644 (36·1%) |

Data are n/N (%) or mean (SD). All participants received three vaccinations, 4 weeks apart as part of the primary series of vaccinations. Day 70 is the timepoint that insecticide-treated net use is assessed, which corresponds to 14 days after the third vaccine (when efficacy follow-up time begins). Adequate use refers to no holes being present. A round of seasonal malaria chemoprevention is three doses of treatment received per month during the malaria season. Seasonal malaria chemoprevention was only administered in areas where it is policy and standard of care (Nanoro, Bougouni, and Dande). WAZ= Weight-for-age Z-score. *Denominators differ due to missing data.

***Table 1:*** **Baseline characteristics of participants in the modified per-protocol population**


### Role of the funding source

Serum Institute of India, the major study funder, reviewed the data from the study and the final manuscript before submission, but the academic authors retained editorial control. The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.


## Results

From April 14, 2021, to Jan 12, 2022, 5477 children aged 5–36 months consented to be screened, of whom 5139 were randomly assigned to control vaccine (n=1705) or R21/Matrix-M (n=3434; figure 1; appendix pp 14–15). 3252 participants in the R21/Matrix-M group and 1626 in the control group received the first dose, and 3103 participants in the R21/Matrix-M group and 1541 in the control group were included in the modified per-protocol analysis. The median follow-up time for the modified per-protocol population, from 14 days after the third dose of the primary series to 12 months, was 351 (IQR 345–351) days (appendix p 16). Baseline characteristics between the R21/Matrix-M group and control group were similar (table 1), with most participants using insecticide-treated nets and receiving at least one round of seasonal malaria chemoprevention where this is national policy (Bougouni, Dande, and Nanoro). The participant retention rate was high (97%) at 12 months across all sites (appendix p 17).

In the modified per-protocol population, when evaluating the primary objective at the seasonal sites, 708 participants had an episode of clinical malaria according to the primary case definition, compared with 383 participants at the standard sites. Comparing the malaria vaccine group with the control group, vaccine efficacy was 75% (95% CI 71–79; p<0·0001) at the seasonal sites and 68% (61–74; p<0·0001) at the standard sites (figure 2; table 2). Efficacy estimates from the per-protocol and modified intention-to-treat analyses were similar (data not shown).

At the Dande site, when evaluating the difference in efficacy between those who had a 3–6 week interval and those who had a 7–16 week interval between the second and third dose, there was no significant difference in vaccine efficacy (p=0·97; appendix p 18). Over 12 months, there was a rate reduction of 868 (95% CI 762–974) cases per 1000 child-years at the seasonal sites and 296 (231–362) cases per 1000 child-years at the standard sites, with the larger number of cases averted at seasonal sites reflecting a much higher incidence of malaria (appendix p 19).

Combining all the sites, 1091 participants had an episode of clinical malaria according to the primary case definition. These cases were in 464 (15·0%) of 3102 participants in the R21/Matrix-M group and 627 (40·7%) of 1541 participants in the control group. Overall, vaccine efficacy was 73% (95% CI 70–76; p<0·0001; figure 2; table 2) and total cases averted over 12 months was 583 (95% CI 520–647; appendix p 19).

When considering multiple episodes of malaria, similar estimates of vaccine efficacy were shown: 75% (95% CI 71–78; p<0·0001) at the seasonal sites and 67% (59–73; p<0·0001) at the standard sites. Across all sites, vaccine efficacy against multiple episodes of malaria was 72% (69–75; p<0·0001; table 2; appendix p 21).

To assess whether vaccine efficacy waned over the course of 12 months and whether there was a difference according to seasonal or standard vaccine administration, a post-hoc efficacy analysis in 3-month periods at seasonal and standard sites was done. Efficacy declined over the first year, from 80% (95% CI 76–84) in months 1–3 to 67% (55–76) in months 10–12 in the seasonal sites, and from 79% (64–87) to 63% (50–73) for the same periods in the standard sites (table 3; appendix p 25). There was a decrease in efficacy over time in seasonal (p<0·0001) and standard sites (p=0·037), but there was no significant difference in rates of decline between the seasonal and standard sites (p=0·53).

The target age group for malaria vaccine field efficacy trials has generally been children aged 5–17 months. When measuring the time to first malaria episode in this trial and dividing all the participants into two age groups of 5–17 months and 18–36 months, vaccine efficacy was significantly higher in the younger age group (78% [95% CI 73–82]) than in the older age group (70% [64–74]; p=0·024; appendix p 26). This finding was observed in both seasonal and standard sites: in the seasonal sites, vaccine efficacy in children aged 5–17 months was 79% (95% CI 73–84) and, at standard sites, this efficacy was 75% (65–83). There was also no evidence that vaccine efficacy was different in children aged 5–8 months compared with those aged 9–17 months (p=0·80; appendix pp 28–36).

When assessing the primary objective according to the secondary case definition, which included clinical malaria cases with a parasitaemia of more than 0 parasites per µL, vaccine efficacy was similar to that with the primary case definition: 74% (95% CI 70–78; p<0·0001) at the seasonal sites, 66% (59–72; p<0·0001) at the standard sites, and 72% (68–75; p<0·0001; appendix p 37) across all sites.

All participants received a booster dose of the same vaccine administered as their primary series at 12 months after their third vaccine. When evaluating the time to first clinical malaria episode at 18 months after the primary series of vaccinations, according to the primary

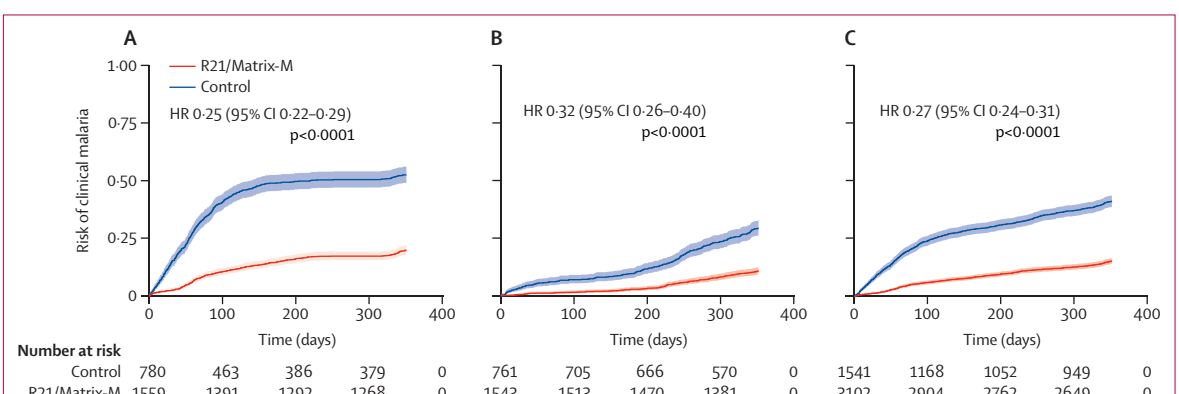


*Figure 2:* **Kaplan-Meier estimates of the time to first episode of clinical malaria in the modified per-protocol population at seasonal sites (A), standard sites (B), and all sites (C)**

Data begin from 14 days after the third vaccination in the primary series to 12 months. Seasonal sites were Bougouni and Nanoro; and standard sites were Dande and the East Africa sites Bagamoyo and Kilifi.

| | Number of participants | Participants with 0 episodes | Participants with 1 episode | Participants with 2 episodes | Participants with 3+ episodes | Rate (events/child-years) | Unadjusted vaccine efficacy (95% CI) | p value | Adjusted* vaccine efficacy (95% CI) | p value |
|---|---|---|---|---|---|---|---|---|---|---|
| **Time to first clinical malaria episode** | | | | | | | | | | |
| All sites | | | | | | | | | | |
| Control | 1541 | .. | .. | .. | .. | 0·59 (627/1061·2) | 1 (ref) | .. | 1 (ref) | .. |
| R21/Matrix-M | 3102 | .. | .. | .. | .. | 0·17 (464/2681·4) | 0·73 (0·69–0·76) | <0·0001 | 0·73 (0·70–0·76) | <0·0001 |
| Seasonal sites | | | | | | | | | | |
| Control | 780 | .. | .. | .. | .. | 0·95 (407/428·4) | 1 (ref) | .. | 1 (ref) | .. |
| R21/Matrix-M | 1559 | .. | .. | .. | .. | 0·24 (301/1275·4) | 0·75 (0·71–0·78) | <0·0001 | 0·75 (0·71–0·79) | <0·0001 |
| Standard sites | | | | | | | | | | |
| Control | 761 | .. | .. | .. | .. | 0·35 (220/632·8) | 1 (ref) | .. | 1 (ref) | .. |
| R21/Matrix-M | 1543 | .. | .. | .. | .. | 0·12 (163/1406·0) | 0·68 (0·60–0·74) | <0·0001 | 0·68 (0·61–0·74) | <0·0001 |
| Nanoro site | | | | | | | | | | |
| Control | 395 | .. | .. | .. | .. | 1·70 (275/161·8) | 1 (ref) | .. | 1 (ref) | .. |
| R21/Matrix-M | 790 | .. | .. | .. | .. | 0·40 (239/598·9) | 0·73 (0·68–0·77) | <0·0001 | 0·73 (0·68–0·78) | <0·0001 |
| Bougouni site | | | | | | | | | | |
| Control | 385 | .. | .. | .. | .. | 0·50 (132/266·6) | 1 (ref) | .. | 1 (ref) | .. |
| R21/Matrix-M | 769 | .. | .. | .. | .. | 0·09 (62/676·5) | 0·80 (0·73–0·85) | <0·0001 | 0·80 (0·73–0·85) | <0·0001 |
| Dande site | | | | | | | | | | |
| Control | 388 | .. | .. | .. | .. | 0·44 (139/313·9) | 1 (ref) | .. | 1 (ref) | .. |
| R21/Matrix-M | 776 | .. | .. | .. | .. | 0·12 (84/717·9) | 0·74 (0·66–0·80) | <0·0001 | 0·74 (0·66–0·80) | <0·0001 |
| Bagamoyo site | | | | | | | | | | |
| Control | 177 | .. | .. | .. | .. | 0·24 (36/150·4) | 1 (ref) | .. | 1 (ref) | .. |
| R21/Matrix-M | 375 | .. | .. | .. | .. | 0·12 (40/335·9) | 0·52 (0·24–0·69) | 0·0016 | 0·53 (0·25–0·70) | 0·0013 |
| Kilifi site | | | | | | | | | | |
| Control | 196 | .. | .. | .. | .. | 0·27 (45/168·5) | 1 (ref) | .. | 1 (ref) | .. |
| R21/Matrix-M | 392 | .. | .. | .. | .. | 0·11 (39/352·2) | 0·59 (0·37–0·73) | <0·0001 | 0·60 (0·39–0·74) | <0·0001 |
| Eastern African sites (Bagamoyo and Kilifi) | | | | | | | | | | |
| Control | 373 | .. | .. | .. | .. | 0·25 (81/318.9) | 1 (ref) | .. | 1 (ref) | .. |
| R21/Matrix-M | 767 | .. | .. | .. | .. | 0·11 (79/688·1) | 0·56 (0·40– 0·68) | <0·0001 | 0·57 (0·41– 0·68) | <0·0001 |
| **Time to all clinical malaria episodes** | | | | | | | | | | |
| All sites | | | | | | | | | | |
| Control | 1541 | 914 (59·3%) | 341 (22·1%) | 139 (9·0%) | 147 (9·5%) | 0·81 (1174/1455·1) | 1 | .. | 1 | .. |
| R21/Matrix-M | 3102 | 2639 (85·1) | 335 (10·8%) | 88 (2·8%) | 41 (1·3%) | 0·22 (652/2922·4) | 0·72 (0·69–0·75) | <0·0001 | 0·72 (0·69–0·75) | <0·0001 |
| Seasonal sites | | | | | | | | | | |
| Control | 780 | 373 (47·8%) | 184 (23·6%) | 101 (12·9%) | 122 (15·6%) | 1·16 (852/731·5) | 1 | .. | 1 | .. |
| R21/Matrix-M | 1559 | 1258 (80·7%) | 211 (13·5%) | 60 (3·8%) | 30 (1·9%) | 0·30 (435/1460·0) | 0·74 (0·71–0·78) | <0·0001 | 0·75 (0·71–0·78) | <0·0001 |
| Standard sites | | | | | | | | | | |
| Control | 761 | 541 (71·1%) | 157 (20·6%) | 38 (5·0%) | 25 (3·3%) | 0·45 (322/723·5) | 1 | .. | 1 | .. |
| R21/Matrix-M | 1543 | 1381 (89·4%) | 124 (8·0%) | 28 (1·8%) | 11 (0·7%) | 0·15 (217/1462·4) | 0·67 (0·59–0·73) | <0·0001 | 0·67 (0·59–0·73) | <0·0001 |
| Nanoro site | | | | | | | | | | |
| Control | 395 | 120 (30·4%) | 100 (25·3%) | 73 (18·5%) | 102 (25·8%) | 1·73 (642/371·3) | 1 | .. | 1 | .. |
| R21/Matrix-M | 790 | 551 (69·7%) | 161 (20·4%) | 49 (6·2%) | 29 (3·7%) | 0·48 (360/744·3) | 0·72 (0·67–0·76) | <0·0001 | 0·72 (0·67–0·76) | <0·0001 |
| Bougouni site | | | | | | | | | | |
| Control | 385 | 253 (65·7%) | 84 (21·8%) | 28 (7·3%) | 20 (5·2%) | 0·58 (210/360·2) | 1 | .. | 1 | .. |
| R21/Matrix-M | 769 | 707 (91·9%) | 50 (6·5%) | 11 (1·4%) | 1 (0·1%) | 0·10 (75/715·7) | 0·82 (0·76–0·87) | <0·0001 | 0·82 (0·75–0·86) | <0·0001 |
| Dande site | | | | | | | | | | |
| Control | 388 | 249 (64·2%) | 102 (26·3%) | 24 (6·2%) | 13 (3·4%) | 0·53 (195/371·3) | 1 | .. | 1 | .. |
| R21/Matrix-M | 776 | 693 (89·2%) | 71 (9·1%) | 9 (1·2%) | 4 (0·5%) | 0·14 (103/742·0) | 0·74 (0·65–0·80) | <0·0001 | 0·73 (0·65–0·80) | <0·0001 |
| Bagamoyo site | | | | | | | | | | |
| Control | 177 | 141 (79·7%) | 25 (14·1%) | 4 (2·3%) | 7 (4·0%) | 0·35 (58/167·3) | 1 | .. | 1 | .. |
| R21/Matrix-M | 375 | 335 (89·3%) | 27 (7·2%) | 11 (2·9%) | 2 (0·5%) | 0·16 (56/354·5) | 0·54 (0·26–0·72) | 0·0016 | 0·54 (0·26–0·71) | 0·0014 |

(Table 2 continues on next page)

| | Number of participants | Participants with 0 episodes | Participants with 1 episode | Participants with 2 episodes | Participants with 3+ episodes | Rate (events/child-years) | Unadjusted vaccine efficacy (95% CI) | p value | Adjusted* vaccine efficacy (95% CI) | p value |
|---|---|---|---|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | | | | | |
| Kilifi site | | | | | | | | | | |
| Control | 196 | 151 (77·0%) | 30 (15·3%) | 10 (5·1%) | 5 (2·6%) | 0·37 (69/185·0) | 1 | .. | 1 | .. |
| R21/Matrix-M | 392 | 353 (90·1%) | 26 (6·6%) | 8 (2·0%) | 5 (1·3%) | 0·16 (58/365·8) | 0·57 (0·32–0·73) | 0·0003 | 0·58 (0·34–0·73) | 0·0002 |
| East African sites (Bagamoyo and Kilifi) | | | | | | | | | | |
| Control | 373 | 292 (78·3%) | 55 (14·7%) | 14 (3·8%) | 12 (3·2%) | 0·36 (127/352·2) | 1 | .. | 1 | .. |
| R21/Matrix-M | 767 | 688 (89·7%) | 53 (6·9%) | 19 (2·5%) | 7 (0·9%) | 0·16 (114/720·3) | 0·56 (0·39–0·68) | <0·0001 | 0·56 (0·39–0·68) | <0·0001 |

The primary case definition was the presence of an axillary temperature ≥37·5°C, or history of fever within the last 24 h, and *Plasmodium falciparum* asexual parasite density >5000 parasites per µL. Events refers to episode of clinical malaria according to primary case definition. Vaccine efficacy (calculated as 1– hazard ratio) is reported as a decimal proportion of 1·0, so 75% efficacy is reported as 0·75. *Adjusting for age at randomisation (5–12 months, 13–24 months, and 25–36 months), sex, bed net use, and number of seasonal malaria chemoprevention rounds received in 2021.

***Table 2:*** **Time to first malaria episode and all clinical malaria episodes according to the primary case definition from 14 days after the third vaccination to 12 months in the modified per-protocol population**

| | Control (events/child-years) | R21/Matrix-M (events/child-years) | Vaccine efficacy (95% CI) | p value | Age-adjusted vaccine efficacy (95% CI) | p value |
|---|---|---|---|---|---|---|
| **Seasonal sites** | | | | | | |
| 1–3 months | 2·37 (461/194·6) | 0·47 (181/388·9) | 0·80 (0·76–0·84) | <0·0001 | 0·80 (0·76–0·84) | <0·0001 |
| 4–6 months | 1·21 (235/194·2) | 0·31 (121/387·5) | 0·74 (0·67–0·80) | <0·0001 | 0·74 (0·67–0·80) | <0·0001 |
| 7–9 months | 0·35 (68/192·6) | 0·20 (75/384·2) | 0·45 (0·21–0·62) | 0·0012 | 0·45 (0·21–0·61) | 0·0014 |
| 10–12 months | 0·59 (88/150·1) | 0·19 (58/299·4) | 0·67 (0·55–0·76) | <0·0001 | 0·67 (0·55–0·76) | <0·0001 |
| **Standard sites** | | | | | | |
| 1–3 months | 0·29 (55/189·8) | 0·06 (24/384·4) | 0·79 (0·64–0·87) | <0·0001 | 0·79 (0·64–0·87) | <0·0001 |
| 4–6 months | 0·18 (35/189·3) | 0·06 (23/382·8) | 0·68 (0·44–0·82) | 0·0001 | 0·68 (0·44–0·82) | 0·0001 |
| 7–9 months | 0·59 (111/188·0) | 0·21 (80/378·1) | 0·64 (0·50–0·74) | <0·0001 | 0·64 (0·51–0·74) | <0·0001 |
| 10–12 months | 0·77 (121/156·5) | 0·28 (90/317·0) | 0·63 (0·50–0·73) | <0·0001 | 0·63 (0·50–0·73) | <0·0001 |

No significant difference in rate of change in vaccine efficacy over 12 months occurred between seasonal and standard sites (p=0·529). Events refers to episode of clinical malaria according to primary case definition. Vaccine efficacy is reported as a decimal proportion of 1·0, so 75% efficacy is reported as 0·75.

***Table 3:*** **Incidence per child-years at risk and vaccine efficacy of all episodes of clinical malaria according to the primary case definition after vaccination with three doses by 3-month study periods in the modified per-protocol population**

case definition, vaccine efficacy was 74% (95% CI 70–77; p<0·0001) at the seasonal sites. Vaccine efficacy was 72% (95% CI 68–75; p<0·0001) against multiple clinical malaria episodes (appendix pp 38–40). Over 6 months after the booster, vaccine efficacy was 75% (95% CI 71–79; p<0·0001) for the first clinical malaria episode and 70% (66–73; p<0·0001) for multiple clinical malaria episodes at the seasonal sites (appendix pp 41–43).

At 12 months, in the modified per-protocol population, there had been only 12 episodes of severe malaria (five cases at the seasonal sites and seven cases at the standard sites) according to the primary case definition, resulting in insufficient power to assess vaccine efficacy against severe malaria. Vaccine efficacy against severe malaria was 67% (95% CI –4 to 90; p=0·058; appendix p 44). Seven more cases occurred at the seasonal sites by the 18-month timepoint, and there was an 18-month vaccine efficacy of 65% (–10 to 89; p=0·073; appendix p 45). Similarly, there was insufficient power to show significant vaccine efficacy against severe anaemia and malaria hospitalisations (appendix pp 46–47).

Cross-sectional blood films at 12 months after the primary series showed asymptomatic parasitaemia that was significantly higher in the control group, with 73 (5·1%) of 1436 participants having parasitaemia without fever, compared with 73 (2·5%) of 2917 participants in the R21/Matrix-M group (p<0·0001). At 18 months at the seasonal sites, 32 (4·4%) of 718 participants in the control group had asymptomatic parasitaemia compared with 29 (2·0%) of 1444 participants in the R21/Matrix-M group (p=0·0014, appendix p 48).

The R21/Matrix-M vaccine, when given as the primary series with a booster vaccination, showed a significantly higher number of local and systemic solicited adverse events within 7 days of vaccinations compared with the control vaccine (p<0·0001). However, severe adverse events were uncommon and most adverse events resolved within 48–72 h. Pain was the most common solicited local adverse event (301 [18·6%] of 1615 participants in the R21/Matrix-M group and 88 [11·0%] of 802 participants in the control group experiencing at least one event) and fever the most

common systemic adverse event (754 [46·7%] of 1615 participants in the R21/Matrix-M group and 201 [25·1%] of 802 participants in the control group experiencing at least one event) with both groups (appendix pp 50–51). The number of unsolicited adverse events were comparable between both vaccine groups, as well as according to sex and age distribution (appendix p 52). There were fewer adverse events after the booster vaccination.

141 serious adverse events in 129 participants were reported, with six of these being assessed as possibly, probably, or definitely related to vaccination (appendix p 53). These six events were all febrile convulsions occurring within 2 days of a vaccination. Four of these events occurred during the primary series of vaccinations and two of these were after the booster vaccination. Five of these febrile convulsions were in the R21/Matrix-M group and one was in the control group, all within 7 days of a vaccination (p=0·67). The number of participants who had serious adverse events in the 5–17 month age group and the 18–36 month age group were similar between the two vaccine groups; however, the overall number of participants who had serious adverse events decreased as age increased (table 4). Sex distribution of those who had serious adverse events was similar between the two different groups, with 77 male participants and 64 female participants reporting a serious adverse event. There was no significant difference in the number of deaths between the malaria vaccine and control group (appendix p 53), with 11 deaths reported in male participants and eight in female participants. There was insufficient power to assess vaccine efficacy against mortality. No deaths were considered related to study vaccinations.

| | Seasonal sites | | Standard sites | | Total sites | |
|---|---|---|---|---|---|---|
| | R21/Matrix-M | Control | R21/Matrix-M | Control | R21/Matrix-M | Control |
| **5–17 month age group** | | | | | | |
| Total population | 788 | 399 | 722 | 372 | 1510 | 771 |
| At least one serious adverse event | 28 (3·6%) | 11 (2·8%) | 29 (4·0%) | 12 (3·2%) | 57 (3·8%) | 23 (3·0%) |
| At least one serious adverse event excluding malaria | 25 (3·2%) | 10 (2·5%) | 27 (3·7%) | 11 (3·0%) | 52 (3·4%) | 21 (2·7%) |
| **18–36 month age group** | | | | | | |
| Total population | 826 | 412 | 916 | 443 | 1742 | 855 |
| At least one serious adverse event | 11 (1·3%) | 8 (1·9%) | 20 (2·2%) | 10 (2·3%) | 31 (1·8%) | 18 (2·1%) |
| At least one serious adverse event excluding malaria | 9 (1·1%) | 6 (1·5%) | 16 (1·7%) | 7 (1·6%) | 25 (1·4%) | 13 (1·5%) |

*Table 4:* **Serious adverse events in the modified intention-to treat population (any participant who received a dose)**

In total, 20 adverse events of special interest were reported over the course of the study to date. These were 16 febrile convulsions, two cases of meningitis, and two cases of cerebral malaria. Both cases of meningitis were in the R21/Matrix-M group and there was one case of cerebral malaria in each group. Six of these 20 adverse events of special interest (all febrile convulsions) were considered likely related to study vaccines (appendix p 53).

NANP-specific IgG was measured in 1456 participants 28 days after their third dose of R21/Matrix-M vaccine. Higher antibody titres were observed at seasonal sites compared with standard sites (p<0·0001; appendix pp 54–55). There were significantly higher antibody titres in the 5–17 month age group compared with the 18–36 month age group (p<0·0001, appendix pp 55–57) at this timepoint, consistent with the higher efficacy observed in the 5–17 month age group. When dividing antibody responses into tertiles, there was a significantly reduced risk of clinical malaria over 12 months in the upper two tertiles compared with the lower tertile across all sites and in the seasonal sites assessed alone (appendix p 58).

## Discussion

In this phase 3 licensure trial of the R21/Matrix-M malaria vaccine, the primary analysis shows vaccine efficacy against clinical malaria of 75% (72–79) at seasonal sites and 67% (59–73) at standard sites across the entire cohort aged 5–36 months over 12 months. There was no significant difference in efficacy between seasonal and standard sites. As expected, malaria incidence was much higher at the seasonal sites, particularly at the Nanoro site in Burkina Faso.

When analysing efficacy in 3-month periods over the first 12 months, there was a decline in efficacy, but it remained at over 60% in the final quarter in both settings. The rate of efficacy decline did not significantly differ between seasonal and standard sites.

This phase 3 trial differs from all previous malaria vaccine trials by evaluating the 5–36 month age group rather than just the 5–17 month age group, despite malaria vaccines likely being deployed preferentially in infants, to offer protection before the peak incidence of malaria deaths at one year of age. In the 5–17 month age group, efficacy was, interestingly, significantly higher compared with that in the 18–36 month age group at seasonal and standard sites, respectively. The mechanism of this age effect is unclear, but NANP-specific IgG responses, which correlate with vaccine efficacy, were significantly higher in the younger age group. Further work will be required to better determine the effect of age at first immunisation on efficacy, and to identify and understand other immunological correlates of efficacy, including antibody avidity measures.

Our findings are consistent with data from a recently completed phase 2b trial at the Nanoro seasonal site,

where vaccine efficacy was 76%[11] and 77%[10] over 1 year and 2 years of follow-up using a four-dose vaccine regimen in participants aged 5–17 months.

Our cross-sectional blood film results at 12 months and 18 months showed significantly reduced parasite rates in participants in the R21/Matrix-M group compared with those in the control group. This finding suggests that the R21/Matrix-M vaccine might not only substantially decrease the number of clinical malaria cases, but could also contribute to programmes to reduce malaria transmission when used with other interventions, particularly if deployed across a wider age range.

As expected with childhood vaccines, pain and fever were the most common adverse events but, overall, low numbers of participants reported these events after each vaccine dose. Most adverse events were mild to moderate in severity. There were no concerning trends observed with unsolicited adverse events or serious adverse events, with no significant imbalance in deaths according to sex or vaccine group. Five febrile convulsions after 11 000 doses of R21/Matrix-M were noted with one in the controls, giving a rate of one additional episode per 3700 R21/Matrix-M doses administered, but a statistically significant difference from rabies vaccination was not observed.

This study had some limitations. The trial was not powered to assess vaccine efficacy against clinical malaria at individual sites nor efficacy against mortality or severe malaria across all sites. However, the point estimate of vaccine efficacy against severe malaria is similar to the that against clinical malaria in the first year. There was also somewhat higher efficacy at the seasonal sites compared with standard sites. This finding might partly relate to the different timing of episodes at these sites: at seasonal sites, 82% of malaria episodes in the first year were recorded in the first 6 months of follow-up, as expected with vaccination before the malaria season, whereas only 26% of malaria episodes over the first year were recorded at the standard sites in the first 6 months. Children in malaria endemic areas receive several childhood vaccines as part of the Expanded Programme on Immunization schedule, typically outside of the 5–7-months age group probably to be preferred for malaria primary series vaccination, but coadministration did not take place during this trial. However, an ongoing trial in Mali (NCT05155579) is assessing coadministration of R21/Matrix-M with the Expanded Programme on Immunization schedule vaccines at 6 weeks, 10 weeks, and 14 weeks of age, as well as 9 months. Data from this study will be available soon. Similarly, the use of R21/Matrix-M in HIV-infected children was not assessed in this trial, but another trial in Uganda is ongoing to explore this (NCT05385510). There have been no safety concerns in these trials to date.

In this phase 3 trial, participants have been followed up for 18 months at the seasonal sites and the trial is still ongoing. With malaria vaccines, there are uncertainties over durability of protection and further data will be helpful to elucidate these uncertainties. The low rate of decline of antibody titres and well maintained efficacy over the second year and third year in the phase 2b trial suggest that efficacy might be well maintained with R21/Matrix-M.[10,11] Follow-up of this phase 3 trial has been extended for two further years to allow for additional safety and efficacy data collection. We have not observed rebound malaria in the recently completed phase 2b trial in Nanoro over 4 years (unpublished).

In addition to high efficacy, a further important advantage of R21/Matrix-M is that initial supply capacity should be of the order of 100–200 million doses annually, with a cost of less than US$4 per dose to public health agencies. This should potentially allow most of the target population of young African children to have access to this vaccine. There has been substantial demand for malaria vaccines from over 20 countries in the past year. Ghana, Nigeria, and Burkina Faso have already approved R21/Matrix-M for use in the expanded age range of 5–36 months, and the vaccine recently received a WHO policy recommendation and prequalification.

Overall, R21/Matrix-M could be widely deployed and a very important addition to help to prevent malaria. Although progress in reducing the burden of this parasitic disease has stalled over the past 5 years, this low-cost vaccine, soon to be available at a scale of over 100 million doses a year, has the potential to reinvigorate progress in the fight against malaria.

#### Contributors

AVSH and MSD conceived and designed the trial and AVSH is the chief investigator. AVSH, MSD, AD, MH, AO, J-BO, HT, HMN, BMG, DC, and KJE contributed to the protocol and design of the study. AD, MH, AO, J-BO, and HT were the study site principal investigators. KJE led laboratory studies of immune responses. EB and JB did the statistical analysis. SB, PSK, HR, US, and SG were responsible for vaccine and adjuvant manufacturing and provision. MSD, AVSH, EB, and JB led on the preparation of the report. AL provided regulatory support and guidance. AD, MH, HMN, MC, YDC, DI, DS, SO, AMS, AO, J-BO, HT, PB, MSD, AVSH, KJE, FRL, LS, RR, and SW contributed to the implementation of the study. EB, JB, MSD, and AVSH have accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

AVSH and KJE are named as co-inventors on patent applications related to R21 and might benefit from any royalty stream. KJE was an employee of the University of Oxford (Oxford, UK) at the time of this work and is now an employee of GlaxoSmithKline. KJE holds restricted shares in the GlaxoSmithKline group of companies. US, SB, PSK, HR, and SG are employees of the Serum Institute of India, co-developer of the R21/Matrix-M vaccine. All other authors declare no competing interests.

#### Data sharing

The study protocol is provided in the appendix. Anonymised participant data will be made available when the trial is complete, upon requests directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigators, and collaborators based on scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement. All data will be made available for a minimum of 5 years from the end of the trial.

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