The public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine: a mathematical modelling study

Nora Schmit, Hillary M Topazian,* H Magloire Natama, Duncan Bellamy, Ousmane Traoré, M Athanase Somé, Toussaint Rouamba, Marc Christian Tahita, Massa dit Achille Bonko, Aboubakary Sourabié, Hermann Sorgho, Lisa Stockdale, Samuel Provstgaard-Morys, Jeremy Aboagye, Danielle Woods, Katerina Rapi, Mehreen S Datoo, Fernando Ramos Lopez, Giovanni D Charles, Kelly McCain, Jean-Bosco Ouedraogo, Mainga Hamaluba, Ally Olotu, Alassane Dicko, Halidou Tinto, Adrian V S Hill, Katie J Ewer, Azra C Ghani, Peter Winskill*

Summary

Background The R21/Matrix-M vaccine has demonstrated high efficacy against *Plasmodium falciparum* clinical malaria in children in sub-Saharan Africa. Using trial data, we aimed to estimate the public health impact and cost-effectiveness of vaccine introduction across sub-Saharan Africa.

Methods We fitted a semi-mechanistic model of the relationship between anti-circumsporozoite protein antibody titres and vaccine efficacy to data from 3 years of follow-up in the phase 2b trial of R21/Matrix-M in Nanoro, Burkina Faso. We validated the model by comparing predicted vaccine efficacy to that observed over 12–18 months in the phase 3 trial. Integrating this framework within a mathematical transmission model, we estimated the cases, malaria deaths, and disability-adjusted life-years (DALYs) averted and cost-effectiveness over a 15-year time horizon across a range of transmission settings in sub-Saharan Africa. Cost-effectiveness was estimated incorporating the cost of vaccine introduction (dose, consumables, and delivery) relative to existing interventions at baseline. We report estimates at a median of 20% parasite prevalence in children aged 2–10 years ($Pf\mathrm{PR}_{2-10}$) and ranges from 3% to 65% $Pf\mathrm{PR}_{2-10}$.

Findings Anti-circumsporozoite protein antibody titres were found to satisfy the criteria for a surrogate of protection for vaccine efficacy against clinical malaria. Age-based implementation of a four-dose regimen of R21/Matrix-M vaccine was estimated to avert 181 825 (range 38 815–333 491) clinical cases per 100 000 fully vaccinated children in perennial settings and 202 017 (29 868–405 702) clinical cases per 100 000 fully vaccinated children in seasonal settings. Similar estimates were obtained for seasonal or hybrid implementation. Under an assumed vaccine dose price of US$3, the incremental cost per clinical case averted was $7 (range 4–48) in perennial settings and $6 (3–63) in seasonal settings and the incremental cost per DALY averted was $34 (29–139) in perennial settings and $30 (22–172) in seasonal settings, with lower cost-effectiveness ratios in settings with higher $Pf\mathrm{PR}_{2-10}$.

Interpretation Introduction of the R21/Matrix-M malaria vaccine could have a substantial public health benefit across sub-Saharan Africa.

Funding The Wellcome Trust, the Bill & Melinda Gates Foundation, the UK Medical Research Council, the European and Developing Countries Clinical Trials Partnership 2 and 3, the NIHR Oxford Biomedical Research Centre, and the Serum Institute of India, Open Philanthropy.

Lancet Infect Dis 2024; 24: 465–75

Published Online February 8, 2024 https://doi.org/10.1016/S1473-3099(23)00816-2

See Comment page 438

*Contributed equally

UK Medical Research Council Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London, UK (N Schmit PhD, H M Topazian PhD, G D Charles MSc, K McCain MSPH, Prof A C Ghani PhD, P Winskill PhD); **Unité de Recherche Clinique de Nanoro, Institut de Recherche en Sciences de la Santé, Nanoro, Burkina Faso** (H M Natama PhD, O Traoré PhD, M A Somé MD, T Rouamba PhD, M C Tahita PhD, M d A Bonko PhD, A Sourabié MSc, H Sorgho PhD, Prof J-B Ouedraogo MD, Prof H Tinto PhD); **The Jenner Institute Laboratories, University of Oxford, Oxford, UK** (D Bellamy MSc, L Stockdale PhD, S Provstgaard-Morys BSc, J Aboagye MSc, D Woods BSc, K Rapi BSc, M S Datoo DPhil, F R Lopez MSc, Prof A V S Hill PhD, Prof K J Ewer PhD); **Institut des Sciences et Techniques-Institut de Recherche en Sciences de la Santé, Bobo-Dioulasso, Burkina Faso** (Prof J-B Ouedraogo, Prof H Tinto); **Centre for Geographic Medicine Research (Coast), Kenya Medical Research Institute–Wellcome Trust Research Programme, Kilifi, Kenya** (Prof M Hamaluba DM); **Clinical Trials and Interventions Unit, Ifakara Health Institute, Bagamoyo, Tanzania** (A Olotu DPhil); **The Malaria Research and Training Centre,**

Introduction

Despite the widespread provision of insecticide-treated bed nets and increased access to first-line treatment, malaria remains a substantial global health burden. In 2021, there were an estimated 619 000 deaths from malaria, the majority in children younger than 5 years in sub-Saharan Africa due to the *Plasmodium falciparum* parasite.[1] Key among additional tools for reducing the burden of malaria is the recommendation for roll-out of the world's first malaria vaccine, RTS,S/AS01 (Mosquirix; GlaxoSmithKline, London, UK), to children living in moderate-transmission and high-transmission settings.[2] In phase 3 clinical trials, age-based implementation of four doses of the vaccine demonstrated an efficacy of 36% (95% CI 32–41) against multiple episodes of *P falciparum* malaria in infants aged 5–17 months over 4 years of follow-up in 11 sites across sub-Saharan Africa.[3] Pilot implementation of this regimen through the Malaria Vaccine Implementation Programme in Ghana, Kenya, and Malawi has demonstrated its feasibility. In these three countries, uptake was high at 76–89% for the first dose, 72–76% for the third dose, and 36–52% for the first booster dose in 2022.[4] The Malaria Vaccine Implementation Programme has further demonstrated vaccine effectiveness against hospital admission with severe malaria (29%, 95% CI 8–46) and all-cause

University of Science, Technology, and Techniques of Bamako, Bamako, Mali (Prof A Dicko PhD); **GSK Vaccines Institute for Global Health (Global Health Vaccines R&D), GSK, Siena, Italy** (Prof K J Ewer)

Correspondence to: Dr Nora Schmit, MRC Centre for Global Infectious Disease Analysis, School of Public Health, Imperial College London, London W2 1PG, UK
n.schmit17@imperial.ac.uk

Research in context

Evidence before this study

RTS,S/AS01 (Mosquirix; GlaxoSmithKline, London, UK) is the first *Plasmodium falciparum* malaria vaccine recommended by WHO. We searched PubMed on June 12, 2023 from inception for published articles using the terms "malaria vaccine" AND "clinical trial" AND "efficacy". RTS,S/AS01 demonstrated 36% efficacy against clinical malaria in phase 3 trials over 4 years of follow-up. In the Malaria Vaccine Implementation Programme, vaccine effectiveness against hospital admission with severe malaria was 29% (95% CI 8–46) and against all-cause mortality was 7% (3–16). In modelling studies, four doses of age-based RTS,S/AS01 were estimated to avert 116 480 clinical cases (range 31 450–160 410) and 484 malaria deaths (range 189–859) per 100 000 fully vaccinated children in regions with parasite prevalence of 10–65%. The median incremental cost-effectiveness ratio compared with existing interventions was US$51 (range 28–437) per clinical case averted and $154 (99–487) per disability-adjusted life-year (DALY) averted, assuming a vaccine cost of $10 per dose. Seasonal implementation was estimated to avert an additional 14 000–47 000 cases per 100 000 children compared with age-based implementation. A second pre-erythrocytic *P falciparum* malaria vaccine, R21/matrix-M, has also been evaluated in clinical trials. In a phase 2b trial with seasonal implementation, vaccine efficacy for four doses of 5 µg R21–50 µg matrix-M was 77% against multiple episodes of malaria over 2 years of follow-up, which correlated with induction of malaria-specific anti-circumsporozoite protein antibodies. In a phase 3 trial, R21/matrix-M had a vaccine efficacy of 72% (95% CI 68–75) in sites with seasonal implementation and 67% (59–73) in sites with age-based implementation in the modified per-protocol analysis. The cost-effectiveness of R21/matrix-M has not been evaluated to date. A systematic review previously estimated the cost-effectiveness of other malaria interventions at a median provider economic cost of $0·3–122 per case averted and $10–45 per DALY averted, although comparisons are complicated by the large heterogeneity within and across interventions. Another systematic review reported cost-effectiveness ratios for vaccines in low-income and middle-income countries in 2010 to be less than $100 per DALY averted in 52% of included studies and less than $500 per DALY averted in 77% of included studies.

Added value of this study

This study estimates the relationship between anti-circumsporozoite protein antibody titres and vaccine efficacy from the R21/matrix-M phase 2b trial, further strengthening the evidence for anti-circumsporozoite protein antibody titres as a surrogate of protection for pre-erythrocytic malaria vaccines. Using the same methods as for previous RTS,S/AS01 analyses and a published mathematical model of malaria transmission, the study provides generalisability of the trial results across a range of transmission settings observed in sub-Saharan Africa. Results suggest that introduction of R21/matrix-M into routine immunisation schedules could have substantial impact on reducing malaria cases and deaths in children. Modelling also provides estimates of cost-effectiveness to inform vaccine introduction in comparison to existing malaria interventions and other childhood vaccines.

Implications of all the available evidence

These findings support the potential role of the R21/matrix-M vaccine in reducing the childhood malaria burden. Implementation of RTS,S/AS01 through existing programmes has shown that malaria vaccines can have a broader effect on childhood mortality, and this study suggests that the addition of a second malaria vaccine will help to further reduce the global burden.

mortality (7%, 3–16).[5] In a phase 3b trial in Burkina Faso and Mali, a four-dose regimen of RTS,S implemented seasonally was shown to be non-inferior to seasonal malaria chemoprevention in preventing clinical malaria, with significantly lower clinical incidence and deaths from malaria if these two interventions were combined.[6]

Continued progress will rely on the development of new tools, including additional malaria vaccine candidates.[1] R21/Matrix-M is a novel pre-erythrocytic malaria vaccine with a similar mechanism of action to RTS,S, but designed to induce increased anti-circumsporozoite protein antibody and lower anti-hepatitis B surface antigen antibody responses.[7] A phase 2b trial in children aged 5–17 months in Nanoro, Burkina Faso, demonstrated safety and effectiveness of a three-dose monthly regimen of R21/Matrix-M delivered before the malaria season with a booster dose 1 year following dose three. For the 5 µg R21/50 µg Matrix-M regimen, vaccine efficacy against multiple clinical malaria episodes was 77% (95% CI 70–82) over 2 years of follow-up.[8] Phase 3 trial results from five sites in east and west Africa of a four-dose regimen demonstrated 72% vaccine efficacy (68–75) in the two sites in which the vaccine was delivered under seasonal implementation over 18 months of follow-up and 67% efficacy (59–73) in the three sites in which the vaccine was delivered under age-based implementation over 12 months of follow-up.[9] R21/Matrix-M was added to the WHO list of prequalified vaccines on Dec 21, 2023.

To support wider-scale roll-out, estimates of R21/Matrix-M public health impact and cost-effectiveness are needed across the full range of malaria transmission settings in sub-Saharan Africa. Mathematical models fitted to trial data have been instrumental in providing evidence for the impact and cost-effectiveness of RTS,S/AS01 in different settings.[10,11] Here, we adopt this approach to estimate the level and duration of protection afforded by the R21/Matrix-M vaccine by fitting a

semi-mechanistic model of the relationship between antibody titres and protection to immunogenicity and clinical incidence data from the phase 2b trial.[12] Integrating this framework within a model of malaria transmission dynamics,[10,13] we provide estimates of the potential public health impact and cost-effectiveness of routine vaccination with R21/Matrix-M in various settings representative of malaria epidemiology in sub-Saharan Africa.

Methods

Data

In this mathematical modelling study, we used data from a phase 2b, double-blind, randomised controlled trial of the R21/Matrix-M vaccine in children aged 5–17 months in Nanoro, Burkina Faso.[8] Malaria transmission in Nanoro is high, with a seasonal peak between June and November.[14] 450 children were randomly assigned to three groups, receiving either 5 µg R21/25 µg Matrix-M, 5 µg R21/50 µg Matrix-M, or rabies (Rabivax-S; Serum Institute of India, Pune, India) vaccinations (control group). The primary vaccination series consisted of three doses administered before the malaria season in 2019. Participants received a booster dose 12 months after the primary series. Approximately two-thirds of participants were re-randomly assigned (2:1, 5 µg R21/50 µg Matrix-M: rabies control vaccine) to receive a second booster dose 24 months after the third dose.

We used individual-level data from the 5µg R21/50 µg Matrix-M vaccine group of the trial, with the vaccine efficacy estimated against multiple clinical malaria episodes over 3 years of follow-up. Immunogenicity was assessed in terms of antibody titres against NANP6, the central repeat of the circumsporozoite protein, measured by ELISA at 28 days, 6 months, and 1 year after the primary series and 28 days, 6 months, and 1 year after the booster doses.[7,8] The primary case definition of a clinical episode of malaria was a temperature of 37·5°C or higher, or a fever within the past 24 h, and *P falciparum* parasitaemia of more than 5000 asexual forms per µL.[8]

Association between antibody dynamics and vaccine efficacy against clinical malaria

The dynamics of anti-circumsporozoite protein antibody titres over time following vaccination, CS(t), were modelled as a biphasic exponential function.[12]

$$CS(t)=CS_{peak}\left(\rho_{peak}e^{-r_s t}+(1-\rho_{peak})e^{-r_l t}\right) \quad \text{for } t<t^{b}_{boost}$$

$$CS(t)=CS^{b}_{boost}\left(\rho_{boost}e^{-r_s(t-t^{b}_{boost})}+(1-\rho_{boost})^{e-r_l(t-t^{b}_{boost})}\right) \quad \text{for } t\geq t_{boost}$$

Titres reach a peak value, CS_{peak}, following the primary vaccination series and wane over time. Here

$$r_s=\frac{\ln(2)}{d_s}$$

and

$$r_l=\frac{\ln(2)}{d_l}$$

are the rates of decay for the short-lived and long-lived components of the antibody response, with d_s representing the half-life of the short-lived component and d_l representing the half-life of the long-lived component, and ρ_{peak} representing the proportion of the response that is short-lived. Titres increase to CS^{b}_{boost} following subsequent booster doses at times t^{b}_{boost}. We assumed the same decay rate after booster doses as following the primary series, but allowed the proportion of the response that is short-lived, ρ_{boost}, to differ to capture different rates of decay in protection.

The estimated antibody titres, CS(t), were related to vaccine efficacy against *P falciparum* infection over time, V(t), using the dose-response curve:

$$V(t)=V_{max}\left(1-\frac{1}{1+\left(\frac{CS(t)}{\beta}\right)^{\alpha}}\right)$$

The parameters v_{max}, α, and β were estimated by fitting a model of clinical malaria incidence to the individual-level trial data on the timing of episodes of clinical malaria. Baseline data and patterns of clinical incidence in the control group were used to capture site characteristics including transmission intensity, seasonality, and bed-net use (appendix 1 pp 3–11). The model was fit using survival analysis methods within a Bayesian framework. Parameters are presented as medians and 95% credible intervals (CrIs) of the estimated posterior distributions.

See Online for appendix 1

Model validation using phase 3 trial data

To validate the model, we compared the model-predicted vaccine efficacy in the five phase 3 trial sites with the reported vaccine efficacy over 12–18 months of follow-up.[9] Clinical efficacy was projected for each site over the period of follow-up, accounting for baseline transmission, seasonality, and uncertainty in the model fit (appendix 1 pp 12–13). We assumed the peak antibody titre parameters were the same as in the phase 2 trial.

Transmission model

A previously developed age-structured individual-based mathematical model of *P falciparum* was used to estimate the public health impact of wider roll-out of the R21/Matrix-M vaccine.[13,15,16] Full analysis code is provided online and technical details are included in appendix 1 (pp 14–27). In the model, individuals become susceptible to infection as their maternal immunity wanes after birth. Infection risk varies with age, leading to asymptomatic infection, clinical disease, or severe disease. Immunity is incorporated on the basis of age

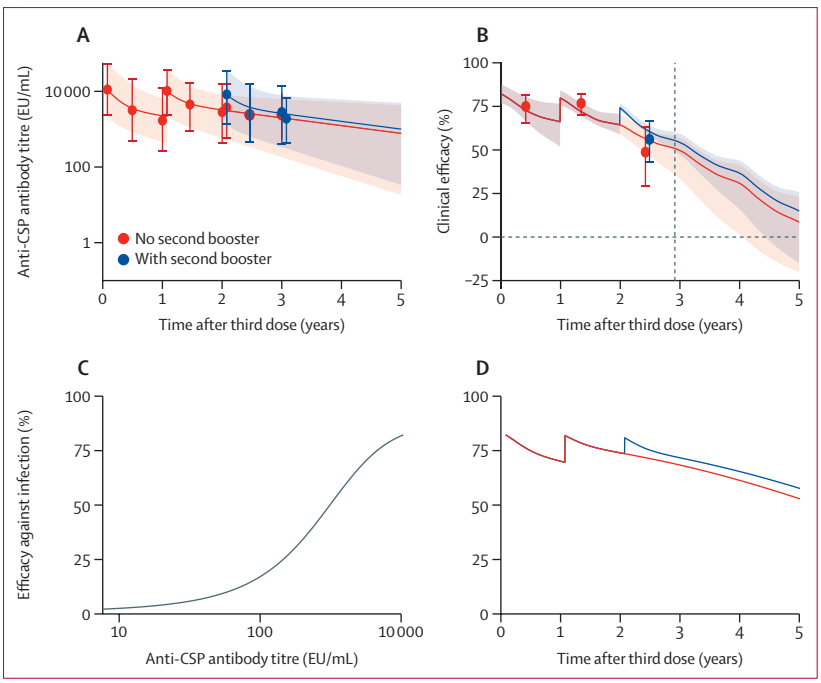

Figure 1: **Association between anti-CSP antibody dynamics and vaccine efficacy**
(A–B) Model fit to trial data after primary vaccination with three doses of 5 µg R21–50 µg matrix-M and booster doses 12 months and 24 months after the third dose. Results are shown separately for the group with (blue) and without (red) a second booster at 24 months. Antibody titre and efficacy estimates from the phase 2 trial are shown as points with 95% CIs. (A) Anti-CSP antibody titres over time. The lines show the median model projection with 95% credible-interval bounds. (B) Estimated vaccine efficacy against multiple clinical malaria episodes over time. The lines show the median model projection (bold) with 50 draws from the posterior parameter set. The dashed vertical line delineates the end of follow-up in the trial. (C) Median model estimate for the dose-response curve for the association between anti-CSP antibody titres and vaccine efficacy against infection. (D) Median model estimate for the vaccine efficacy against infection over time. CSP=circumsporozoite protein.

and past exposure. Treatment in the model clears infection and provides temporary partial protection against re-infection. Mosquito vectors are modelled through their lifecycle and can become infected by biting humans. Vaccination with R21 is included using the estimated parameters from the phase 2b fits, with efficacy assumed to begin following the third dose of the primary series.

Model scenarios

We estimated the impact of R21/Matrix-M vaccine roll-out across a range of malaria transmission settings. Each was characterised by malaria transmission intensity (*P falciparum* prevalence in children aged 2–10 years [$PfPR_{2-10}$] ranging from 3% to 65%) which was assumed to incorporate the effect of other existing malaria interventions and seasonality (a perennial and seasonal setting). We assumed that access to care remained constant with 45% of clinical cases successfully treated with artemether–lumefantrine.[10] Simulations used a population of 200 000 people and a demographic profile corresponding to the 2021 population age structure in sub-Saharan Africa.[17] We modelled age-based R21 vaccination following WHO guidelines and Malaria Vaccine Implementation Programme experience,[2,5] with three doses at 6 months, 7 months, and 8 months, a booster dose 12 months after dose three, and an optional second booster. For seasonal vaccination, doses were administered to children aged 5–17 months and timed relative to the peak in clinical incidence. A hybrid approach combined age-based and seasonal timing, with specific intervals between doses (appendix 1 pp 26–27). In line with Malaria Vaccine Implementation Programme results,[4] coverage for doses one to three was assumed to be 80% of eligible children, and 64% for the booster dose. 50 unique parameter draws for both the antibody titre model and transmission model were run for each scenario to capture model uncertainty.

Model outputs were summarised as clinical cases, severe disease cases, malaria deaths, and disability-adjusted life-years (DALYs; appendix 1 p 28). Outputs are reported as the cumulative impact over a 15-year time horizon to capture rebound effects.[10] Fully vaccinated children were defined as those having received at least three doses. Estimates are presented as the median and 95% range (2·5th and 97·5th percentile) of projections in each transmission setting.

Cost data and cost effectiveness

Costs were estimated from a national government perspective in 2023 US dollars. Given that economic data were not collected in the R21/Matrix-M trials, unit costs for vaccine introduction and case management were derived from secondary data sources. These costs included the cost of consumables and delivery of the vaccine, and the cost of diagnosis and treatment of clinical and severe malaria cases with antimalarial drugs. We evaluated the cost-effectiveness of R21/Matrix-M introduction under a central cost assumption per dose of \$3 for the vaccine, \$0·97 for other consumables, and \$1·48–\$3·75 for vaccine delivery depending on the implementation, with age-based delivery assumed to be the least costly.[5,18,19] Results are also presented in reference to a vaccine cost of \$2 and \$4 per dose (holding delivery costs constant; costs are detailed in appendix 1 pp 28–33).

Costs and health outcomes were discounted at 3% per annum. The incremental cost per case and per DALY averted was calculated by comparing the absolute cost and health impact for each vaccination implementation to the same baseline scenario with no vaccination programme in each setting. The impact and cost of other interventions was assumed to remain constant and equal between the baseline and vaccine introduction scenarios. We did an additional extended dominance analysis to compare the different implementation and dose regimen scenarios relative to each other, and a sensitivity analysis on the key drivers of cost (appendix 1 pp 34–35).

Ethical approval

The phase 2 trial was approved by the Comité d'Ethique pour la Recherche en Santé, Burkina Faso (2019-01-012),

	Parameter	Prior	Posterior
d_s	Half-life of short-lived component of antibody response, days	100·0 (27·0–371·0)	44·6 days (40·8–49·0)
d_l	Half-life of long-lived component of antibody response, days	1805 (266·6–13 151·6)	533·0 days (460·8–620·9)
ρ_{peak}	Proportion of short-lived component following primary regimen	0·50 (0·12–0·87)	0·69 (0·66–0·72)
ρ_{boost}	Proportion of short-lived component following booster dose	0·50 (0·12–0·87)	0·52 (0·48–0·56)
β	Scale parameter of dose-response curve, EU/mL	5580 (279–10 880)	471 (52–1210)
α	Shape parameter of dose-response curve	0·94 (0·29–2·21)	0·91 (0·41–2·09)
V_{max}	Maximum efficacy against infection	91% (74–98)	87% (77–97)

Priors and posterior estimates are presented as median (95% credible intervals). The following priors were assumed for the other parameters: log-normal for d_s and d_l, normal for the logit of ρ_{peak} and ρ_{boost}, uniform for β, gamma for α, and beta for V_{max}. β represents the antibody at which vaccine efficacy is 50% of its maximum, with the prior range (0–11 159) based on the observed maximum titre in the model.

Table 1: **Model parameter estimates for anti-CSP antibody dynamics and the dose-response relationship between antibody tires and efficacy against *Plasmodium falciparum* infection**

and the national regulatory authority, Agence National de Régulation Pharmaceutique, Burkina Faso (5005420193EC0000). Ethical approval was also granted in the UK by the Oxford Tropical Research Ethics Committee (19-19). Ethical approval for the secondary data analysis was granted by Imperial College London (6278940).

The phase 3 trial was approved by the following ethics committees: L'Université des Sciences, des Techniques, et des Technologies de Bamako, Faculté de Médecine et d'Odonto-Stomatologie, Faculté de Pharmacie, Bamako, Mali; Comité d'Ethique pour la Recherche en Santé, Ministère de l'Enseignement Supérieur, de la Recherche Scientifique et de l'Innovation, Ministère de la Santé, Ouagadougou, Burkina Faso; Kenya Medical Research Institute, Scientific and Ethics Review Unit, Nairobi, Kenya; and the National Institute for Medical Research, Dar es Salaam, Tanzania. Ethical approval was also granted in the UK by the Oxford Tropical Research Ethics Committee (8-21).

Role of the funding source

The funders of the study had no role in study design, data analysis, data interpretation, or writing of this report.

Results

The observed decay in anti-circumsporozoite protein antibody titres was well captured by a biphasic exponential decay model (figure 1A). We estimated a half-life of 44·6 days (95% CrI 40·8–49·0) for the short-lived component and 533·0 days (460·8–620·9) for the long-lived component (table 1). Our estimates suggest a higher proportion of long-lived antibody response (calculated as 1 minus the proportion of the short-lived component) following the booster doses (48%, 95% CrI 44–52) compared to following primary vaccination (31%, 28–34). Projected vaccine efficacy against clinical malaria over time followed these patterns of decay in antibody titres (figure 1B). In the phase 2 trial, clinical efficacy of the R21/Matrix-M vaccine remained high in the first 2 years of the trial but declined to 49% (95% CI 29–64) in the third year for the vaccine group without a second booster, and to 56% (43–67) for participants who received a second booster (figure 1B). Given that antibody titres following the second booster reached a peak that was similar to that observed following the first booster, our model overestimated clinical efficacy in the third year of follow-up. However, median model projections still fall within the 95% CIs for the vaccine efficacy data (figure 1B).

The resulting relationship between anti-circumsporozoite protein antibody titre and protection against infection shows a smooth monotonic increase, with no clear threshold for protection (figure 1C). Our estimate of R21/Matrix-M vaccine efficacy against infection remains high over a 5-year period (figure 1D), beginning at a peak of 82% and waning to 57% 5 years following primary vaccination in the regimen in which booster doses were delivered 12 months and 24 months after dose three. In the absence of booster doses, we estimated that vaccine efficacy against infection would decline to 70% after 12 months and 36% after 5 years.

The model-predicted R21/Matrix-M vaccine efficacy against multiple episodes of malaria for the phase 3 data in each of the five trial sites was calculated (figure 2). Modelled vaccine efficacy against clinical malaria fell within the 95% CIs of the trial data for the three higher transmission sites. In the lower transmission non-seasonal sites in east Africa (Bagamoyo and Kilifi), where trial efficacy was lower and more uncertain, model estimates fell just outside the upper bound of the 95% CI of the trial observation. Although vaccine efficacy against clinical disease varied across sites in the trial, we did not predict significant variation in the model over the 12–18 month follow-up period.

The absolute impact of the R21/Matrix-M vaccine, as summarised by clinical cases or malaria deaths averted over a 15-year time horizon, is projected to increase with increasing $Pf\text{PR}_{2–10}$ (figure 3). In perennial settings, we estimated that a four-dose age-based implementation could avert between 30% and 44% of cases in children

See Online for appendix 2

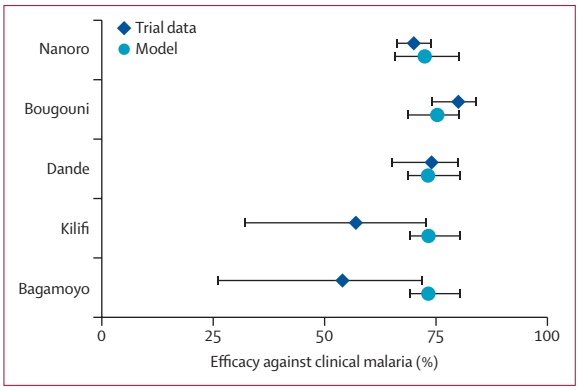

***Figure 2*: Model validation against phase 3 data**
Median model estimates with 95% credible intervals for the fitted model (light blue points and error bars) are shown in relation to trial estimates of vaccine efficacy against multiple episodes of clinical malaria (modified per-protocol analysis) with 95% CIs (dark blue diamonds and error bars). In Nanoro and Bougouni, participants received the seasonal regimen and had a follow-up of 18 months. In Dande, Kilifi, and Bagamoyo, participants received the standard regimen and had a follow-up of 12 months. Nanoro, Bougouni, and Dande are west African sites. Bagamoyo and Kilifi are located in east Africa. The model projections are made over the same time periods as each of the trial sites.

younger than 5 years (table 2; appendix 2). In seasonal settings, we estimated that between 29% and 45% of cases could be averted in children younger than 5 years under a four-dose regimen administered via age-based implementation (table 2; appendix 2). Implementation of R21/Matrix-M under age-based, hybrid, and seasonal methods resulted in similar numbers of cases averted. The median percentage of deaths from malaria averted in children younger than 5 years ranged from 21% to 43% in perennial settings and from 19% to 46% in seasonal settings across all implementations.

All vaccine introduction scenarios incurred higher costs and positive health impacts compared with the baseline of no vaccination. Although different implementations and dose regimens had similar health benefits, they differed more in their incremental costs (appendix 1 pp 36–38). Across all implementation and dose regimens, R21/Matrix-M was estimated to have a lower incremental cost per case and per DALY averted at higher transmission intensities than at lower transmission intensities (figure 4; appendix 2). At a vaccine cost of $3 per dose and under age-based implementation of four doses in perennial settings,

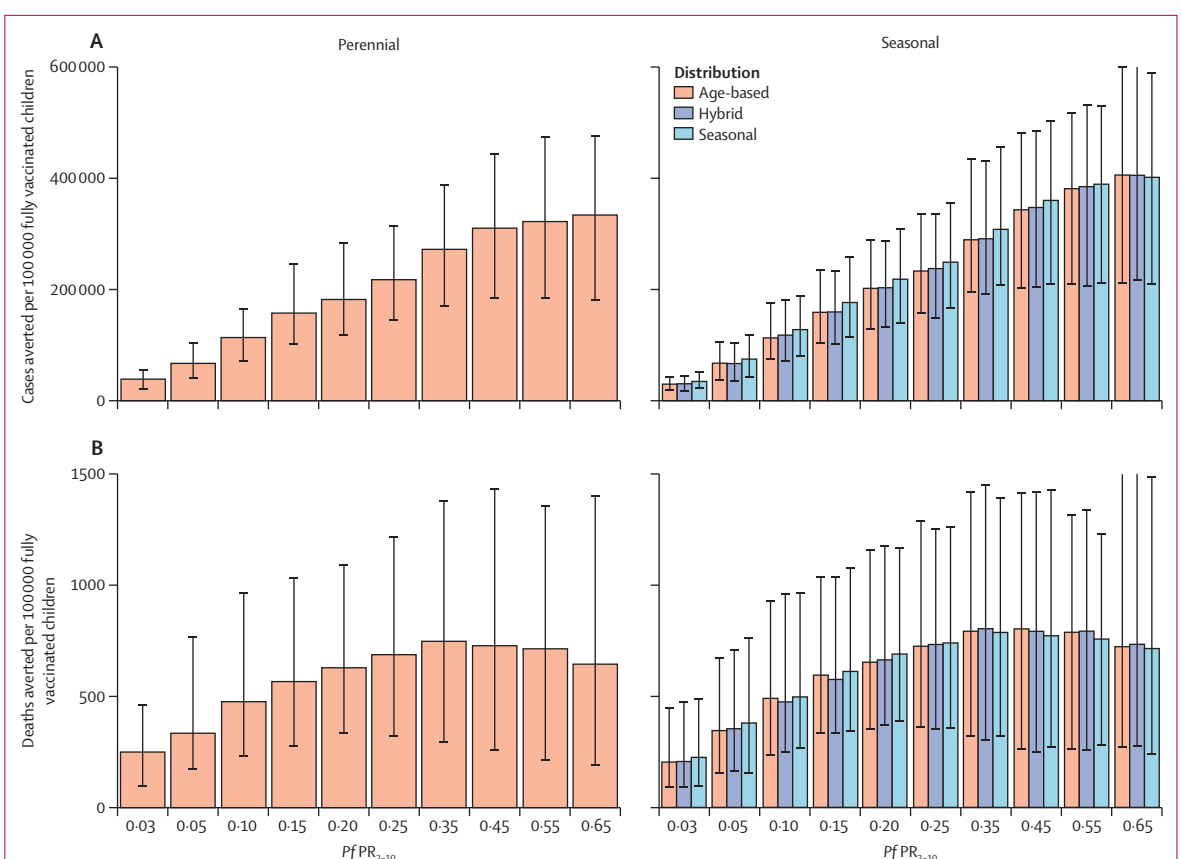

***Figure 3*: Cases averted per 100 000 fully vaccinated children (A) and malaria deaths averted per 100 000 fully vaccinated children (B), stratified by $PfPR_{2-10}$, seasonality, and implementation method**
Error bars represent the 2·5th and 97·5th percentiles around median estimates. All scenarios represented assume a four-dose regimen. Outcomes were simulated over a 15-year time horizon and discounted at 3% per annum. $PfPR_{2-10}$=*Plasmodium falciparum* parasite prevalence in children aged 2–10 years.

	Perennial settings		Seasonal settings					
	Age-based implementation		Age-based implementation		Seasonal implementation		Hybrid implementation	
	Single booster	Double booster	Single booster	Double booster	Single booster	Double booster	Single booster	Double booster
Proportion of clinical cases averted in children younger than 5 years	40·2% (44·3, 30·0)	40·7% (45·0, 30·7)	40·1% (45·2, 28·9)	40·7% (46·1, 29·4)	42·4% (48·3, 29·1)	42·8% (49·4, 29·6)	40·4% (45·4, 29·0)	41·0% (46·2, 29·6)
Proportion of deaths averted in children younger than 5 years	33·6% (43·0, 21·4)	33·8% (42·9, 21·0)	33·8% (43·8, 20·2)	33·6% (45·0, 20·4)	34·4% (46·4, 19·0)	34·7% (47·8, 19·1)	33·0% (43·8, 20·3)	34·1% (46·2, 20·9)
Clinical cases averted per 100 000 fully vaccinated children	181 825 (38 815, 333 491)	188 509 (39 310, 340 359)	202 017 (29 868, 405 702)	210 101 (31 874, 412 643)	218 472 (34 680, 401 635)	224 811 (35 723, 412 499)	203 134 (30 557, 405 220)	210 883 (31 427, 416 787)
Deaths averted per 100 000 fully vaccinated children	629 (250, 646)	647 (256, 668)	653 (204, 723)	697 (226, 735)	690 (225, 715)	706 (238, 699)	664 (207, 734)	690 (214, 736)
Cost per 100 000 fully vaccinated children (in 2023 US dollars)	1 306 540 (1 857 736, 1 201 482)	1 563 519 (2 130 577, 1 437 446)	1 267 065 (1 898 376, 1 037 507)	1 525 176 (2 170 321, 1 278 694)	2 030 775 (2 708 678, 1 891 009)	2 398 187 (3 097 235, 2 251 878)	1 585 799 (2 217 845, 1 344 305)	1 878 173 (2 530 583, 1 638 328)
Cost per clinical case averted (in 2023 US dollars)								
$2 per dose	$5 (35, 2)	$5 (41, 3)	$4 (47, 1)	$5 (51, 2)	$7 (65, 3)	$8 (71, 4)	$6 (57, 2)	$6 (64, 3)
$3 per dose	$7 (48, 4)	$8 (54, 4)	$6 (63, 3)	$7 (68, 3)	$9 (78, 5)	$11 (87, 5)	$8 (73, 3)	$9 (81, 4)
$4 per dose	$10 (60, 5)	$11 (68, 6)	$9 (79, 4)	$10 (85, 4)	$12 (92, 6)	$13 (101, 7)	$10 (88, 5)	$11 (98, 5)
Cost per DALY averted (in 2023 US dollars)								
$2 per dose	$22 (103, 18)	$26 (115, 22)	$19 (129, 12)	$22 (135, 15)	$37 (183, 34)	$43 (203, 40)	$26 (161, 18)	$31 (172, 24)
$3 per dose	$34 (139, 29)	$40 (154, 38)	$30 (172, 22)	$35 (180, 26)	$48 (221, 45)	$55 (246, 53)	$38 (204, 29)	$44 (219, 35)
$4 per dose	$47 (174, 42)	$54 (193, 52)	$42 (214, 33)	$47 (226, 38)	$59 (260, 55)	$68 (288, 65)	$50 (247, 38)	$57 (265, 47)

Estimates represent median values at 20% $Pf\mathrm{PR}_{2\text{–}10}$ (approximately corresponding to the mean 2019 value across areas in sub-Saharan Africa with >1% $Pf\mathrm{PR}_{2\text{–}10}$) and intervals represent median values at 3% $Pf\mathrm{PR}_{2\text{–}10}$ and 65% $Pf\mathrm{PR}_{2\text{–}10}$. Although absolute health effects are larger in the 65% $Pf\mathrm{PR}_{2\text{–}10}$ setting than at 3%, the opposite is true for the proportions and the cost per clinical case and per DALY averted; presented intervals therefore go from a high to a low number. The modelled vaccine schedules include four (single booster) or five (double booster) doses. Costs and health outcomes for all implementations are incremental to the baseline of no vaccination and were discounted at 3% per annum. Total costs underlying these estimates include the cost of vaccine delivery and other consumables, but only vaccine costs varied between $2 and $4. Cost estimates for R21/matrix-M introduction per 100 000 fully vaccinated children reflect different delivery costs for age-based, seasonal, and hybrid implementation, different numbers of vaccine doses being administered (single *vs* double booster), and different case management cost savings (eg, for the same scenario at different transmission intensities). DALY=disability-adjusted life-year. $Pf\mathrm{PR}_{2\text{–}10}$=*Plasmodium falciparum* parasite prevalence in children aged 2, 10 years.

Table 2: **Public health impact, cost, and cost-effectiveness estimates for the roll-out of the R21/matrix-M vaccine in children over a 15-year time horizon according to implementation method and number of booster doses**

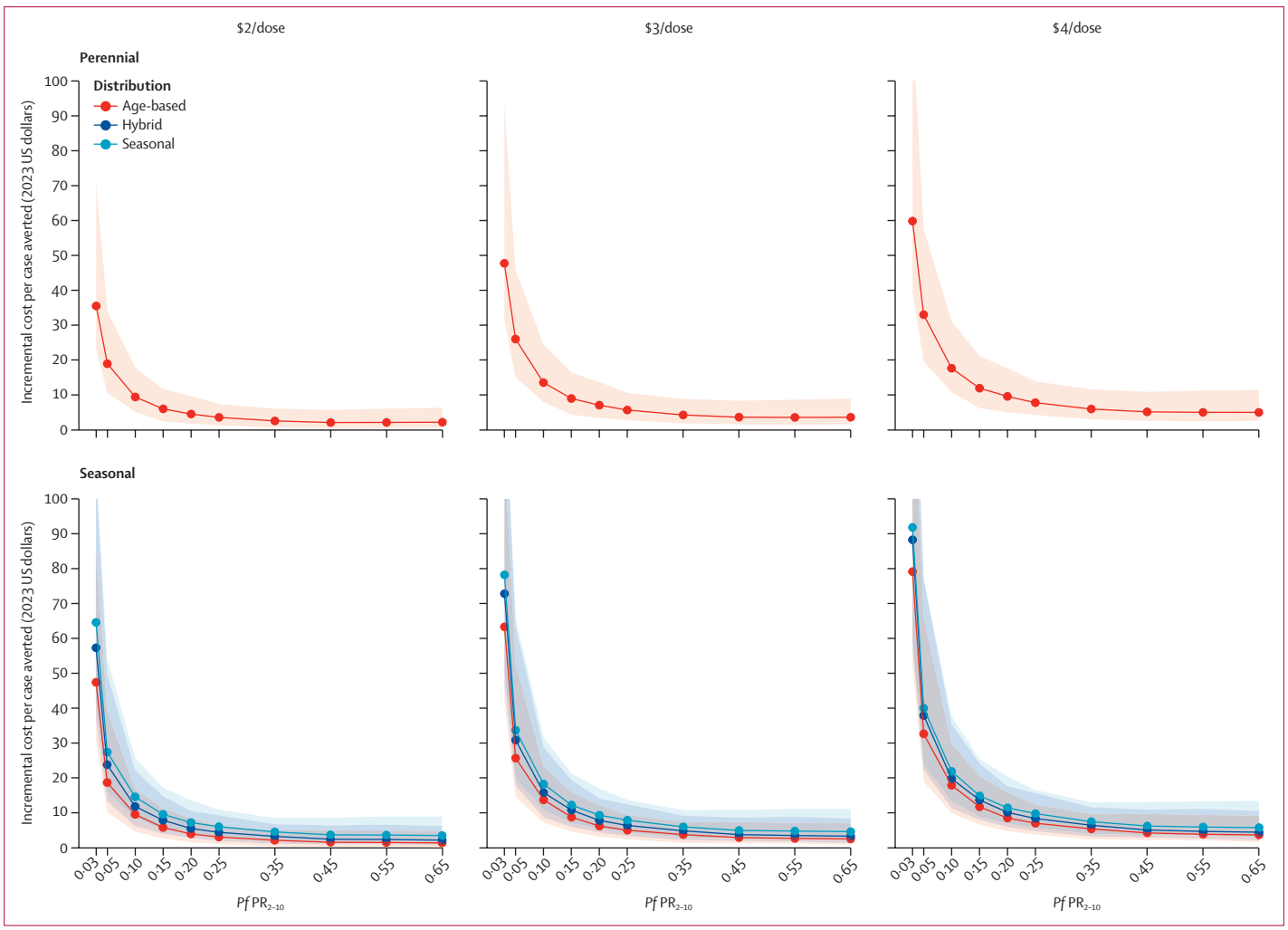

Figure 4: **Incremental cost per case averted by four doses of R21/matrix-M at different levels of *Plasmodium falciparum* prevalence in children aged 2–10 years**

Estimates are stratified by vaccine cost per dose, seasonality, and implementation method. Point estimates represent median values, and shaded areas represent the 2·5th and 97·5th percentiles of the outputs from 50 vaccine efficacy and transmission model parameter uncertainty runs. Costs and cases averted for all implementations are incremental to the baseline of no vaccination, were simulated over a 15-year time horizon and discounted at 3% per annum. Total costs underlying these estimates included the cost of vaccine delivery and other consumables, but only vaccine costs were varied between US$2–4 in the three panels. The corresponding graphs for cost per disability-adjusted life-year averted are shown in appendix 1 (p 38).

cost-effectiveness values ranged from a median of $48 (95% range 31–93) per case averted in the 3% *Pf*PR$_{2–10}$ setting to $7 (3–14) in the 20% *Pf*PR$_{2–10}$ setting and $4 (2–9) in the 65% *Pf*PR$_{2–10}$ setting. Corresponding costs per DALY averted were $139 (70–360) in the 3% *Pf*PR$_{2–10}$ setting, $34 (16–68) in the 20% *Pf*PR$_{2–10}$ setting, and $29 (12–119) in the 65% *Pf*PR$_{2–10}$ setting (table 2; appendix 2). The incremental cost per case and per DALY averted relative to the baseline of no vaccination was similar in seasonal settings under age-based, hybrid, or seasonal implementation (figure 4; table 2). In sensitivity analyses on the cost of the vaccine, vaccine delivery and case management, all estimates were less than or equal to $10 per case averted and $49 per DALY averted in settings with at least 20% *Pf*PR$_{2–10}$ (appendix 1 pp 46–50).

Comparing the incremental cost-effectiveness ratios (ICERs) of different implementations and booster schedules relative to each other, age-based implementation with a single booster (four doses) was never dominated and had the lowest incremental cost per case and per DALY averted across all seasonality and prevalence settings. ICERs and dominance for other scenarios varied depending on the setting and assumptions about delivery costs (appendix 1 pp 39–46).

Discussion

Our results demonstrate that introducing R21/Matrix-M into routine childhood immunisation in malaria-endemic areas of sub-Saharan Africa could have a substantial public health impact. Across settings with rates of *P falciparum* transmission between 3% and 65%, *Pf*PR$_{2–10}$, age-based introduction of four doses of the vaccine could avert 181 825 clinical cases (range 38 815–333 491) and 629 malaria deaths (range 250–646)

for every 100 000 fully vaccinated children in perennial settings, and 202 017 clinical cases (29 868–405 702) and 653 malaria deaths (204–723) per 100 000 fully vaccinated children in seasonal settings over 15 years. These averted deaths translate to preventing one malaria death for every 159 children vaccinated (155–400) in perennial settings and 153 children vaccinated (138–490) in seasonal settings.

Our study demonstrates that anti-circumsporozoite protein antibody titres to the Asn-Ala-Asn-Pro (NANP) repeat region are a level 1 surrogate of protection for the vaccine.[20] Given that anti-circumsporozoite protein antibody titres met the level 2 surrogate of protection criteria in multisite data for the RTS,S/AS01 vaccine,[12] this finding might also apply to R21/Matrix-M. The half-lives for the short-lived and long-lived components of the humoral immune response were similar to those previously estimated for the RTS,S/AS01 vaccine.[12] However, for the R21/Matrix-M vaccine, we estimated a greater contribution from the long-lived component, resulting in a slower decay in anti-circumsporozoite protein antibody titres over time, and hence predicting more durable vaccine efficacy. Data from the phase 2b study demonstrated a restoration of anti-circumsporozoite protein antibody titres following booster doses to levels observed following the primary vaccination series. By contrast, titres following the booster dose administered 18 months after dose 3 in the phase 3 study of RTS,S/AS01 under age-based implementation did not restore titres to the same levels.[3] Similarly lower titres were observed following boosting 12 months after dose three in the study of seasonal implementation of RTS,S/AS01.[21] Incorporating the observed restoration of immunogenicity following boosters for R21/Matrix-M into our simulations, our results show similar public health impact for age-based, seasonal, and hybrid implementation. As previously seen for RTS,S/AS01, the modelled impact is partially offset by a rebound in clinical incidence in vaccinated children at older ages due to reduced malaria exposure and an associated delay in immunity acquisition.[10,12,22]

We validated our model by comparing model-predicted vaccine efficacy over 12–18 months of follow-up with data from the phase 3 R21/Matrix-M trial. Although the model predicts relatively little difference in expected vaccine efficacy between the sites over this shorter period of follow-up, the trial data showed lower vaccine efficacy in the lower transmission sites Kilifi and Bagamoyo (albeit with high uncertainty given the low number of malaria cases). It is worth highlighting that these two sites were both located in east Africa, where seasonal malaria chemoprevention has not been implemented. Interpretation of the observed lower vaccine efficacy in specific study sites also warrants careful consideration because of several factors: the site level estimates in the low transmission sites were inherently more statistically noisy because of the smaller number of events recorded at these sites; at the time of publication, there remained insufficient evidence to fully explain differences in observations between Kilifi and Bagamoyo; and an inverse relationship was identified for the RTS,S/AS01 vaccine, which exhibited higher efficacy in areas of lower transmission compared with those with higher transmission,[3] underscoring the complexity of vaccine performance across varying epidemiological contexts. As a result of these uncertainties, it is currently unclear whether the model accurately captures vaccine impact in low-transmission settings, and this question requires further research once longer-term follow-up data become available.

Our median estimated ICERs of $4–13 per case averted and $19–68 per DALY averted at 20% $Pf\mathrm{PR}_{2-10}$ are similar to those estimated for other existing malaria interventions,[23] and were lowest for age-based implementation with a single booster dose. In low-transmission settings, cost-effectiveness ratios were higher than in high-transmission settings, but remained similar to other interventions. Our estimates for R21/Matrix-M are lower than previous estimates for RTS,S/AS01,[10] driven both by the lower dose cost (currently $3·90 per dose for R21/Matrix-M *vs* €9·30 per dose for RTS,S/AS01)[18] and by our estimated more durable vaccine efficacy. The cost per DALY averted was also similar to estimates for other childhood vaccines in Africa.[24]

There were several limitations to our analysis. First, our modelled relationship between anti-circumsporozoite protein antibody titres and vaccine efficacy was based on fits to immunogenicity and vaccine efficacy from a single site. We used these data because the phase 2b trial includes the longest period of follow-up (3 years) with both immunogenicity and clinical data. Although our model validation against the phase 3 data is reassuring, the model will need to be refitted to all trial sites once longer follow-up data are available. Although data were available for 3 years of follow-up, projected vaccine efficacy beyond this period has large associated uncertainty bounds. Second, in fitting we did not explicitly model the other interventions that were in place in the phase 2b trial. Interventions might be synergistic (as observed between seasonal malaria chemoprevention and RTS,S/AS01),[6] hence further research is needed to understand and capture these effects. Third, the estimated association between antibody dynamics and vaccine efficacy was based on models previously developed for the RTS,S/AS01 vaccine,[12] but potential bias introduced through model or previous mis-specification was not investigated. Although the duration of protection and waning of vaccine efficacy over time followed the pattern in antibody titres following the primary doses and the first booster dose, there appeared to be some divergence following the second booster dose. However, because only a small subset of trial participants received the second booster and follow-up was limited to 1 year at the

time of the analysis, further evaluation of these findings will be required. Finally, our modelled generalised settings do not capture the full diversity of sub-Saharan African contexts. Tailored models using local epidemiology and cost data, along with comparisons to other interventions, are crucial for adapting these findings to specific settings.

The feasibility and broader benefits of childhood vaccination against *P falciparum* malaria, including a reduction in all-cause childhood mortality, have already been demonstrated through the pilot implementation of the RTS,S/AS01 vaccine. However, wider roll-out of this vaccine has been limited to date given restrictions on its availability, with 4 million doses available in 2023 and an expected increase to 15 million doses annually by 2026.[26] Thus, introductions have been prioritised to areas of highest need.[4] The greater supply of R21/Matrix-M, up to 200 million doses annually,[25] offers the potential for more rapid roll-out across sub-Saharan Africa. Given the similarities between RTS,S/AS01 and R21/Matrix-M in terms of their mechanism of action (both inducing anti-circumsporozoite protein antibodies as their primary target) and similar or slightly higher vaccine efficacy of R21/Matrix-M, the availability of R21/Matrix-M as an alternative vaccine offers the opportunity to reverse recent increasing trends in malaria burden and put the continent back on track towards achieving the 2030 sustainable development goals.

Contributors

PW, ACG, KJE, and AVSH conceived the study. NS, HMT, GDC, and PW developed the model code and undertook the data analysis and modelling. KM contributed to the modelling. HMN, MAS, HS, MSD, HT, AVSH, and KJE contributed to the protocol and design of the phase 2 and 3 trials. HMN, OT, MAS, TR, MCT, MdAB, AS, HS, MSD, HT, AVSH, and KJE contributed to the implementation of the phase 2 and 3 trials. SP-M, JA, and FRL contributed to implementation and data collection in the phase 2 and 3 trials. DB, LS, DW, KR, and KJE contributed to laboratory studies of immunogenicity in the phase 2 trial. AD, J-BO, MAS, MH, and AO contributed to the design and implementation of the phase 3 trial. NS, HMT, and PW have accessed and verified the data. NS, HMT, PW, and ACG contributed to the first draft of the manuscript and were responsible for the decision to submit the manuscript. All authors reviewed and contributed to the final manuscript. NS, HMT, PW, and ACG 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 are entitled to a royalty share on any future income in conformity with the University of Oxford's policy. KJE was an employee of the University of Oxford at the time of the work and is now an employee of GSK. KJE holds restricted shares in the GSK group of companies. The University of Oxford has received funding from the Serum Institute of India to support funding of several African trials including the ongoing phase 3 trial of R21/Matrix-M. AVSH is chief investigator of these trials. PW has received funding from Gavi and the Wellcome Trust in the past 36 months. ACG has received funding from Gavi and NIH and consulting fees from the Global Fund in the past 36 months and is a trustee at Malaria No More UK. All other authors declare no competing interests.

Data sharing

The code required to rerun the analysis in this study is available at https://github.com/mrc-ide/r21_vacc_antibody_model/. The transmission model is available at https://github.com/mrc-ide/malariasimulation/. All model estimates of impact and cost-effectiveness are provided in appendix 2. Access to anonymised participant data from the phase 2 trial used in the model fitting is detailed in the original publication.

Acknowledgments

This work was supported by a joint investigator award to ACG and Prof Katharina Hauck from the Wellcome Trust (220900/Z/20/Z). PW acknowledges support from the Bill & Melinda Gates Foundation (INV-043624). ACG, NS, HT, and PW acknowledge funding from the UK Medical Research Council (MRC) Centre for Global Infectious Disease Analysis (MR/X020258/1), funded by MRC. This UK-funded award is carried out in the frame of the Global Health EDCTP3 Joint Undertaking. The phase 2 trial was mainly funded by a European and Developing Countries Clinical Trials Partnership grant (funded in turn by the EU) to the Multi-Stage Malaria Vaccine Consortium (RIA2016V-1649), with additional support from the Wellcome Trust through Translation Award 205981/Z/17/Z, and from the UK National Institute for Health Research to the Oxford Biomedical Research Centre's Vaccines for Emerging and Endemic Diseases theme. Vaccine manufacture and supply was supported and undertaken by the Serum Institute of India, and the Matrix-M adjuvant was provided by Novavax. The phase 3 trial was mainly funded by the Serum Institute of India with additional funding to some trial sites from open philanthropy. For the purpose of open access, the author has applied a creative commons attribution licence to any author-accepted manuscript version arising from this submission. We thank Prof Katharina Hauck for helpful discussions on the cost-effectiveness aspect of this work.

References

1 WHO. World malaria report 2022. Geneva: World Health Organization, 2022.
2 WHO. Malaria vaccine: WHO position paper, March 2022. *Weekly Epidemiol Record* 2022; **97:** 60–78.
3 RTSS Clinical Trials Partnership. 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. *Lancet* 2015; **386:** 31–45.
4 Malaria Policy Advisory Group. Malaria Policy Advisory Group to the WHO: day 1 of the April 2023 meeting. Geneva: World Health Organization, 2023.
5 Malaria Vaccine Implementation Programme (MVIP) Programme Advisory Group. Full evidence report on the RTS,S/AS01 malaria vaccine. 2021. https://cdn.who.int/media/docs/default-source/immunization/mvip/full-evidence-report-on-the-rtss-as01-malaria-vaccine-for-sage-mpag-%28sept2021%29.pdf (accessed Oct 26, 2023).
6 Chandramohan D, Zongo I, Sagara I, et al. Seasonal malaria vaccination with or without seasonal malaria chemoprevention. *N Engl J Med* 2021; **385:** 1005–17.
7 Datoo MS, Natama MH, Somé A, et al. Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial. *Lancet* 2021; **397:** 1809–18.
8 Datoo MS, Natama HM, Somé A, et al. Efficacy and immunogenicity of R21/Matrix-M vaccine against clinical malaria after 2 years' follow-up in children in Burkina Faso: a phase 1/2b randomised controlled trial. *Lancet Infect Dis* 2022; **22:** 1728–36.
9 Datoo MM, Dicko A, Tinto H, et al. Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: a multicentre, double-blind, randomised, phase 3 trial. *Lancet* 2024; published online Feb 1. https://doi.org/10.1016/S0140-6736(23)02511-4.
10 Penny MA, Verity R, Bever CA, et al. Public health impact and cost-effectiveness of the RTS, S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. *Lancet* 2016; **387:** 367–75.
11 Thompson HA, Hogan AB, Walker PG, et al. Seasonal use case for the RTS, S/AS01 malaria vaccine: a mathematical modelling study. *Lancet Glob Health* 2022; **10:** e1782–92.
12 White MT, Verity R, Griffin JT, et al. Immunogenicity of the RTS, S/AS01 malaria vaccine and implications for duration of vaccine efficacy: secondary analysis of data from a phase 3 randomised controlled trial. *Lancet infect Dis* 2015; **15:** 1450–58.

13 Griffin JT, Bhatt S, Sinka ME, et al. Potential for reduction of burden and local elimination of malaria by reducing *Plasmodium falciparum* malaria transmission: a mathematical modelling study. *Lancet Infect Dis* 2016; **16:** 465–72.

14 Natama HM, Rovira-Vallbona E, Somé MA, et al. Malaria incidence and prevalence during the first year of life in Nanoro, Burkina Faso: a birth-cohort study. *Malar J* 2018; **17:** 163.

15 Griffin JT, Hollingsworth TD, Okell LC, et al. Reducing *Plasmodium falciparum* malaria transmission in Africa: a model-based evaluation of intervention strategies. *PLoS Med* 2010; **7:** 8.

16 Charles GD, Winskill P, Topazian HM, Challenger J, Fitzjohn R. malariasimulation: an individual based model for malaria. R package version 1.4.3. 2022. https://mrc-ide.github.io/malariasimulation/ (accessed Oct 26, 2023).

17 United Nations Department of Economic and Social Affairs Population Division. World population prospects 2022 demographic indicators by region, subregion and country, annually for 1950–2100. 2022. https://population.un.org/wpp/ (accessed Oct 26, 2023).

18 UNICEF Supply Division. Malaria vaccine: questions and answers on vaccine supply, price, and market shaping October 2023. 2023. https://www.unicef.org/supply/media/19456/file/Malaria%20-%20Vaccine%20-%20QA%20-%20October%202023%20-%20English%20.pdf (accessed Oct 26, 2023).

19 Diawara H, Bocoum FY, Dicko A, et al. Cost of introducing and delivering malaria vaccine (RTS,S/AS01(E)) in areas of seasonal malaria transmission, Mali and Burkina Faso. *BMJ Glob Health* 2023; **8:** 4.

20 Qin L, Gilbert PB, Corey L, McElrath MJ, Self SG. A framework for assessing immunological correlates of protection in vaccine trials. *J Infect Dis* 2007; **196:** 1304–12.

21 Sagara I, Zongo I, Cairns M, et al. The anti-circumsporozoite antibody response of children to seasonal vaccination with the Rts, S/As01e malaria vaccine. *Clin Infect Dis* 2022; **75:** 613–22.

22 WHO. Technical consultation on the malaria rebound phenomenon. 2022. https://www.who.int/publications/i/item/9789240055582 (accessed Nov 16, 2023).

23 Conteh L, Shuford K, Agboraw E, Kont M, Kolaczinski J, Patouillard E. Costs and cost-effectiveness of malaria control interventions: a systematic literature review. *Value in Health* 2021; **24:** 1213–22.

24 Ozawa S, Mirelman A, Stack ML, Walker DG, Levine OS. Cost-effectiveness and economic benefits of vaccines in low-and middle-income countries: a systematic review. *Vaccine* 2012; **31:** 96–108.

25 Serum Institute of India. R21/Matrix-M malaria vaccine developed by University of Oxford receives regulatory clearance for use in Ghana. 2023. https://www.seruminstitute.com/press_release_sii_130423.php (accessed April 13, 2023).