Background paper

Full evidence report on the R21/Matrix-M™ malaria vaccine

Prepared by the SAGE/MPAG Working Group on Malaria Vaccines to support the joint review of the R21/Matrix-M malaria vaccine by the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Group (MPAG)

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List of abbreviations

ACTs	artemisinin-based combination therapies
AESI	adverse event of special interest
API	annual parasite
BBIL	Bharat Biotech
CI	confidence interval
CIOMS	Council for International Organization of Medical Science
CSP	circumsporozoite protein
DALY	disability-adjusted life year
DHS	Demographic and Health Survey
GACVS	Global Advisory Committee on Vaccine Safety
Gavi	Gavi, the Vaccine Alliance
HepB	Hepatitis B
HIV	human immunodeficiency virus
ICER	incremental cost-effectiveness ratio
IPTi	Intermittent preventive treatment of malaria in infants (now known as perennial malaria chemoprevention)
IPTp	Intermittent preventive treatment of malaria in pregnancy
IPTsc	Intermittent preventive treatment of malaria in school-aged children
IRS	indoor residual spraying
ITN	insecticide-treated net
LLIN	long-lasting insecticidal net
mITT	modified intention-to-treat
MIS	Malaria Indicator Survey
MPAG	Malaria Policy Advisory Group (formerly MPAC)
mPP	modifed per protocol
MVIP	Malaria Vaccine Implementation Programme
PCV	pneumococcal conjugate vaccine
PDMC	post-discharge malaria chemoprevention
PfPR	*Plasmodium falciparum* parasite rate
PIRI	periodic intensification of routine immunization
PMC	perennial malaria chemoprevention (formerly known as intermittent preventive treatment in infants [IPTi])
PP	per protocol
RDT	rapid diagnostic test
SAE	serious adverse event
SAGE	Strategic Advisory Group of Experts on Immunization
SIIPL	Serum Institute of India Pvt Ltd
SMC	Seasonal malaria chemoprevention
SUSAR	suspected unexpected serious adverse reactions
WHO	World Health Organization

1. Executive summary

Background

In October 2021, WHO recommended the first malaria vaccine, RTS,S/AS01, for the prevention of *Plasmodium falciparum (P. falciparum)* malaria in children living in regions with moderate to high transmission, as defined by WHO. The vaccine can be given as a 3-dose primary schedule with a later fourth dose to prolong duration of protection. In areas of highly seasonal malaria or perennial malaria transmission with seasonal peaks, countries may consider providing the vaccine in a 5-dose strategy seasonally, just prior to the peak transmission season, to increase impact.

As of August 2023, RTS,S/AS01 had been delivered to over 1.8 million children through the immunization programmes of Kenya, Ghana, and Malawi in pilot introductions as part of the Malaria Vaccine Implementation Programme (MVIP). During the first 24 months after vaccine introduction, in the context of 65–70% coverage with the first three vaccines doses, an approximate 30% reduction in hospitalizations for severe malaria was measured in children age-eligible for the vaccine. In addition, although not yet powered to measure impact on mortality, vaccine introduction was associated with a 9% reduction in all-cause mortality. This level of impact was seen even in the setting of high long-lasting insecticidal net (LLIN) coverage and good access to care.

Gavi, the Vaccine Alliance, has reported "unprecedented demand" for malaria vaccines. Over 28 countries responded favourably to a Gavi call for expression of interest in introducing the malaria vaccine. As of August 2023, 17 countries have been approved by Gavi to receive support for malaria vaccine introduction and additional applications are under review. Gavi estimates annual global demand for malaria vaccines at 40–60 million doses by 2026, growing to 80–100 million doses or more each year by 2030.

However, the initial supply of RTS,S/AS01 is insufficient to meet demand. Based on a supply agreement with UNICEF, GSK is expected to deliver 18 million doses of RTS,S/AS01 during the 2023–2025 period; these doses have already been allocated to a sub-set of approved countries for subnational introductions-limited to areas where malaria burden and death are highest - according to the Framework for allocation of limited malaria vaccine supply. Expansion within countries or to other countries is dependent on additional malaria vaccine supply becoming available.

Given the ongoing challenge of malaria burden reduction, the demonstrated value of a safe and effective malaria vaccine as a complementary malaria control tool, the insufficient supply of RTS,S/AS01, and the interest in a healthy malaria vaccine market, there remains a continued need for new malaria vaccines such as R21/Matrix-M, should the evidence demonstrate their safety and potential public health impact.

R21/Matrix-M technical specifications

The R21/Matrix-M vaccine aims to reduce clinical malaria due to *P. falciparum* in infants and young children. Similar to RTS,S/AS01, R21/Matrix-M generates immunity against the *P. falciparum* pre-erythrocytic circumsporozoite protein (CSP).

R21/Matrix-M malaria vaccine, manufactured by the Serum Institute of India Pvt Ltd (SIIPL), is formulated with the saponin-based adjuvant Matrix-M, which is manufactured by Novavax AB.

R21/Matrix-M Phase 1 and 2 studies

In a Phase 2b trial in Burkina Faso in an area with highly seasonal malaria transmission, three vaccinations were administered at 4-week intervals just prior to the malaria season, with dose 4 administered 1 year later, prior to the next malaria season. Three groups of 150 children aged 5–17 months were enrolled: group 1 received 5 µg R21 plus 25 µg Matrix-M; group 2 received 5 µg R21 plus 50 µg Matrix-M; and

group 3, the control group, received rabies vaccine. At the end of the transmission season, 6 months after dose 3, comparing group 1 with group 3 resulted in vaccine efficacy (VE) against all episodes of clinical malaria of 74% (95% CI: 63–82; $P < 0.0001$); comparing group 2 with group 3 resulted in 77% efficacy (67–84; $P < 0.0001$). Because very few cases occurred during the 6 months of the dry season, VE estimates were essentially unchanged at 12 months post dose 3.

In the 12 months following dose 4, VE against all episodes of clinical malaria was 71% (95% CI: 60–78) in group 1, and 80% (72–85) in group 2. Overall, vaccine efficacy against all episodes of clinical malaria during the 24 months) following the primary series of vaccinations (and 12 months following dose 4)was 63% (95% CI: 55–71; $P < 0.0001$) in group 1 and 77% (69–83; $P < 0.0001$) in group 2.

R21/Matrix-M Phase 3 trial

Study design and overview

A double-blind, randomized, controlled Phase 3 trial began in late April 2021 to assess the safety and protective efficacy of R21/Matrix-M against clinical malaria caused by *P. falciparum* in children 5–36 months of age at first vaccination using a seasonal vaccination strategy, whereby the primary series and dose 4 given 12 months after dose 3 are given just prior to the malaria transmission season in Nanoro, Burkina Faso, and Bougouni, Mali, (areas of highly seasonal transmission), or using an age-based 4-dose ("standard") vaccine strategy (also referred to in the trial as a "standard" strategy), in Bagamoyo, Tanzania, and Kilifi, Kenya, (areas of low/moderate perennial transmission) and Dandé, Burkina Faso, (an area of highly seasonal moderate transmission).

Participants were randomized 2:1 to receive vaccination with 5 µg R21 adjuvanted with 50 µg Matrix-M, or a control vaccination (a licensed rabies vaccine). Efficacy of vaccination was assessed by comparing incidence of passively detected cases of malaria in the investigational vaccine arm with the control (rabies vaccine) arm in the seasonal vaccination group and the age-based or "standard" vaccination group. The R21/Matrix-M vaccine arm participants received three vaccinations in monthly intervals by intramuscular route, followed by a fourth vaccination 12 months following the third vaccination. The control arm participants received three vaccinations given intramuscularly with an internationally licensed rabies vaccine, followed by a fourth vaccination with rabies vaccines given 12 months following the third vaccination.

The primary efficacy objectives were:

- to assess the protective efficacy of R21/Matrix-M against clinical malaria caused by *P. falciparum*, in children aged 5–36 months living in a malaria endemic area, 12 months after completion of the primary course (standard vaccination);
- to assess the protective efficacy of R21/Matrix-M against clinical malaria caused by *P. falciparum*, in children aged 5–36 months living in a malaria endemic area, 12 months after completion of the primary course (seasonal vaccination).

The target sample size was 3 200 children in the R21/Matrix-M arm and 1600 children in the control arm, divided equally among seasonal (1 600/800) and standard (1 600/800) sites. For this report, the primary analyses for safety and efficacy were based on the modified intention-to-treat population (mITT), defined as the population who received at least one dose of vaccine. Results based on the per protocol population (PP) were similar to the mITT analysis and are included in Annex 3.

R21/Matrix-M efficacy and duration of protection

VE against all episodes of clinical malaria

- Among children of all ages (5–36 months at first vaccine dose) and when combining the data from the two sites where R21/Matrix-M was provided seasonally in areas of highly seasonal malaria transmission, VE against all episodes of clinical malaria 12 months following dose 3 was 75% (95% CI: 71–78), and did not differ significantly by site. In the 18 months following dose 3 (6 months following dose 4), the combined VE and per site VE remained similar to the 12-month estimates.
- Among children of all ages (5–36 months at first vaccine dose) and when combining the data from sites where R21/Matrix-M was given in a standard schedule in areas of low to moderate or highly seasonal moderate transmission, VE against all episodes of clinical malaria 12 months following dose 3 was 61% (95% CI: 53–67). As observed in seasonal sites, VE was not significantly different when the first vaccine dose was given in younger children (5-17 months at first vaccine dose) compared to older children (18-36 months at first vaccine dose).
- VE was reasonably high after 12 months in settings of low to moderate transmission and showed good durability over 12 months (prior to dose 4). In areas of highly seasonal transmission, VE also showed good durability over 6 months post dose 4.

VE against severe malaria

- Few cases of severe malaria were observed in the trial, and the power to assess VE against severe malaria was low.
- At seasonal sites, among all age children (5–36 months at first vaccine dose) through 18 months of follow-up, there were 16 cases of severe malaria, with 8 occurring in the R21/Matrix-M and 8 in the control arm, resulting in a VE estimate of 50%, with confidence intervals that included zero.
- At standard sites, through 12 months of follow-up, there was a slightly higher rate of severe malaria cases in the R21/Matrix-M arm (7 cases) compared to the control arm (3 cases). Confidence intervals were wide.

VE against malaria hospitalization or all-cause mortality

- As observed with severe malaria, malaria hospitalization or participant death were relatively infrequent events compared to clinical malaria.
- At seasonal sites, among all age children (5–36 months at first vaccine dose) through 18 months of follow-up, 16 cases of malaria hospitalization were recorded, with 8 occurring in the R21/Matrix-M and 8 in the control arm, resulting in estimates of VE against malaria hospitalization of 50% (95% CI: -32 to 81), noting wide confidence intervals. At standard sites, during 12 months follow-up post dose 3, there were 9 cases of malaria hospitalization in the R21/Matrix-M arm and 4 cases in the control arm, resulting in estimates of VE against malaria hospitalization of -8% (95% CI: -250 to 67), again nothing the wide confidence intervals.
- A statistically non-significant imbalance in number of deaths was observed, with 15 deaths in the R21/Matrix-M and 4 deaths in the control arm (noting the 2:1 randomization). No VE estimates against all-cause mortality were statistically significant by site or when stratified by age group at which the first vaccine dose was given.

VE against all episodes of clinical malaria by sex

- VE estimates against all episodes of clinical malaria did not differ by the sex of the participant.

Duration of protection against all episodes of clinical malaria

- At sites with highly seasonal malaria and seasonal administration, among children of all ages (5–36 months at first vaccine dose), VE point estimates remained high for the first 6 months following dose 3 (81% during months 1–3 and 74% during months 4–6), then dropped significantly during months 7–9 (44%), but increased again in months 10–12 (prior to dose 4) to 67%. After dose 4, protective efficacy was maintained during the following 6 months, with point estimates of 79% (13–15 months) and 69% (16–18 months).
- At standard administration sites among children of all ages (5–36 months at first vaccine dose), VE point estimates declined slowly over time, with point estimates decreasing from 79% during 1–3 months post dose 3, to 68% during 4–6 months, 64% during 7–9 months, and 63% during 10–12 months (confidence limits overlapped). This pattern did not differ significantly by site. Of interest is that the efficacy observed in Dandé during the first year was similar to that seen in the sites where the vaccine was given seasonally, even though vaccination in Dandé was administered about 6 months before the high transmission season, indicating durability of protection during the 12-month follow-up period.

R21/Matrix-M safety

An expert working group convened to assess R21 safety (the R21 Safety Working Group) and the Global Advisory Committee for Vaccine Safety (GACVS) reviewed the available safety data on R21/Matrix-M and concluded that no major safety concerns were noted that would warrant a delay in recommendation of R21/Matrix-M for public health use. A thorough review resulted in the following conclusions and recommendations:

- Overall, the frequency of SAEs was balanced among children randomized to receive the R21/Matrix-M vaccine and those who received the control (rabies) vaccine.
- There was a higher number and clustering of febrile convulsions within 3 days after vaccination among children in the R21/Matrix-M arm (5 [0.15%]) compared to the control arm (1 [0.062%]), noting 2:1 randomization. A *post-hoc* analysis of the attributable risk of febrile convulsions within 0–3 days after vaccination compared to 4–27 days after vaccination showed that the risk difference for the R21/Matrix-M arm is 0.000 36 (0.000 008–0.000 71, $P = 0.004$) and the risk difference for the control arm is 0.000 16 (–0.000 15 to 0.000 47, $P = 0.28$). The risk difference of 0.00036 translates to an attributable risk of 1/2800 doses administered. This shows evidence of clustering in the R21/Matrix-M arm ($P = 0.004$) but not in the control arm ($P = 0.28$). This is in the range of the attributable risk for febrile convulsions with other childhood vaccines, for example RTS,S/AS01, which was 2.5/1000 doses, and for measles vaccine, which was 1/2000–3000 doses.
- The GACVS noted the limited number of young children who have received Matrix-M to date compared to adults, although no specific issues or concerns have been identified.
- In the setting of a small number of overall deaths in the trial, an imbalance in deaths was noted; excluding trauma or accidents, and noting 2:1 randomization, there were 12 deaths (0.4%) in the R21/Matrix-M arm, and 3 (0.2%) in the control arm. However, the imbalance was not statistically significant and may have been a chance finding. Not deaths were assessed as causally related to vaccination, there was no pattern among deaths in relation to timing of

vaccination, and there were no observed patterns or consistency among causes of death.

- Meningitis and cerebral malaria were uncommon, and no imbalance was noted between the R21/Matrix-M and control arms.
- GACVS recommended post-introduction safety monitoring for adverse events of special interest (AESIs) including deaths, seizures, febrile convulsions within 7 days, and severe fever (which can lead to febrile convulsions), especially in the context of co-administration with other vaccines. The need for additional areas of post-marketing surveillance or studies will be considered once additional data are presented to GACVS, including the safety data related to the co-administration of other vaccines.
- Rebound malaria should be assessed during the ongoing clinical trial in alignment with recommendations from the WHO Technical consultation on the malaria rebound phenomenon; GACVS noted that a WHO recommendation for vaccine use does not need to wait for such an assessment.
- As with all new vaccines with limited experience, GACVS recommends overall adequate pharmacovigilance for post-introduction safety monitoring of the new R21/Matrix-M vaccine should WHO issue a policy recommendation approving its use.

Other ongoing R21/Matrix-M studies

Single-vial presentation

R21/Matrix-M is available in a two-vial presentation, containing one vial of R21 antigen and one vial of Matrix-M adjuvant. In an ongoing clinical trial, a single-vial presentation with a composition of R21 and Matrix-M is being evaluated for efficacy.

R21/Matrix-M safety and immunogenicity in HIV-positive children

In a Phase 1b trial (VAC092 – NCT05385510), 100 HIV-positive (WHO HIV stage 1 or 2 disease) Ugandan children aged 5–36 months have been enrolled to receive R21/Matrix-M vaccine to assess safety and immunogenicity. Initial safety and immunogenicity data should be available in 2023.

Programmatic considerations

High, equitable vaccine coverage was achieved during the pilot introductions of RTS,S/AS01. Given the similar characteristics of R21/Matrix-M to RTS,S/AS01 (target populations, delivery strategies and schedules), that experience is assumed to be applicable if R21/Matrix-M is included under the current WHO recommendation for malaria vaccines.

Vaccine presentation

R21/Matrix-M is currently available in a two-vial presentation, with a single-vial presentation currently being evaluated. The storage temperature of the vaccine is 2–8 °C.

Feasibility and acceptability

The feasibility data generated during the MVIP with RTS,S/AS01 introduction and scale-up are encouraging; findings would likely be similar with the introduction R21/Matrix-M. Although, at pilot initiation, RTS,S/AS01 was a new vaccine delivered through childhood immunization programmes and required additional visits in the vaccination schedule, reasonably high coverage of the first three doses was achieved in all three pilot countries in a relatively short time period and in the context of COVID-19 pandemic challenges. While achieving high fourth-dose coverage remains challenging in Malawi and

Kenya, in Ghana, dose 4 coverage has increased considerably after the immunization schedule was changed to administer dose 4 at 18 months of age rather than 24 months of age; dose 4 administration now coincides with administration of the meningococcal A vaccine and dose 2 of measles-rubella vaccine.

Qualitative studies conducted as part of the MVIP show that caregivers and health care providers generally have positive attitudes towards the current malaria vaccine.

Economic and financial attributes

To the extent R21/Matrix-M is expected to have similar delivery strategies, schedule, and target population as RTS,S/AS01, currently available cost of delivery estimates on RTS,S/AS01 are assumed to be the most applicable. Direct comparison of cost estimates across vaccine delivery costing studies should be made with caution as the methods, delivery strategies, settings, and context can vary widely. However, in broad terms, the resources required for malaria vaccine delivery are comparable to those needed for other new vaccine introductions. The cost of delivery estimates from the RTS,S/AS01 pilot countries drawn from phased subnational introduction (rather than a full national introduction) are comparable to costs of human papillomavirus (HPV) vaccine costs per dose delivered under a pilot setting.

Equity considerations

Endline household surveys from the MVIP show that the RTS,S/AS01 malaria vaccine was delivered equitably by sex and by socioeconomic status (across rural and urban residences in Kenya and Ghana; higher coverage was observed among rural residences in Malawi compared to urban residences).

Household survey data also showed that introduction of the malaria vaccine expanded the percentage of children accessing at least one malaria prevention measure – an ITN or the malaria vaccine - with coverage increasing from 61% to 94% (with 52% of children benefitted from both an LLIN and the vaccine) in Ghana, 78% to 95% (with 62% benefitting from both interventions) in Malawi, and 94% to 98% (with 79% benefitting from both interventions) in Kenya.

Co-administration with other vaccines

A study underway in Mali is assessing the safety and immunogenicity of co-administration of R21/Matrix-M dose 3 with yellow fever and measles-rubella vaccine at 9 months of age, and will assess the co-administration of R21/Matrix-M with pentavalent (diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b), rotavirus, pneumococcal, and oral polio vaccines at 6, 10 and 14 weeks of age. This study is expected to be completed in August 2024. No co-administration studies are currently planned with R21/Matrix-M and meningococcal A, typhoid conjugate, cholera, Japanese encephalitis, tick-borne encephalitis, rabies, mumps, influenza or varicella vaccines.

Evaluation and management of malaria rebound within the public health system

Malaria rebound, defined as a period of increased malaria risk after time-limited protection from malaria, has been shown to occur infrequently and, when present, does not appear to have a measurable cumulative negative impact. Deployment of effective interventions should not be delayed to measure rebound. It is useful to assess rebound over longer periods of follow-up. In the context of vaccines with gradually waning protection, rebound could be assessed through continued follow-up of clinical trial participants following a policy recommendation. If evidence of rebound is identified, programmatic measures tailored to the local context should be taken to ameliorate risk.

Regulatory review

In September 2022, the Drugs Controller General of India granted SIIPL a license for export of R21/Matrix-M to the United Kingdom. To date, national regulatory authorities of Ghana, Nigeria and Burkina Faso

have approved R21/Matrix-M for use in their country (7,8).

Vaccine supply

SIIPL has stated publicly that it has established capacity to manufacture more than 200 million doses annually. Current projections suggest that, if R21/Matrix-M was recommended and prequalified by the end of 2023, the combined availability of RTS,S/AS01 and R21/Matrix-M would greatly improve the supply situation and likely result in sufficient supply to meet demand during the first half of 2024.

Modelled public health impact and cost-effectiveness estimates of R21/Matrix-M

Modelling predictions suggest that the introduction of R21/Matrix-M into childhood immunization programmes could have a substantial impact on reducing malaria cases and malaria deaths in children living in settings with endemic malaria in Africa. The model estimates that the introduction of R21/Matrix-M in a four-dose schedule using an age-based, seasonal or hybrid strategy could avert between 32 324 and 398 726 clinical malaria cases and between 216 and 733 malaria deaths for every 100 000 fully vaccinated children over a 15-year time horizon in settings with 3% and 65% *P. falciparum* parasite rate in 2—10 year old children ($PfPR_{2–10}$), respectively. This represents approximately one-third of all malaria deaths in children under 5 years of age. Assuming a R21/Matrix-M vaccine price of US$ 3 per dose, the model estimates costs of US$ 69 and $ 3 per clinical case averted and US$ 202 and $27 per disability-adjusted life year (DALY) averted in the same settings (3% and 65% PfPR2–10).

Estimates of R21/Matrix-M cost-effectiveness are comparable with other malaria interventions and other childhood vaccines across a range of low to high transmission settings in sub-Saharan Africa. In lower transmission settings (between 1—10% $PfPR_{2–10}$), the cost-effectiveness decreases, however the vaccine still provides comparable cost-effectiveness to other interventions. Cost-effectiveness ratios were considerably higher and more uncertain in the lowest transmission setting (1% $PfPR_{2-10}$).

As is the case for other cost-effectiveness studies, the results are highly context-specific and can vary depending on the assumed levels of prevention and treatment measures already in place at the time of vaccine introduction.

Conclusions and recommendations for SAGE and MPAG consideration

The SAGE/MPAG Working Group on Malaria Vaccines recommends the programmatic use of R21/Matrix-M for the prevention of *P. falciparum* malaria in children living in malaria endemic areas, prioritizing areas of moderate and high transmission. Thus, the R21/Matrix-M vaccine would be recommended as a second pre-erythrocytic malaria vaccine to be included under the current WHO recommendations for malaria vaccines.

The vaccine should be provided in a schedule of four doses in children from around 5 months of age[1] for the reduction of *P. falciparum* malaria disease and burden.

A dose 5, given 1 year after dose 4, may be considered in areas where there is a significant malaria risk remaining in children a year after receiving dose 4. More details on implementation considerations are provided in section 11.5.2.

[1] Vaccination programmes may choose to give dose 1 at a later age based on operational consideration. Studies with RTS,S/AS01 indicated lower efficacy if dose 1 was given around 6 weeks of age. However, it seems unlikely that efficacy would be substantially reduced if some children received the dose 1 at 4 rather than 5 months, and providing vaccination at an age younger than 5 months may increase coverage or impact.

Countries may consider providing the vaccine using an age-based, seasonal or hybrid delivery strategies in areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks.

Countries should prioritize vaccination in areas of moderate and high transmission, but may also consider providing the vaccine in low transmission settings. Both R21/Matrix-M and RTS,S/AS01 are efficacious in areas of low malaria transmission, and clinical trial data and mathematical modelling estimate considerable impact, including in areas of low malaria transmission. With a second vaccine coming to market and other market shaping efforts, there is a high potential for lower vaccine cost and improved vaccine cost-effectiveness. Decisions on expanding to low transmission settings should be considered at a country level, based on the overall malaria control strategy, cost-effectiveness, affordability and programmatic considerations, such as whether including such areas will simplify delivery.

The SAGE/MPAG Working Group on Malaria Vaccines notes that the standard sites in the Phase 3 trial are areas of low to moderate transmission, and information on VE and duration of protection with R21/Matrix-M in high transmission perennial sites is currently lacking. The SAGE/MPAG Working Group on Malaria Vaccines recommends that as the vaccine is deployed under programmatic conditions in high burden areas with perennial transmission, post-licensure monitoring of impact should be undertaken to provide this information.

Evidence to date shows that the R21/Matrix-M has an acceptable safety profile. However, the SAGE/MPAG Working Group on Malaria Vaccines and GACVS note that, although the Matrix-M adjuvant has been widely used in other vaccines, the available safety data are primarily in adults. Because young children are the main target population for R21/Matrix-M, post-licensure monitoring in children receiving R21/Matrix-M is recommended to obtain additional safety information in this age group, including monitoring the frequency of febrile convulsions. The SAGE/MPAG Working Group on Malaria Vaccines also agrees with the GACVS recommendations for post-authorization monitoring of AESIs, including monitoring of deaths, and continued follow-up of trial participants to measure duration of protection and assessment of potential rebound.

The availability of a second malaria vaccine is welcome at a time when progress in malaria control has stalled in recent years, and other current malaria control tools face challenges in terms of biological threats such as drug and insecticide resistance, and in the context of continuing and unacceptably high levels of malaria illness and death. Demand for a malaria vaccine is very high, and supply of the first malaria vaccine is currently not able to meet demand. A second malaria vaccine, in addition to RTS,S/AS01, could help close the gap between supply and demand, enabling broader access and saving tens of thousands of lives each year. A second vaccine would also create a healthier malaria vaccine market that is not reliant on a single product.

2. Introduction

In October 2021, WHO recommended the first malaria vaccine, RTS,S/AS01, for the prevention of *Plasmodium falciparum (P. falciparum)* malaria in children living in regions with moderate to high transmission, as defined by WHO *(1,2).* The vaccine can be given as a three-dose primary schedule with a later fourth dose to prolong duration of protection. In areas of highly seasonal malaria or perennial malaria with seasonal peaks, the vaccine can be delivered seasonally, just prior to the peak transmission season, to increase impact. The recommendation was based on evidence from clinical trials and the ongoing Malaria Vaccine Implementation Programme (MVIP) that demonstrated the safety and public health impact of the vaccine *(9)*.

As of August 2023, RTS,S/AS01 had been delivered to over 1.8 million children through the childhood immunization programmes of Kenya, Ghana, and Malawi in pilot introductions as part of MVIP. Vaccine delivery has expanded throughout the pilot areas as part of the phased introductions. Demand for the malaria vaccine is high; over 28 countries have expressed interest to receive support from Gavi, the Vaccine Alliance, for introduction of the vaccine. As of August 2023, a year since opening a funding window for malaria vaccines, Gavi has approved applications from 17 African countries. The 18 million doses of RTS,S/AS01 made available by the manufacturer for the years 2023–2025 have been allocated to countries according to the Framework for allocation of limited malaria vaccine supply *(10,11)*. In addition to the MVIP countries of Ghana, Kenya, and Malawi, which will continue vaccine implementation in pilot areas, nine other countries have been allocated vaccine for subnational phased introductions, beginning in areas of highest malaria burden and child mortality. Other countries, already approved for support from Gavi for malaria vaccine introduction, await further supply availability. GSK, the vaccine manufacturer, is increasing production volumes of RTS,S/AS01, with a plan to produce up to 15 million doses annually from 2026 *(12)*. An ongoing product transfer to Bharat Biotech (BBIL) aims to enable higher supply capacity and more sustainable production and is expected to be completed by 2028.

The R21/Matrix-M vaccine, like RTS,S/AS01, targets the circumsporozoite protein (CSP) of *P. falciparum* and showed promising results in a Phase 2b trial in areas of highly seasonal malaria transmission using a four-dose schedule in which doses were delivered just prior to the high transmission season *(13,14)*. A Phase 3 trial began in late April 2021 to assess the safety and protective efficacy of R21/Matrix-M against clinical malaria caused by *P. falciparum* in children 5–36 months using a seasonal vaccination strategy in Nanoro, Burkina Faso, and Bougouni, Mali (areas of highly seasonal transmission) or an age-based ("standard") strategy in Bagamoyo, Tanzania, and Kilifi, Kenya, (areas of low to moderate perennial transmission) and Dandé, Burkina Faso (an area of highly seasonal moderate transmission). Consistent with the current WHO recommendation for a malaria vaccine, R21/Matrix-M is for use in infants and young children for the reduction of *P. falciparum* malaria disease and burden.

The SAGE/MPAG Working Group on Malaria Vaccines of the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Group (MPAG) met in July 2023 to review the R21/Matrix-M Phase 3 evidence to date. As of 31 March 2023, the Phase 3 trial had completed the planned follow-up time for its primary outcome measures of 12 months of follow-up following administration of vaccine dose 3 for both seasonal and standard delivery strategies. Data used for review by the SAGE/MPAG Working Group on Malaria Vaccines in July 2023 include those collected during 18 months of follow-up for seasonal vaccine administration sites (starting from 2 weeks after dose 3) and 12 months of follow-up for the standard vaccine administration sites (starting from 2 weeks after dose 3).

This report summarizes evidence available on R21/Matrix-M from the Phase 3 trial, as well as other available data from Phase 2 and cost-effectiveness studies, regarding the vaccine's safety, efficacy and impact on *P. falciparum* malaria. It also considers relevant lessons learned from experience to date with

the first malaria vaccine, RTS,S/AS01, and its pilot introduction through the MVIP. The report concludes with the SAGE/MPAG Working Group on Malaria Vaccines' assessment and recommendations on R21/Matrix-M vaccine use for consideration by SAGE and MPAG.

3. Background

The 2021 RTS,S/AS01 malaria vaccine full evidence report – section 3 *(9)* contains a detailed discussion of malaria epidemiology, parasites and pathogenesis, and immune response to malaria infection.

3.1. Disease burden of malaria

WHO estimates that in 2021 there were 247 million malaria cases in 84 malaria endemic countries, representing an increase of 2 million cases compared with 2020 *(15)*. Estimated malaria deaths in 2021 were 619 000, essentially unchanged from 2020. Over 95% of cases and deaths occur in sub-Saharan Africa, with most malaria deaths in Africa occurring in children younger than 5 years.

After steady reductions in malaria morbidity and mortality between 2000 and 2015, progress in sub-Saharan Africa has slowed in recent years, and, in some countries, incidence has increased. From 2019 through 2021 in the WHO African Region, malaria cases and deaths increased by 7% and 9%, respectively. Initiatives have been established to support high burden countries in Africa *(16)*, focusing on supporting increased political will and country leadership, a coordinated multi-sector national response, better use of strategic information to drive impact, and improved WHO guidance and strategies for adaptation to the local context.

3.2. Current status of malaria prevention and control measures (updates since 2021)

Given the stalling progress in malaria control (see section 3.1), the world is not on track to achieve the targets to reduce malaria morbidity and mortality set forth in the *Global technical strategy for malaria 2016–2030 (17)*. In 2019, the WHO Strategic Advisory Group on Malaria Eradication concluded that eradication would not be possible by 2050, even with full scale-up of current interventions, and highlighted the pivotal role of effective malaria vaccines. In this context of stalled progress, along with ongoing implementation challenges, the limited efficacy of available interventions, and biological threats to current prevention approaches, WHO recommended the use of malaria vaccines in 2021, which currently includes RTS,S/AS01, as an additional tool for malaria prevention.

In most African countries, substantial malaria prevention and control efforts have been implemented, including the widespread deployment of insecticide-treated nets (ITN), including long-lasting insecticidal nets (LLIN), the use of indoor residual spraying (IRS) of insecticides in some settings, chemoprevention strategies high-risk groups such as pregnant women or young children living in areas of highly seasonal malaria transmission, and prompt diagnosis and treatment using quality assured rapid diagnostic tests (RDTs) and artemisinin-based combination therapies (ACTs). In some settings, these measures have substantially reduced the annual incidence of malaria.

Malaria prevention and control measures recommended by WHO as of 2023 are summarized in Table 1 *(1)*. The additional tools and strategies recommended by WHO since the first malaria vaccine evidence review in 2021 are discussed in sections that follow.

Table 1. WHO-recommended malaria prevention and control measures (WHO Guidelines, 2023)

Strategy	Intervention
Prevention – vector control	• Insecticide-treated nets (ITNs) • Indoor residual spraying (IRS) • Larviciding[a]
Prevention – chemotherapies	• Intermittent preventive treatment of malaria in pregnancy (IPTp) • Seasonal malaria chemoprevention (SMC) • Perennial malaria chemoprevention (PMC) • Post-discharge malaria chemoprevention (PDMC) • Intermittent preventive treatment of malaria in school children (ITPsc) • Mass drug administration (MDA)
Prevention – vaccine	• Malaria vaccine for children
Case management	• "3T" approach – Test fever or history of fever, Treat, Track outcomes • Parasitological diagnosis (using RDT or microscopy) • Treatment of uncomplicated malaria (ACTs) • Treatment of severe malaria (parenteral artesunate or alternatives)

[a] Larviciding is recommended where optimal coverage with ITNs or IRS has been achieved, where aquatic habitats are few, fixed and findable, and where its application is both feasible and cost-effective.

3.2.1. Vector control

Insecticide treated nets (ITNs), including long-lasting insecticidal nets (LLINs), or indoor residual spraying (IRS) of houses with insecticide are long-standing malaria prevention tools. Both interventions are recommended for children and adults living in areas with ongoing malaria transmission, including areas where malaria has been eliminated but the risk of reintroduction remains. ITNs have traditionally relied on a single class of insecticides – pyrethroids – to repel and/or kill the *Anopheles* mosquitoes that transmit the malaria parasite. However, their effectiveness has been challenged by increasing pyrethroid resistance in the vector.

New ITNs treated with other ingredients are now available. These include ITNs that combine pyrethroid with chlorfenapyr – an insecticide that has a different mode of action from pyrethroids – which are recommended for deployment instead of pyrethroid-only LLINs in areas with pyrethroid resistance. Another new ITN contains pyrethroids in combination with pyriproxyfen, which is an insect growth regulator. As these new ITNs may be more costly than standard pyrethroid-only products, national malaria control programmes need to make careful assessments when deciding on whether to introduce or switch, based on local entomological and epidemiological data and cost-effectiveness analysis. In 2023, WHO provided guidance to support programmes in prioritizing ITN product choice and distribution in resource-limited settings *(18)*.

3.2.2. Chemoprevention

The recommendations for seasonal malaria chemoprevention (SMC), perennial malaria chemoprevention (PMC – formerly known as intermittent preventive treatment of malaria in infants [IPTi]), and intermittent preventive treatment of malaria in pregnancy (IPTp) have recently been modified and made more flexible to encourage programmes to adapt elements of these strategies to the local context. New guidance has also been provided on intermittent preventive treatment of malaria in school-aged children (IPTsc) and post-discharge malaria chemoprevention (PDMC).

SMC is a strategy to reduce malaria illness and death in children by providing a therapeutic course of an

antimalarial drug monthly during the high transmission season in areas of highly seasonal malaria. Malaria programmes are encouraged to assess the suitability of SMC based on local malaria epidemiology (including duration of the high transmission season), allowing flexibility in the number of rounds delivered and the age range targeted according to the groups most at risk of severe malaria and available resources. In some circumstances, SMC may be delivered for more than four monthly cycles, and to an age range that extends beyond 5 years. SMC might also be used in areas with perennial transmission with marked seasonal peaks, including in eastern and southern Africa.

In areas of moderate to high perennial malaria transmission, the recommendation for PMC delivery now includes the consideration for provision of PMC beyond 1 year of age to provide protection to children beyond infancy who are at high risk of severe malaria. PMC was previously only recommended in infants under 12 months of age (referred to as IPTi), but new data have documented the value of malaria chemoprevention in children up to 24 months of age. The childhood immunization platform remains important for delivering PMC, and other methods of delivery can be explored to optimize access to PMC. The efficacy and effectiveness of PMC in combination with the malaria vaccine have not yet been evaluated, though a clinical trial to evaluate the efficacy of adding PMC to RTS,S/AS01 administered through the childhood immunization platform in Ghana will begin in 2023.

Until recently, IPTp has been provided during antenatal care visits. WHO recommendations have been modified to include consideration of other delivery options, such as provision of IPTp by community health workers.

IPTsc can be considered for use in school-aged children (5–15 years of age) living in settings with moderate to high perennial or seasonal malaria transmission. IPTsc involves giving a full therapeutic course of antimalarial medicine at predetermined times to reduce disease burden. The regimen should be informed by local malaria epidemiology. National malaria control programmes can consider IPTsc as a strategy if resources allow, while assuring that it does not compromise chemoprevention interventions for those carrying the highest burden of severe disease, such as children under 5 years of age.

PDMC can be considered for use in children living in settings with moderate to high malaria transmission and admitted to hospital with severe anaemia. PDMC consists of a full therapeutic course of an antimalarial medicine at predetermined times following discharge from hospital to reduce the risk of re-admission or death.

Mass drug administration can be used to reduce malaria burden or transmission in particular contexts according to transmission level and parasite species (*P. falciparum* or *P. vivax*), in emergency situations, and for anti-relapse therapy for *P. vivax*. Further details can be found in the WHO guidelines for malaria *(1)*.

3.2.3. Case management

Pyronaridine–artesunate is a new ACT recommended by WHO in 2022; there are now six recommended ACTs for treatment of uncomplicated malaria. In recognition of the continuing threat of antimalarial drug resistance, and especially artemisinin resistance, WHO has developed a strategy to respond to antimalarial drug resistance in Africa, based on four pillars:

1. strengthening surveillance of antimalarial drug efficacy and resistance
2. optimizing use and regulation of diagnostics and therapeutics to limit drug pressure
3. limiting the spread of antimalarial drug-resistant parasites
4. stimulating research and innovation for improved and new tools against resistance *(19)*.

3.2.4. Need for additional tools

Although current malaria prevention and control tools remain generally effective, there are limitations, particularly with respect to prevention. Most are moderately effective (e.g. ITNs *(20)*, IRS *(21)*, PMC (formerly IPTi) *(22)*, RTS,S/AS01 *(23)*, SMC *(24)*) and higher impact can be achieved by layering the different interventions *(25)*. In many areas, malaria transmission and burden remain high even with good coverage of LLINs or IRS *(26)*. Furthermore, substantial barriers limit the ability to bring all recommended preventive tools to scale. In 2021, 68% of households in sub-Saharan Africa had at least one ITN, but only 38% of households owned at least one ITN for every two people *(1)*. PMC has not yet been widely implemented due to concerns about drug resistance. Although substantial scale-up of SMC has occurred with important impact *(27)*, it requires considerable human and financial resources to deliver and maintain high coverage, as well as assure adherence. In most areas where SMC is now deployed, malaria remains the main cause of death and hospitalization in young children, highlighting the need for additional interventions to be added to those currently implemented *(1)*.

Moreover, vector control and drug-based malaria control tools are challenged by important biological threats, such as insecticide resistance or antimalarial drug resistance. The emergence of malaria parasites that do not express the HRP-2 marker that is detected by the most widely used RDTs also threatens the ability to identify malaria when cases occur *(28)*. These challenges underscore the urgency of scaling up additional preventive tools, including existing and new malaria vaccines, which can complement insecticide- and drug-based approaches.

3.3. WHO malaria vaccine recommendation and status update

3.3.1. WHO recommendation on malaria vaccines (2021)

The RTS,S/AS01 malaria vaccine should be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high malaria transmission, as defined by WHO. The RTS,S/AS01 vaccine should be provided in a 4-dose schedule in children from 5 months of age.

- WHO recommends that the first dose of vaccine be administered from 5 months of age.
- There should be a minimum interval of 4 weeks between doses.
- The vaccine should be administered in a three-dose primary schedule, with a fourth dose provided approximately 12–18 months after the third dose to prolong the duration of protection.
- However, there can be flexibility in the schedule to optimize delivery, for example, to align the fourth dose with other vaccines given in the second year of life. Children who begin their vaccination series should complete the four-dose schedule.

Optional schedule: Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a five-dose strategy, in areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks.

- This strategy seeks to maximize vaccine impact by ensuring that the period of highest vaccine efficacy (just after vaccination) coincides with the period of highest malaria transmission.
- The primary series of three doses should be provided at monthly intervals, with additional doses provided annually, prior to peak transmission season.
- *[updated and additional guidance (March 2023)]* Flexibility in schedule is supported to increase uptake or improve impact. As an example, when countries choose to implement the malaria

vaccine using a hybrid strategy in seasonal settings, in which the first three doses are provided year-round at monthly intervals from five months of age, and doses 4 and 5 are provided annually just prior to the start of the peak transmission season, some children will receive dose 4 less than 12 months after dose 3. Although there is a lack of direct evidence for this strategy to seasonally time dose 4 (or 5), the available data suggest that impact could be optimized and that the benefits of a reduced minimum interval of 6 months between doses 3 and 4 would be substantially greater than any potential risks associated with reducing the dosing interval.

Co-administration: The RTS,S/AS01 vaccine may be administered simultaneously with other vaccines of the childhood immunization programme.

Vaccine safety: The RTS,S/AS01 vaccine is safe and well tolerated. There is a small risk of febrile seizures within 7 days (mainly within 2–3 days) of vaccination. As with any vaccine introduction, proper planning and training of staff to conduct appropriate pharmacovigilance should take place beforehand.

Vaccination of special populations:[2] Malnourished or HIV-positive infants may be vaccinated with the RTS,S/AS01 vaccine using a standard schedule. The vaccine should be provided to infants and young children aged 5–17 months who relocate to an area of moderate to high transmission, including during emergency situations.

Surveillance: As for all new vaccines, the effectiveness and safety of the RTS,S/AS01 vaccine should be monitored post-introduction. Countries that choose seasonal deployment of the RTS,S/AS01 vaccine are strongly encouraged to document their experience, including adverse events following immunization.

For more information, see:

- Malaria vaccine: WHO position paper – March 2022 (https://apps.who.int/iris/handle/10665/352337)
- WHO guidelines for malaria, 14 March 2023 (https://apps.who.int/iris/handle/10665/366432)
- Meeting of the Strategic Advisory Group of Experts on Immunization, March 2023: conclusions and recommendations. Weekly Epidemiological Record, 2 June 2023. 254–5. (https://apps.who.int/iris/handle/10665/368488).

3.3.2. Lessons learned from RTS,S/AS01

In October 2021, following the results of the Malaria Vaccine Implementation Programme (MVIP) in the pilot countries of Ghana, Kenya and Malawi showing that RTS,S/AS01 was safe and reduced the burden of malaria, WHO recommended that the vaccine be used as an additional tool for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission. Following this recommendation, in late 2021, the Board of Gavi, the Vaccine Alliance, established a malaria vaccine programme, with introductions primarily expected to take place in sub-Saharan African countries where the burden of *P. falciparum* is greatest.

As described in more detail below, the lessons learned from the multisite Phase 3 trial of RTS,S/AS01 from 2009 to 2014 (MAL055), and from the ongoing MVIP that was designed to answer key outstanding questions after the Phase 3 trial, are useful when considering the evidence for new malaria vaccines.

[2] The vaccine has been developed for use in young children living in malaria-endemic settings, and has not undergone full clinical testing in adults; nor is it recommended for adults. The vaccine is not indicated for travellers, who should use chemoprophylaxis and vector control methods to prevent malaria when travelling to endemic settings.

High uptake and high impact

The MVIP has shown that community demand and health worker acceptance of the malaria vaccine is high (see section 9.4). By 18 months after introduction, coverage had reached levels that met or surpassed expectations for a new vaccine, even in the setting of the global COVID-19 pandemic and associated health system disruptions. No reduction in the uptake of other vaccines, ITN use or changes in health seeking behaviour for fever were associated with vaccine introduction. Impact was high; 24 months after vaccine introduction, in the context of 65–70% coverage with the first three doses, an approximate 30% reduction in hospitalizations for severe malaria was measured in children age-eligible for the vaccine. In addition, although not yet powered to measure impact on mortality, vaccine introduction was associated with a 9% reduction in all-cause mortality. This level of impact was seen even in the setting of high ITN coverage and good access to care. These data show the added value and impact that a malaria vaccine can have in addition to the impact achieved with currently available malaria control tools.

Severe disease end-points

The large multisite Phase 3 trial of RTS,S/AS01 (MAL055) illustrated how the improved quality of case management required to capture the primary end-point (clinical malaria) may compromise a trial's ability to measure more severe clinical end-points. Access to both outpatient and inpatient care was improved as part of the trial procedures, as was the quality of clinical and laboratory care (e.g. availability of essential medicines, oxygen and blood, and increased clinical staffing). Data from the health and demographic surveillance system in the trial site in Siaya, Kenya, estimated a 70% reduction in all-cause mortality associated with enrollment in the RTS,S/AS01 trial, regardless of study arm *(29)*. Study investigators have noted in published literature that the high standard of care provided to all trial participants may have limited the ability of the trial to detect an effect on secondary severe disease outcomes *(30)*. As outlined in the WHO preferred product characteristics for malaria vaccines *(37)*, while end-points on severe malaria, malaria-related hospitalizations or mortality, and all-cause mortality are of high relevance to public health, they would require considerably larger sample sizes in a Phase 3 trial due to the low incidence of these conditions relative to clinical malaria, and their evaluation may be more feasible in post-licensure studies.

Imbalance in mortality in settings of reduced malaria

The RTS,S/AS01 Phase 3 trial was not powered to show impact on mortality, and none was observed. As noted above, trial procedures resulted in a greatly reduced overall mortality in both malaria vaccine and comparator vaccine recipients. In the context of this overall reduced mortality and the reduced severe malaria that met the predefined case definition, a higher number of all-cause deaths was observed in the RTS,S/AS01 arm than in the control arm, and an imbalance in deaths by gender was noted. The MVIP was designed to rigorously evaluate the impact of vaccine introduction on severe malaria and mortality, including by gender, and included sentinel hospital surveillance and community-based mortality surveillance. Findings from the first 24 months of the MVIP showed a substantial reduction in malaria hospitalizations and a reduction in all-cause mortality among children age-eligible for vaccination even with incomplete vaccine uptake (vaccine coverage of first 3 doses was 65–70%), and no differential impact by gender *(9)*.

Malaria rebound

Malaria rebound is defined here as malaria occurring in individuals during a period of increased malaria risk after time-limited protection from malaria (i.e. after chemoprevention, vaccination or vector control), relative to individuals of the same age from the same population who did not receive the intervention. In March 2022, a WHO technical consultation was convened by the Global Malaria Programme to discuss

the malaria rebound phenomenon and concluded that the deployment of effective interventions should not be delayed for the purposes of assessing rebound *(31)*.

Although the available evidence suggests that rebound is a real, measurable phenomenon, a systematic review showed that the extent of malaria rebound has not outweighed the benefits of malaria interventions; rebound does not appear to be of a frequency or magnitude to warrant serious concern about current interventions. Two follow-up studies of RTS,S/AS01 vaccination documented a statistically significant increase in the incidence of clinical malaria in older children during extended follow-up: one during the fifth year after dose 3 (the last dose) of the vaccine for the group of children who had higher-than-average malaria parasite exposure in an area of overall low transmission *(32)*, and the other during the 4 to 7 years post-vaccination in a single study site with highly seasonal malaria transmission *(33)*. However, there was no statistically significant rebound of severe malaria observed and a cumulative benefit of the malaria vaccine was still maintained across the entire 7-year follow-up in the latter study.

Policy recommendations for highly effective interventions, where rebound is more likely to occur, should consider the cumulative benefit of the intervention. Evidence on rebound could be accrued in parallel with the policy formulation process. For interventions such as vaccines, longer periods of follow-up (over 1 year) to assess rebound under conditions of gradually waning protection could occur following policy recommendation through continued follow-up of clinical trial participants. Importantly, the technical consultation concluded that the deployment of highly effective interventions should not be delayed.

3.3.3. Current malaria vaccine demand and supply situation

Gavi has reported "unprecedented demand" for malaria vaccines. Over 28 countries responded favourably to a Gavi call for expression of interest in introducing the malaria vaccine. During 2022, Gavi approved funding requests from Ghana, Kenya and Malawi to support continued implementation of malaria vaccination in the pilot areas once the MVIP concludes at the end of 2023. Gavi-eligible non-pilot countries with moderate to high transmission of *P. falciparum* malaria were first able to apply for Gavi support in January 2023, with subsequent application windows in April and July 2023, and future opportunities 3–4 times per year. As of August 2023, 17 countries have been approved by Gavi to receive support for malaria vaccine introduction, based on high-quality applications; additional applications are under review. Gavi estimates that the annual global demand for malaria vaccines will be 40–60 million doses by 2026, increasing to 80–100 million doses or more each year by 2030 *(11)*.

The initial supply of RTS,S/AS01 is insufficient to meet demand. Based on a supply agreement with UNICEF, GSK is expected to deliver 18 million doses of RTS,S/AS01 during the 2023–2025 period *(12).* As long as the global supply shortage persists, the Framework for allocation of limited malaria vaccine supply (the Framework) will be applied to guide how available doses will be distributed, based on ethical principles on a foundation of solidarity *(10)*. The Framework was operationalized for the first time in May 2023 to allocate the 18 million doses of RTS,S/AS01 available for 2023–2025 to 12 African countries for subnational introductions, prioritizing areas where malaria burden and death are highest in line with the Framework principles *(34)*. Expansion within countries or to other countries is dependent on additional malaria vaccine supply becoming available.

Following the restart of GSK's antigen manufacturing facility in 2019, production volumes are now increasing, with plans to produce up to 15 million doses annually by 2026. A product transfer from GSK to Bharat Biotech (BBIL) is expected to enable supply capacity to increase beyond 15 million doses per year *(3)*. The agreement includes the transfer of manufacturing of the RTS,S antigen and the granting of a license to BBIL to commercialize and supply the RTS,S/AS01 malaria vaccine in the future. GSK will retain the production of the adjuvant (AS01) and will supply it to BBIL. The transfer is underway, and completion is expected by 2028 at the latest. While efforts are made to accelerate the product transfer, without

availability of a second malaria vaccine, supply would likely remain insufficient to meet demand *(4)*.

Gavi's market shaping roadmap identifies the availability of a second licensed and prequalified malaria vaccine as a key objective and a requirement to improve the supply situation and achieve a healthier malaria vaccine market *(5)*. Given the ongoing challenge of malaria burden reduction, the demonstrated value of a safe and effective malaria vaccine as a complementary malaria control tool, the insufficient supply of RTS,S/AS01, and the interest in a healthy malaria vaccine market, there remains a continued need for new malaria vaccines such as R21/Matrix-M, should the evidence demonstrate their safety and potential public health impact.

4. R21/Matrix-M overview

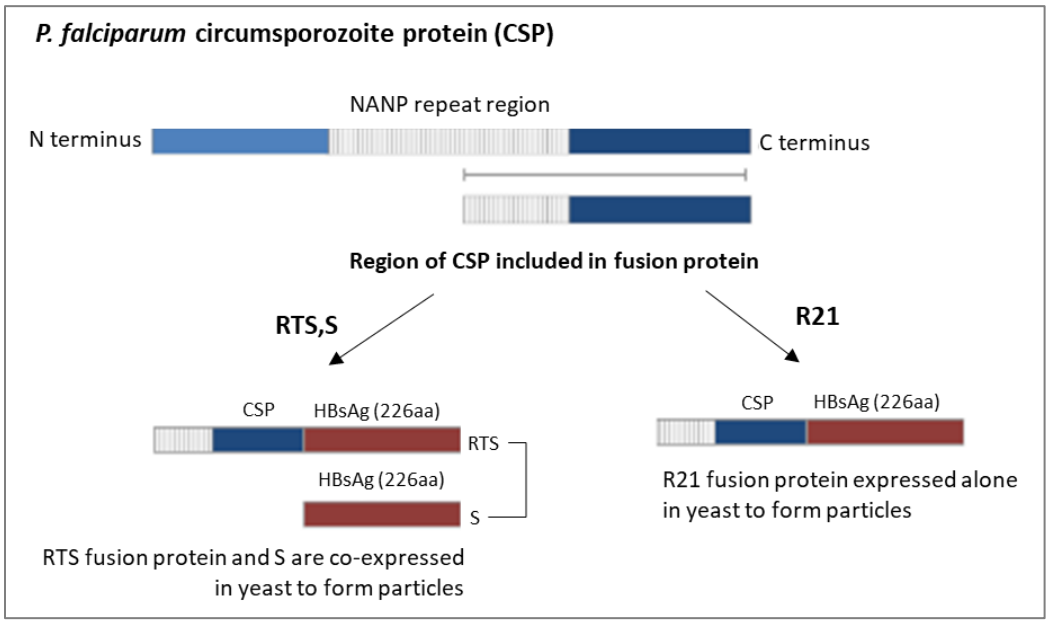
Further information on the R21/Matrix-M vaccine and Phase 1 and 2 studies is provided in the Phase 3 trial protocol (Annex 1).

4.1. Technical specifications

The R21/Matrix-M vaccine aims to reduce clinical malaria caused by *P. falciparum* in infants and young children. Similar to RTS,S, R21 targets generation of immunity to the central repeat region of tandemly repeated NANP sequences in the *P. falciparum* pre-erythrocytic circumsporozoite protein (CSP). CSP plays a key role in sporozoite development and hepatocyte invasion *(6)*.

R21 is a virus-like particle of about 23 nm in diameter and is comprised of a fusion protein of the central repeats and C-terminus of CSP to the N-terminus of the hepatitis B surface antigen (hBsAg). These repeats contain many copies of the four amino acid sequence NANP. The R21 fusion protein is similar to that in RTS,S, but the latter includes unfused hBsAg molecules, while R21 does not contain unfused hBsAg molecules (Fig. 1).

Fig. 1. Schematic diagram showing RTS,S and R21
Adapted from R21/Matrix-M Phase 3 protocol (Annex 1)



R21/Matrix-M malaria vaccine is formulated with the adjuvant Matrix-M (also known as Matrix-M1). Matrix-M contains purified saponin obtained from a crude extract of the plant *Quillaja saponaria* Molina, cholesterol from plants and phosphatidylcholine (a lipidic constituent of eggs). Its saponin content is a mix of 85% Matrix-A and 15% Matrix-C w/w ratio. Matrix-M adjuvant GMP bulk is manufactured by Novavax AB and provided to Serum Institute of India Pvt Ltd (SIIPL), at a saponin concentration of 1 mg/mL. The bulk was released after testing, by the SIIPL quality control department.

A summary of R21/Matrix-M and RTS,S/AS01 characteristics is presented in Table 2.

Table 2. Summary of R21/Matrix-M and RTS,S/AS01 vaccine characteristics

Characteristic	RTS,S/AS01	R21/Matrix-M
Platform	hBsAg nanoparticle	hBsAg nanoparticle
Target	CSP	CSP
Yeast used for production	*Saccharomyces cerevisiae*	*Hansenula polymorpha*
Ratio of CSP fusion protein to unfused hBsAg	1:4	1:0
Adjuvant	AS01 (saponin extract)	Matrix-M (saponin extract)
Primary series	3 doses, 1 month apart	3 doses, 1 month apart
Dose 4	12–18 months following dose 3, but flexibility allowed to reduce interval below 12 months	12 months following dose 3
Dose 5	12 months after dose 4	Optional dose 5, data from Phase 3 trial not yet available

4.2. Available data on R21/Matrix-M: preclinical data, immunogenicity, Phase 1 and 2 results

4.2.1. Preclinical data

Initial preclinical assessment of immunogenicity in BALB/c mice showed high titres of NANP-specific IgG following three doses of R21 with a saponin-based adjuvant (Abisco-100, essentially identical to Matrix-M) *(35)*. Efficacy was tested by sporozoite challenge in BALB/c mice (1000 sporozoites per mouse injected intravenously using transgenic *P. berghei* parasites). R21 + adjuvant was given twice, 8 weeks apart, and mice were challenged 3 weeks after dose 2. R21 + Abisco-100 sterilely protected 100% of the challenged mice ($P \leq 0.0001$) and R21 + Matrix-M sterilely protected 87.5% ($P = 0.0002$), a finding confirmed in a second independent challenge ($P \leq 0.0001$); differences were not significant between these groups.

4.2.2. Phase 1 and 2 studies

Prior to the Phase 3 efficacy trial, R21/Matrix-M was evaluated in several Phase 1 and 2 studies (Table 3). These studies have assessed safety, immunogenicity, and protective efficacy in different age groups, including adults, as well as different immunization schedules and dose regimens. Key findings from these studies are summarized in Table 3. Further details on these can be found in Annex 1.

Table 3. Summary of R21/Matrix-M Phase 1 and 2 studies

Trial number and phase	Study objectives and trial population	Trial design and schedule	Key study attributes and findings	Reference
VAC053 **Phase 1a** *Completed 2017*	1°: safety and immunogenicity of R21 administered alone and with Matrix-M 31 adults, United Kingdom	3 doses R21, intramuscularly 4 weeks apart 4 groups: 10 µg R21/50 µg Matrix-M, 50 µg R21 alone, 50 µg R21/50 µg Matrix-M, 2 µg R21/50 µg Matrix-M	**First-in-human administration** Increased antibody response with Matrix-M Higher titres at day 238 with 10 µg than with 50 µg or 2 µg dose R21	Annex 1
VAC060 **Phase 1b** *Completed 2017*	1°: safety and immunogenicity of R21/Matrix-M in West African adults 13 adults aged 18–45 years, Burkina Faso	3 doses 10 µg R21/Matrix-M on days 0, 28 and 56	**Safety and immunogenicity in adults living in malaria endemic setting** Dose 3 failed to increase antibody response, resulting in lower antibody titres at day 84 compared to UK adults Higher antibody avidity in Burkina Faso adults compared to UK adults	*(36)*
VAC072 **Phase 1 and 2a** *Completed 2021*	1°: safety and tolerability, and protective efficacy against sporozoite challenge of R21/Matrix-M using different immunization schedules 64 adults received at least one vaccine dose, 60 completed the primary series. 12 control participants, United Kingdom	• 3 doses (10 µg R21/50 µg Matrix-M) at 4-week intervals, dose 4 at 12 months after primary series • 3 doses (10 µg R21/50 µg Matrix-M) at 0, 4 and 24 weeks, dose 4 at 56–80 weeks • 3 doses (10 µg R21/50 µg Matrix-M) at 0, 4 and 8 weeks, dose 4 at 40–60 weeks • 2 doses (50 µg R21/50 µg Matrix-M) at 0 and 4 weeks and fractional dose 3 (10 µg R21/50 µg Matrix-M) at 24 weeks • 2 doses (10 µg R21/50 µg Matrix-M) at 0 and 4 weeks and fractional dose 3 (2 µg R21/50 µg Matrix-M) at 24 weeks	**Evaluation of different dose schedules** Robust antibody responses to NANP; suggestion of increased antibody response with delayed dose 3 at 6 months. Controlled Human Malaria Infection (CHMI) challenge 28 days after third vaccination showed sterile protection ranging from 62.5-75% of volunteers depending on group	Annex 1
VAC073	1°: safety and tolerability of R21 in healthy adults, then	3 doses, 4 weeks apart	**Age de-escalation and dosage study**	Annex 1

Trial number and phase	Study objectives and trial population	Trial design and schedule	Key study attributes and findings	Reference
Phase 1 and 2a *Completed 2022*	children and infants 2°: immunogenicity 20 adults, 20 children (1–5 years) and 21 infants (5–12 months), Kenya	• Full (10 µg R21/50 µg Matrix-M) • Intermediate (5 µg R21/50 µg Matrix-M) • Half (5 µg R21/25 µg Matrix-M)	Highest antibody responses 1 month post dose 3 in young children and infants; high responses with both full and intermediate regimens	
VAC076 **Phase 2b** *Completed 2020*	1°: protective efficacy against clinical malaria from 14 days after dose 3 to 6 months 2°: protective efficacy against clinical malaria from 14 days after dose 3 to 12 months; efficacy over 2, 3 and 4 years of follow-up with a fourth dose at 12 months and dose 5 and 6 in a subgroup of participants after 24 and 36 months 450 children aged 5–17 months, Nanoro, Burkina Faso	**Seasonal administration** 3 doses, 4 weeks apart given prior to the malaria season, dose 4 given 1 year after dose 3 Group 1: 5 µg R21/25 µg Matrix-M Group 2: 5 µg R21/50 µg Matrix-M Group 3: control (rabies vaccine) Fourth dose at 12 months and fifth and sixth dose in a subgroup of participants after 24 and 36 months.	**Efficacy of seasonal administration in seasonal transmission setting** Higher antibody response and point estimates of protective efficacy with 50 µg Matrix-M compared to 25 µg (for a summary of study findings, see section 4.2.3) In the four-dose regimen of Group 2 (corresponding to the dose advanced to the Phase 3 trial) of a primary series plus a fourth dose at 12 months, vaccine efficacy at 1 year was 77% (95% CI: 67-84), at two years with a fourth dose at 24 months was 75% (95% CI: 66 to 81), and at four years of follow-up without further doses was 71% (95% CI: 58-81) in time to event analysis. (unpublished).	*(13,14)*

1°: primary objective; 2°: secondary objective

4.2.3. Phase 2b study in a highly seasonal setting

A Phase 2b double-blind, randomized, controlled trial to assess the safety, immunogenicity and efficacy of R21/Matrix-M was conducted in children in Nanoro, Burkina Faso, from the second quarter of 2019 *(13)*. Safety data are summarized in section 7.

R21 vaccine was formulated with two different doses of adjuvant Matrix-M and administered to children aged 5–17 months in Nanoro, Burkina Faso, a highly seasonal setting where malaria transmission is largely limited to 4 or 5 months of the year.

Doses 1, 2 and 3 were administered at 4-week intervals just prior to the malaria season, and dose 4 was administered 1 year after dose 3, prior to the next malaria season. All vaccines were administered intramuscularly into the thigh. Group 1 received 5 µg R21 plus 25 µg Matrix-M; group 2 received 5 µg R21 plus 50 µg Matrix-M; and group 3, the control group, received rabies vaccine. To ensure antibody responses were highest during the seasonal peak of malaria transmission, the three doses in the primary vaccination series were administered largely before the malaria season. Of the 442 participants, 383 (87%) used ITNs before the malaria season. IRS was done in 65 (15%) of 441 households, and 300 (68%) of 442 participants had at least one round seasonal malaria chemoprevention.

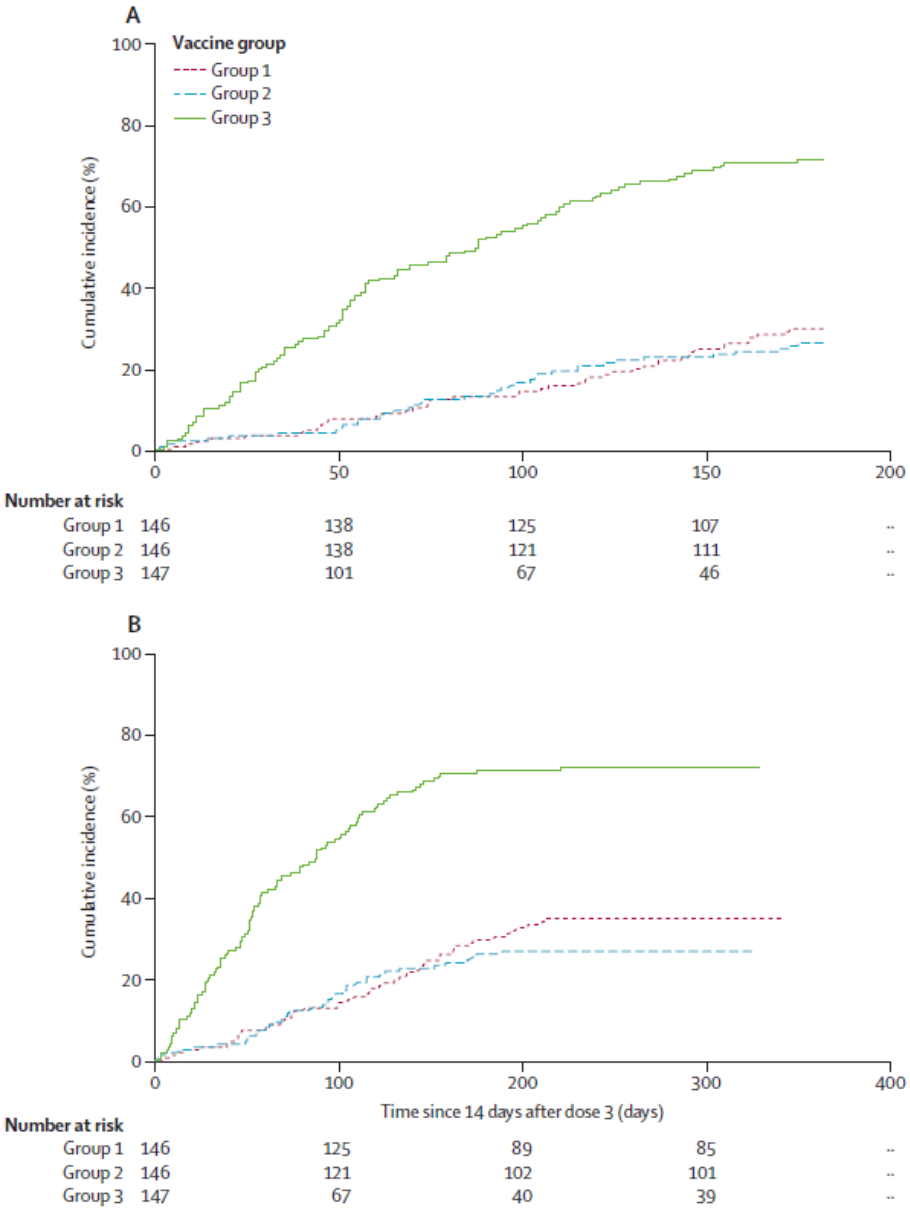
Children were randomly assigned (1:1:1) to groups 1, 2 and 3. Vaccine safety, immunogenicity and efficacy were evaluated over 1 year. The primary objective assessed the protective efficacy of R21/Matrix-M from 14 days to 6 months after dose 3. Malaria was detected by passive surveillance. Primary analyses of vaccine efficacy (VE) were conducted from 14 days after dose 3 based on a modified intention-to-treat population, which included all participants who received three vaccinations, allowing for inclusion of participants who received the wrong vaccine at any timepoint.

A total of 498 children aged 5–17 months were screened, and 48 were excluded; the remaining 450 children were enrolled and received at least one vaccination. Among those enrolled, 150 were allocated to each of groups 1, 2 and 3.

A total of 186 participants had clinical malaria according to the primary case definition (presence of an axillary temperature of 37·5 °C or higher and/or history of fever within the past 24 hours and *P. falciparum* asexual parasitaemia > 5000 parasites/µL) when assessing the primary objective of efficacy against clinical malaria of R21/Matrix-M from 14 days to 6 months after dose 3. These cases of clinical malaria occurred in 43 (29%) of 146 participants in group 1, 38 (26%) of 146 participants in group 2, and 105 (71%) of 147 participants in group 3. A Cox regression model comparing group 1 with group 3 resulted in VE of 74% (95% CI: 63–82; $P < 0.0001$) at 6 months. Comparing group 2 with group 3 resulted in VE of 77% (95% CI: 67–84; $P < 0.0001$Fig. 2) at 6 months (Fig. 2). At 1 year, VE was 71% (95% CI: 59–79; $P < 0.0001$) for group 1 and 77% (95% CI: 67–84; $P < 0.0001$) for group 2. Analyses adjusted for potentially confounding factors (sex, age at randomization, adequate bednet use, and seasonal malaria chemoprevention) did not substantially change the efficacy estimates.

Fig. 2. Kaplan–Meier estimates of the time to first episode of clinical malaria

The primary analysis was from 14 days after dose 3 based on a modified intention-to-treat population. Group 1 received 5 µg R21/25 µg Matrix-M; group 2 received 5 µg R21/50 µg Matrix-M; and group 3, the control group, received rabies vaccinations (Rabivax-S). (A) Data from 14 days to 6 months after dose 3. (B) Data from 14 days to 12 months after dose 3.

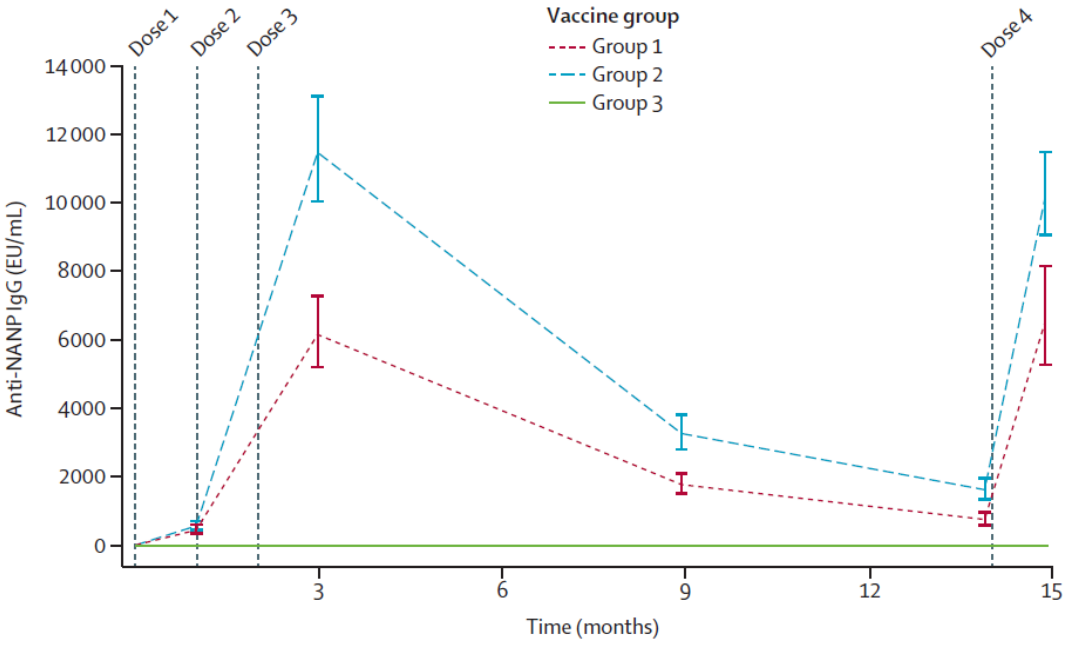


At baseline, no participant had detectable NANP IgG antibody levels (Fig. 3). Group 1 titres reached a geometric mean of 6133 (95% CI: 5161–7289) at 28 days after the third vaccination. In group 2 (higher dose of adjuvant), the level was significantly higher at 11 438 (95% CI: 9985–13 102; $P < 0.0001$). These titres dropped over the following 12 months, but, in both groups 1 and 2, 28 days after dose 4, antibodies increased to levels similar to those after dose 3 (Fig. 3). The antibody levels 28 days after dose 3 were assessed for correlation with VE. After dividing antibody response levels to NANP of the combined group 1 and 2 participants into terciles, there was a significantly reduced risk of malaria over 6 months for participants in the upper tercile compared with participants in the lower tercile (hazard ratio: 0.34;

95% CI: 0.19–0.63; *P* < 0.0001), and for participants in the upper tercile compared with participants in the middle tercile (0.46; 95% CI: 0.25–0.86; *P* < 0.015).

Fig. 3. Antibody responses to R21/Matrix-M, geometric mean antibody titres (95% CI)

Anti-NANP antibodies were measured by enzyme-linked immunosorbent assay (ELISA) at baseline; 28 days after dose 1; 28 days, 6 months, and 1 year after dose 3; and 28 days after dose 4, which was administered 1 year after dose 3. Group 1 received 5 µg R21/25 µg Matrix-M; group 2 received 5 µg R21/50 µg Matrix-M; and group 3, the control group, received rabies vaccine. NANP=Asn-Ala-Asn-Pro.



In a follow-up study from the same trial, investigators recently reported additional data on safety, immunogenicity and efficacy over 2 years of follow-up, following administration of dose 4 of R21/Matrix-M *(14)*. Dose 4 was administered intramuscularly approximately 12 months after the primary series. Participants were excluded from the efficacy analysis if they withdrew from the trial within the first 2 weeks of receiving dose 4.

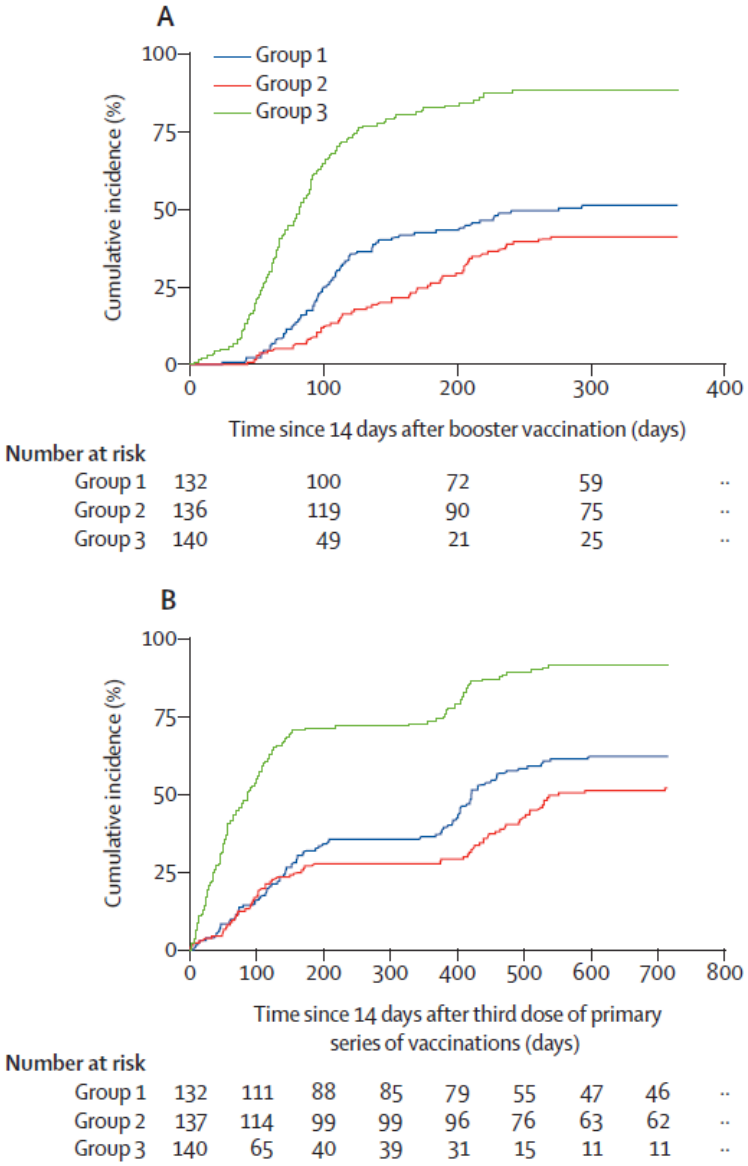
Of the 450 children initially enrolled, a total of 409 children returned to receive dose 4. The same vaccine was administered for dose 4 as for the primary series of vaccinations: 132 participants received 5 µg R21 with 25 µg Matrix-M; 137 received 5 µg R21 with 50 µg Matrix-M; and 140 received the control vaccine. There was no significant difference between baseline characteristics of children lost to follow-up and those remaining in the trial. Safety data are summarized in section 7.

VE remained high in the high-dose adjuvant (50 µg) group, as seen with previous findings at 1 year after the primary series of vaccinations. Following dose 4, 67 (51%) of 132 children who received R21/Matrix-M with low-dose adjuvant, 54 (39%) of 137 children who received R21/Matrix-M with high-dose adjuvant, and 121 (86%) of 140 children who received the rabies vaccine developed clinical malaria by 12 months. VE was 71% (95% CI: 60–78) in the low-dose adjuvant group and 80% (95%CI: 72–85) in the high-dose adjuvant group. VE estimates were not substantively changed when adjusted for sex, age at randomization (5–9 months, 10–12 months, and over 12 months), adequate bednet use, and having received at least one round of seasonal malaria chemoprevention.

Efficacy was further assessed at 24 months (range: 660–731 days) following the primary series of vaccinations; all of these participants received dose 4. VE was 66% (95% CI: 55–74; $P < 0.0001$) for group 1 and 75% (95% CI: 66–81; $P < 0.0001$) for group 2. Time to first malaria episode is shown in Fig. 4.

Fig. 4. Kaplan–Meier estimates of the time to first episode of clinical malaria according to the primary case definition

The primary case definition of clinical malaria in this study was the presence of an axillary temperature of 37·5 °C or higher and/or history of fever within the past 24 hours, and *P. falciparum* parasitaemia > 5000 parasites per µL. Analyses of VE included all participants who received dose 4. (A) Data from 14 days to 12 months after dose 4 (booster). (B) Data from 14 days to 24 months after dose 3 (of primary series of vaccinations). Group 1 received 5 µg R21/25 µg Matrix-M; group 2 received 5 µg R21/50 µg Matrix-M; and group 3, the control group, received rabies vaccine.



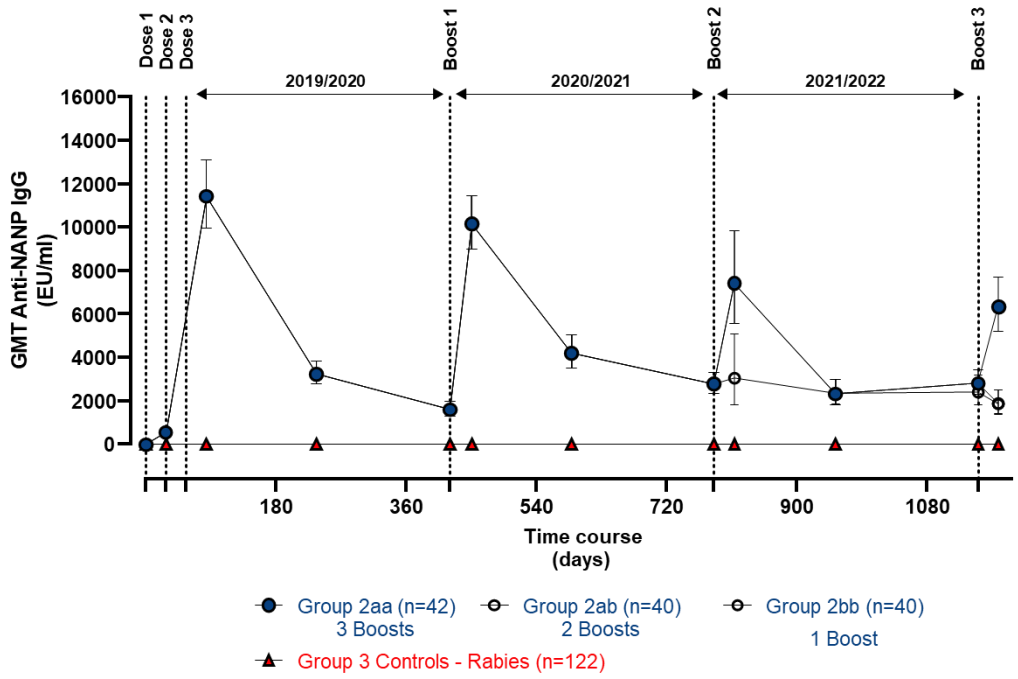
When VE was assessed against multiple episodes of malaria over the 24-month period, VE was similar to the analysis of a first or only event: 63% (95% CI: 55–71; $P < 0.0001$) in group 1 and 77% (95% CI: 69–83; $P < 0.0001$) in group 2.

Among participants receiving dose 4, at 28 days following their last R21/Matrix-M vaccination, titres of malaria-specific anti-NANP antibodies correlated positively with protection against malaria in both the first year of follow-up after dose 3 (Spearman's ρ: –0.32; 95% CI: –0.45 to –0.19; $P = 0.0001$) and the second year of follow-up after dose 4 (Spearman's ρ: –0.20; 95% CI: –0.34 to –0.06; $P = 0.02$).

Additionally, as shown in Fig. 5, higher nadir anti-NANP antibody titres were observed at 12 months post dose 4 (booster 1) and 12 months post dose 5 (booster 2), compared to 12 months post dose 3. These data suggest a lower rate of decline in antibody levels following doses 4 and 5 when compared to the rate of decline after the primary series (doses 1, 2 and 3). However, there was a lower peak antibody response immediately following doses 5 and 6. To date, no data have been provided on cell-mediated immunity and a validated correlate of protection against clinical malaria has not yet been established.

Fig. 5. Antibody titres following R21/Matrix-M doses 4 and 5 in Phase 2b trial

Unpublished, figure provided by University of Oxford



GMT = geometric mean titre
Boost 1 = dose 4; Boost 2 = dose 5; Boost 3 = dose 6
1 boost = 4 doses total; 2 boosts = 5 doses total; 3 boosts = 6 doses total

5. R21/Matrix-M Phase 3 study design and methods overview

5.1. Overview

VAC078 is a double-blind, randomized, controlled trial, evaluating the efficacy of R21/Matrix-M in children aged 5–36 months, using different vaccination strategies in malaria endemic regions. Sites were selected to receive either seasonal vaccine administration (termed seasonal group), whereby vaccination is given just prior to the malaria transmission season, or age-based ("standard") vaccine administration (termed standard group).

5.2. Design

Participants aged 5–36 months were randomized 2:1 to receive vaccination with 5 µg R21 adjuvanted with 50 µg Matrix-M, or a control vaccination (a licensed rabies vaccine). Efficacy of vaccination was assessed by comparing incidence of passively detected cases of malaria in the investigational vaccine arm compared to the control arm in the standard vaccination group and the seasonal vaccination group (Table 4).

Table 4. VAC078 study design

A. Standard site dosing schedule (Dandé, Burkina Faso; Bagamoyo, Tanzania; Kilifi, Kenya)

	Dose 1 Day 0	**Dose 2 Day 28**	**Dose 3 Day 56**	**Dose 4 (1 year after dose 3)**
Group 1 (*n* = 1600)	5 µg R21 / 50 µg Matrix-M	5 µg R21 / 50 µg Matrix-M	5 µg R21 / 50 µg Matrix-M	5 µg R21 / 50 µg Matrix-M
Group 2 (*n* = 800)	Control vaccine (Rabies)	Control vaccine (Rabies)	Control vaccine (Rabies)	Control vaccine (Rabies)

B. Seasonal site dosing schedule (Bougouni, Mali; Nanoro, Burkina Faso)

	Dose 1 April/May (Day 0)	**Dose 2 May/June (Day 28)**	**Dose 3 June/July (Day 56)**	**Dose 4 (1 year after dose 3)**
Group 1 (*n* = 1600)	5 µg R21 / 50 µg Matrix-M	5 µg R21 / 50 µg Matrix-M	5 µg R21 / 50 µg Matrix-M	5 µg R21 / 50 µg Matrix-M
Group 2 (*n* = 800)	Control vaccine (Rabies)	Control vaccine (Rabies)	Control vaccine (Rabies)	Control vaccine (Rabies)

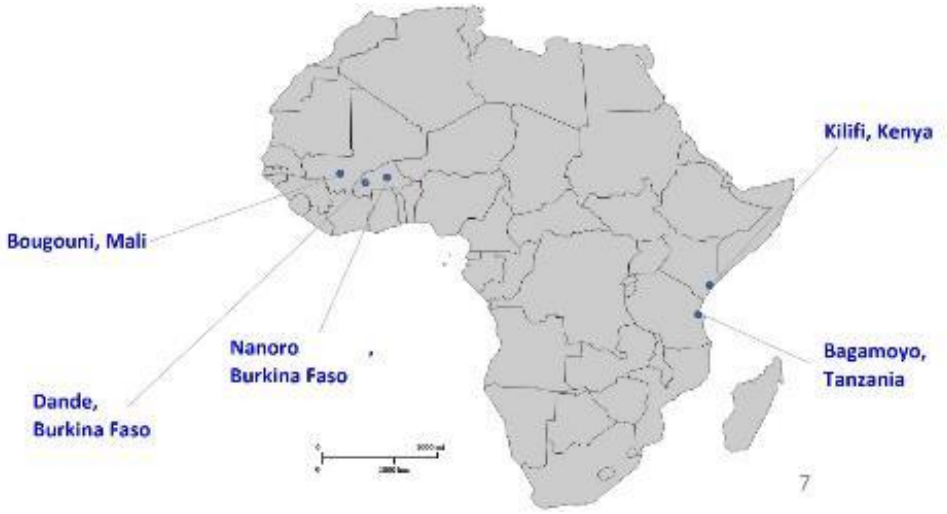
The R21/Matrix-M vaccine arm participants received 3 vaccinations of R21 5 µg with 50 µg Matrix-M by intramuscular route, followed by dose 4 12 months after dose 3. The control arm participants received three vaccinations given intramuscularly with an internationally licensed rabies vaccine, followed by dose 4 12 months after dose 3.

A minimum 2-week interval was maintained between administration of any study vaccine and any childhood immunization vaccine as a precaution to avoid any potential interference between the immunogenicity of the vaccines, and to facilitate assessment of study vaccine-related adverse events, independent of childhood immunization vaccine-related adverse events.

5.3. Study sites

The locations of the Phase 3 study sites are shown in Fig. 6.

Fig. 6. Map of Phase 3 study sites



5.3.1. Seasonal sites

Nanoro is a rural area located about 90 km from Ouagadougou, the capital city of Burkina Faso. ITN coverage is estimated at 80%, and seasonal malaria chemoprevention (SMC) in children from 3 to 59 months has been implemented since 2017. *P. falciparum* is responsible for more than 90% of all clinical malaria cases.

Bougouni is in the region of Sikasso, Mali, 150 km south of Bamako. Malaria is the primary cause of outpatient consultations, hospital admissions and deaths in children under 5 years of age. ITN and SMC coverage are high. *P. falciparum* is the predominant species, responsible for more than 95% of clinical malaria cases.

At both these sites, malaria transmission is highly seasonal; transmission iFig. 7s largely limited to 4 or 5 months of the year during Fig. 7the rainy season from June to November, and is markedly reduced during other months (Fig. 7Fig. 7A–B and Fig. 8 in Section 6).

In both sites, SMC is administered during the peak transmission season according to national guidelines by the government through door-to-door campaigns.

5.3.2. Standard sites

Dandé is located around 60 km north of Bobo-Dioulasso in south-west Burkina Faso and Fig. 7is also an area of highly seasonal malaria transmission, with peaks during the rainy season (June to November). ITN and SMC coverage are high, and, as with the other highly seasonal sites (Nanoro and Bougouni), SMC is provided according to national guidelines by the government through door-to-door campaigns. Although malaria is highly seasonal in Dandé (Fig. 7Fig. 7C and Fig. 8 in Section 6) this study site received standard administration in the Phase 3 trial.

Bagamoyo in Tanzania typically has a short rainy season from October to December, a long rainy season from March to May, and the driest months from July to September.

Kilifi in Kenya typically has long rains in May–July and short rains in November–December.

Transmission of malaria usually peaks during or after the long and short rainy seasons.

5.4. Study population

Participants were recruited from children 5–36 months of age living in the study area who met eligibility criteria (see Annexes 1 and 2 for further details).

5.5. Study objectives and case definitions for clinical malaria

The primary efficacy objectives were:

- to assess the protective efficacy of R21/Matrix-M against clinical malaria caused by *P. falciparum*, in children aged 5–36 months living in a malaria endemic area, 12 months after completion of the primary course (standard vaccination group);
- to assess the protective efficacy of R21/Matrix-M against clinical malaria caused by *P. falciparum*, in children aged 5–36 months living in a malaria endemic area, 12 months after completion of the primary course (seasonal vaccination group).

The primary case definition for clinical malaria was:

- presence of axillary temperature of 37.5 °C or higher and/or history of fever within the past 24 hours, and *P. falciparum* asexual parasitaemia > 5000 parasites/µL.

The secondary case definitions for clinical malaria included:

- presence of axillary temperature of 37.5 °C or higher and/or history of fever within the past 24 hours, and *P. falciparum* asexual parasitaemia > 0 parasites/µL;
- presence of axillary temperature of 37.5 °C or higher and/or history of fever within the past 24 hours, and *P. falciparum* asexual parasitaemia > 2500 parasites/µL.

The primary safety objective was:

- to assess the safety and reactogenicity of R21/Matrix-M, in both seasonal and standard vaccination groups, in children living in a malaria endemic area, in the month following each vaccination, and in the 12 months after completion of the primary course (doses 1, 2 and 3).

Other secondary objectives included:

- efficacy against clinical malaria after dose 4
- efficacy against asymptomatic *P. falciparum* infection
- efficacy against severe malaria disease
- efficacy according to different transmission settings
- efficacy against incident severe anaemia, blood transfusion requirement and malaria hospitalization
- safety and reactogenicity (including serious adverse events (SAEs) and any deaths) following dose 4 and for the duration of the study
- assessment of humoral immunogenicity by anti-CSP antibody concentrations measured 12 months after completion of the primary series (doses 1, 2 and 3) and 12 months after dose 4.

5.6. Sample size and power calculations

A complete statistical analysis plan (SAP), which provides details on sample size, assumptions on disease rates, and analytic approaches for assessment of safety and efficacy outcomes, is provided in Annex 2.

The study was designed with conservative estimates of malaria disease rates to meet the primary end-point of efficacy against clinical malaria disease over 1 year for each of the two vaccination strategies. The total sample size provides safety data on at least 3000 subjects in the malaria vaccine arm (3200 to be enrolled) and 1600 control vaccinees.

The incidence rates of clinical malaria assumed in the calculations for power and sample size are listed in Table 5. All sample sizes were based on a type 1 error rate of 5% (i.e. inference will be based on two-sided 95% confidence intervals).

Table 5. Power calculations and sample size requirements for individual study centres for calculating sufficient sample size to evaluate efficacy against R21/Matrix-M

Site	Sample size (R21/Matrix-M : controls)	Assumed malaria incidence per year	Power to detect 50% efficacy with $P < 0.05$	Sample size required for 80% power to detect 50% efficacy (R21/Matrix-M: controls)
Seasonal sites				
Bougouni, Mali	1200 (800:400)	0.45	> 95%	309 (206:103)
Nanoro, Burkina Faso	1200 (800:400)	0.71	> 99%	213 (142:71)
Standard sites				
Dandé, Burkina Faso	1200 (800:400)	0.40	> 95%	339 (226:113)
East Africa pooled (Bagamoyo and Kilifi)	1200 (800:400)	0.165	95.0%	753 (502:251)
Bagamoyo, Tanznia*	600 (400:200)	0.25	86.3%	513 (342:171)
Kilifi, Kenya*	600 (400:200)	0.08	39.3%	1500 (1000:500)

* Analysis of the two East African sites will be exploratory, given the smaller total sample size of 600 in each centre and the low incidence rate in Kenya.

Pooling results from the two seasonal administration sites, the expected incidence rate is 0.58 cases per child per year among the 800 control vaccinees. With this sample size, and assuming that the true vaccine efficacy (VE) is 50% over 12 months, the study has > 95% power to exclude a lower limit of efficacy of 30%.

Pooling results from the three standard administration sites, the expected incidence rate is 0.28 cases per child per year among the 800 control vaccinees. With this sample size, and assuming that the true VE is 50% over 12 months, the study has 84% power to exclude a lower limit of efficacy of 30%.

5.7. Study populations and statistical analysis

For analytic purposes, the study populations were defined as described in Table 6.

Table 6. Phase 3 study populations and statistical analysis

Population	Definition	Analytical method
Per protocol (PP)	All participants eligible to participate (according to the trial inclusion and exclusion criteria) and received all allocated vaccinations without any contraindications to vaccine administration. Participants must have a 3–6-week interval between doses 1 and 2; and a 3–6-week interval between doses 2 and 3. Children who receive a dose outside these 3–6-week intervals will be included in the PP analysis if the reason for the delay is for reasons specified in section 6.4.1 of the protocol (temperature ≥ 37.5 °C (99.5 F) at the time of vaccination; acute disease at the time of vaccination). To be included in the PP population in analyses that use the second year of data, children must receive dose 4 within the time window specified in the protocol (365 days +/– 35 days post dose 3).	Month 2.5 (M2.5, 14 days after dose 3) to indicated time point, allowing 3–6 weeks between doses 2 and 3
Modified per protocol 1 (mPP1)	Population defined in the same way as the PP population but allowing the interval between doses 2 and 3 to be between 3 and 16 weeks, thus allowing for delayed attendance caused by factors that required a pause in vaccinations, which was a particular problem at the Dandé site.	Month 2.5 (M2.5, 14 days after dose 3, allowing 3–6 weeks between doses 2 and 3 as per protocol) to indicated time point Or 14 days after delayed dose 3 (allowing 6–16 weeks between doses 2 and 3) to indicated time point This analysis combines the PP population and the population receiving a delayed dose 3
Modified per protocol 2 (mPP2)[a]	Population defined is the same as the primary PP, but only including participants with the interval between doses 2 and 3 to be between 6 and 16 weeks (i.e. participants who were delayed in receiving dose 3).	14 days after delayed dose 3 (allowing 6–16 weeks between doses 2 and 3) to indicated time point (i.e. population limited to those with delayed dose 3)
Modified intention-to-treat (mITT)[b]	Population who received at least one dose of vaccine	M0 (timing of dose 1) to indicated time point

D1, D2, D3 = vaccine doses 1, 2 and 3, respectively, provided (scheduled 1 month apart); D4 = dose 4 of vaccine provided (scheduled 12 months after dose 3); M0 = timing of D1, M1 = timing of D2, M2 = timing of D3, M2.5 = 14 days post D3

[a] Additional analyses requested by the SAGE/MPAG Working Group on Malaria Vaccines for evidence review; population was not separately defined in SAP

[b] Requested by SAGE/MPAG Working Group on Malaria Vaccines that time at risk for mITT analyses must start at M0 (timing of dose 1), not "14 days after the final vaccination received" as indicated in the SAP

The primary analyses for safety and efficacy were based on the mITT population.

It should be noted that according to the SAP and the protocol, the investigator's primary outcome is time to first (or only) episode of malaria, over a period of 365 days of follow-up after dose 3 based on the modified per protocol population. However, for WHO evidence review, the primary outcome assessed is VE against all episodes of clinical malaria *(37)* (primary case definition) based on the mITT population, with time at risk measured from dose 1 to 14 months after dose 1 (12 months after dose 3). For seasonal vaccination sites, data on VE at an additional time point were also assessed, with time at risk measured from dose 1 to 20 months after dose 1 (18 months after dose 3 and 6 months after dose 4), reflecting VE over two malaria transmission seasons.

Table 7 describes the primary case definitions and safety outcome definitions used for analytic purposes.

Table 7. Primary case definitions

Outcome	Primary case definition
Clinical malaria	Presence of axillary temperature of 37.5 °C or higher and/or history of fever within the past 24 hours, and *P. falciparum* asexual parasitaemia > 5000 parasites/µL
Severe malaria	Clinical diagnosis of severe malaria and presence of *P. falciparum* asexual parasitaemia > 5000 parasites/µL • and one or more signs of disease severity: prostration, respiratory distress, Blantyre coma score ≤ 2, seizures (2 or more), hypoglycemia < 2.2 mmol/L, acidosis BE ≤ –10.0 mmol/L, lactate ≥ 5.0 mmol/L, anaemia < 5.0 g/dL • and without any of the following diagnosis of co-morbidity: pneumonia (confirmed by x-ray), meningitis (confirmed by cerebrospinal fluid examination), sepsis (with positive blood culture), gastroenteritis with dehydration. Laboratory tests and other examinations (chest x-ray, lumbar puncture, blood culture) to exclude co-morbidities were performed only if there was a clinical suspicion/diagnosis justifying additional investigations.
Mortality	Death, excluding those as a result of trauma and elective surgery
Malaria hospital admission	Medical hospitalization with confirmed *P. falciparum* asexual parasitaemia > 5000 parasites/µL

Safety outcome	Definition
Solicited adverse events	Collected for the first 50% of participants enrolled at each site Occurrence of solicited local/systemic reactogenicity signs and symptoms for 7 days following the vaccination Local adverse events include: pain at injection site, swelling at injection site, redness/discolouration at injection site Systemic adverse events include: fever, irritability/fussiness, drowsiness, loss of appetite
Unsolicited adverse events	Occurrence of unsolicited adverse events for 28 days following the vaccination
Serious adverse events	Occurrence of SAEs for the whole study duration. An SAE is an adverse event that

Safety outcome	Definition
(SAEs)	results in any of the following outcomes, whether or not considered related to study intervention: • death (i.e. results in death from any cause at any time); • life-threatening event – this does not include an adverse event that, if it occurred in a more serious form, might have caused death; • persistent or significant disability or incapacity; • hospitalization or prolongation of hospitalization, regardless of length of stay, even if precautionary measure for continued observation; • important medical event; • congenital anomaly or birth defect.
Adverse events of special interest (AESIs) as defined for this trial	Reported as SAEs: • febrile convulsions • meningitis • cerebral malaria.

5.8. Other study procedures

Additional information on blinding and randomization; replacement/withdrawal of subjects; study schedule, visits, procedures and treatments; adverse event reporting; laboratory methods; case detection; other clinical definitions; data management; and adverse event definitions, severity grading, reporting, and overall assessment of safety can be found in the Phase 3 trial protocol (Annex 1).

6. R21/Matrix-M efficacy and duration of protection

As noted in section 5.5, the primary objectives of the Phase 3 trial were to assess the protective efficacy of R21/Matrix-M against clinical malaria caused by *P. falciparum*, in children 5–36 months of age at first vaccination, living in a malaria endemic area at 1) standard vaccination sites, and 2) seasonal vaccination sites. Clinical malaria was ascertained through passive case detection and was defined, as noted in section 5.7, as the presence of an axillary temperature of 37.5 °C or higher and/or history of fever within the past 24 hours, and *P. falciparum* asexual parasitaemia > 5000 parasites/µL. Vaccine efficacy (VE) against all episodes of clinical malaria and severe malaria was assessed using a negative binomial random-effects model, and estimates were adjusted for study site, age at randomization (5–12, 13–24, 25–36 months), and sex. VE in seasonal sites combined was also adjusted for number of SMC rounds received in 2021 and in standard sites, for number of SMC rounds received in 2021 and bed net use. Due to non-convergence, SMC and bed net use could not be adjusted for in site-specific VE, nor could VE in seasonal sites combined be adjusted for bed net use.

The efficacy estimates presented here are based on analysis using the per protocol (PP) population, which included all participants receiving all allocated vaccinations in the specified time window defined in Table 6, and the modified intention-to-treat (mITT) population, which included all participants receiving at least one dose of vaccine.

The reported efficacy estimates detailed below may differ from efficacy estimates that have been previously cited or published. This is because 1) mITT analysis, with follow-up time beginning after dose 1 is shown below, whereas prior reports may have been based on a modified per protocol (mPP) population (as described in Table 6) or an intention-to-treat (ITT) analysis with follow-up time beginning 14 days after last vaccine dose received; and 2) efficacy estimates reported here are against all episodes of clinical malaria, not first or only episode, as efficacy against all episodes better reflects the public health relevance of the vaccine *(38)*.

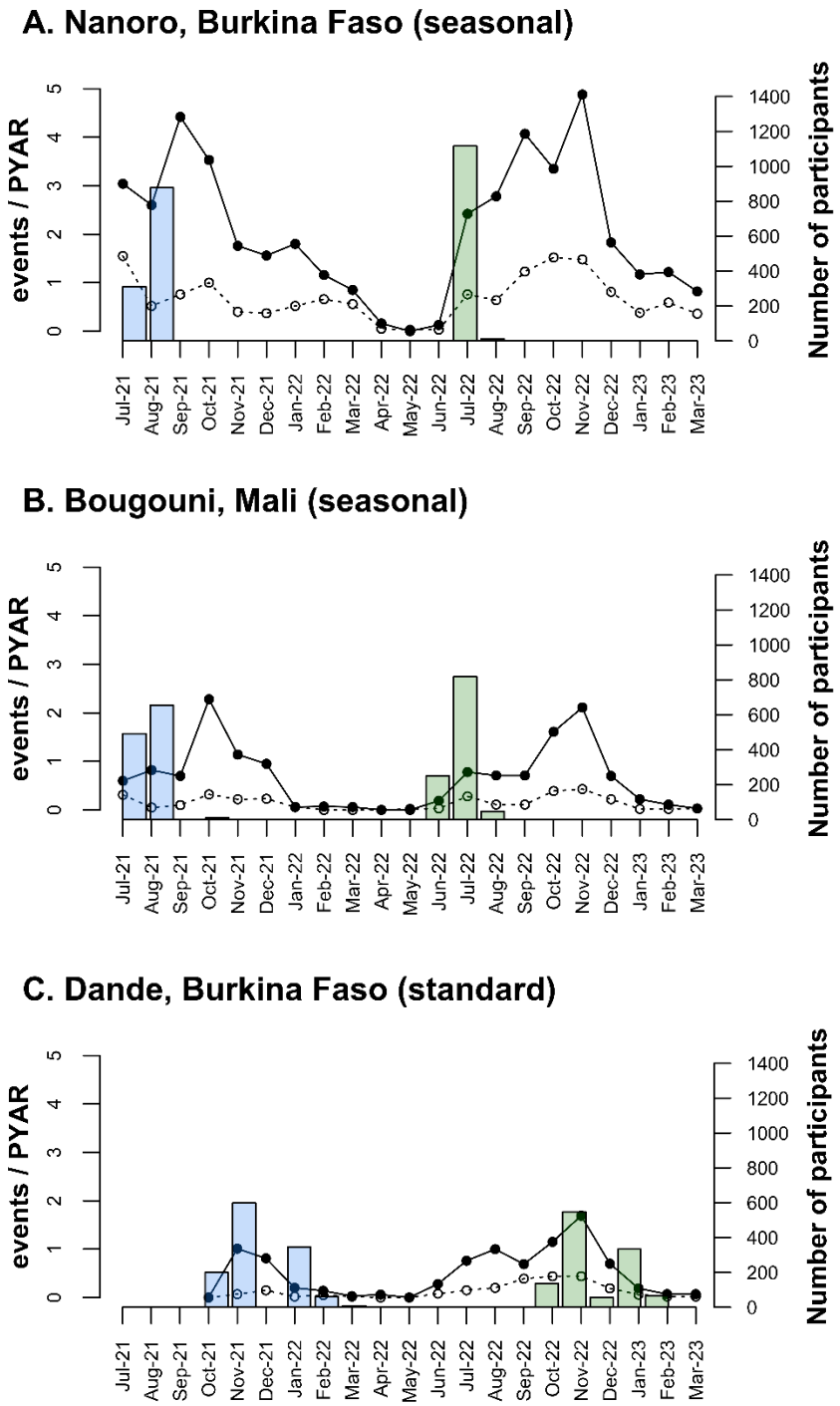
Secondary objectives reported here include VE against severe malaria, malaria hospitalizations and mortality; the effect of sex on VE; duration of protection (by 3-month intervals); the effect of a delayed dose 3 (mPP2 vs. mPP1); and the effect of SMC and nutritional status on VE.

6.1. Clinical malaria incidence rates by month by study site

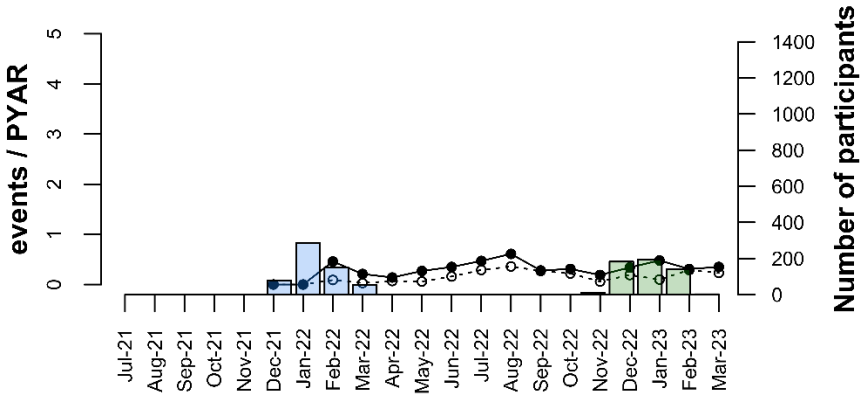
Fig. 7 depicts the incidence of all episodes of clinical malaria (primary case definition, see section 5.7) from the Phase 3 trial by month and by study site in the R21/Matrix-M vaccine recipients and the control (rabies vaccine) recipients. The median monthly rate of clinical malaria episodes in the control arm is also shown in Fig. 8 by dry season (January–June) and wet season (July–December). The rates are calculated using the mPP1 study population (as defined in Table 6).

Fig. 7. Monthly rate of clinical malaria in R21/Matrix-M Phase 3 trial, by study site and study arm

Solid lines indicate rate of clinical malaria in the control arm, dotted lines indicate the rate of clinical malaria in the R21/Matrix-M arm, blue bars indicate the number of participants in each month starting per protocol and modified per protocol follow-up (14 days after receiving dose 3), and green bars indicate the number of participants in each month who have received dose 4.



D. Bagamoyo, Tanzania (standard)



E. Kilifi, Kenya (standard)

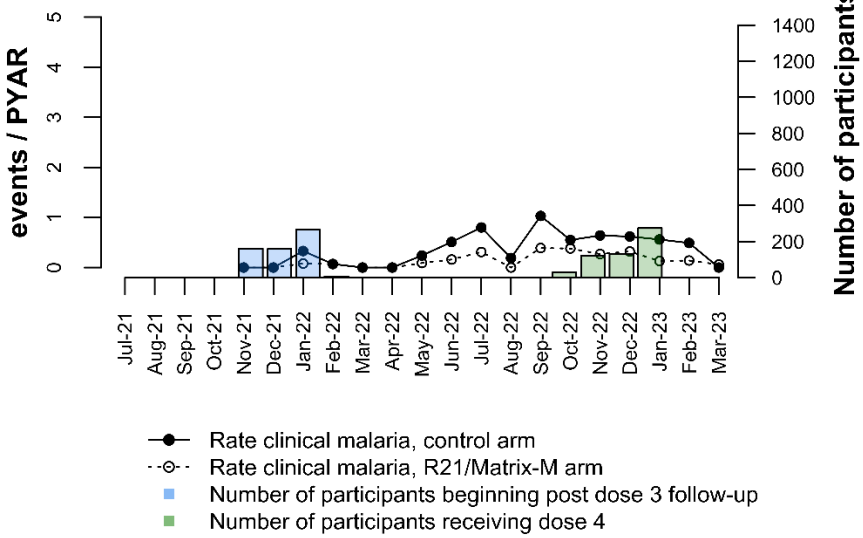
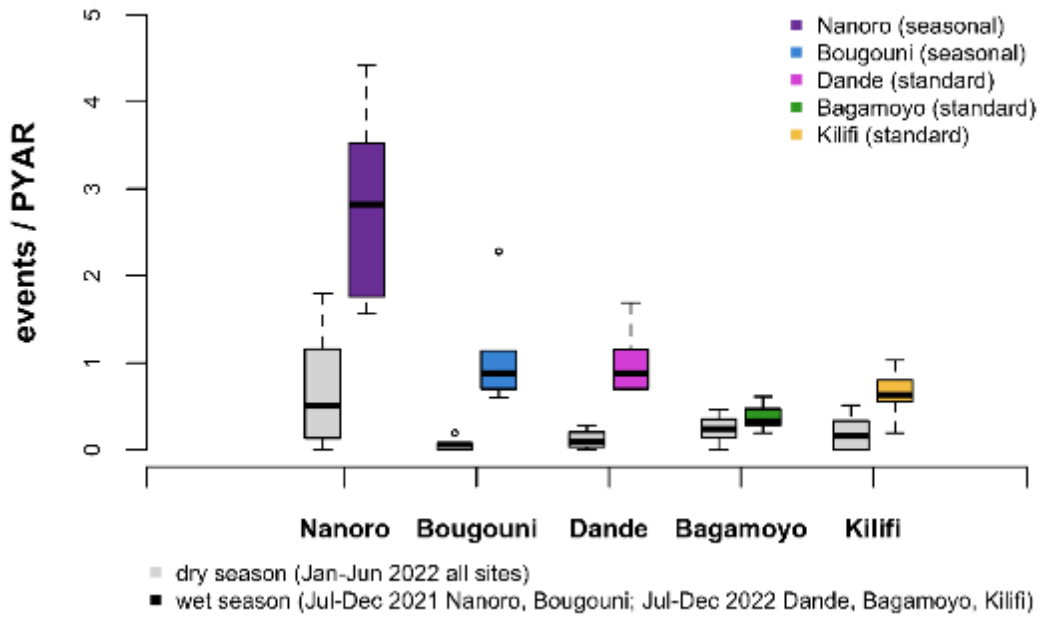


Fig. 8. Median monthly rate of clinical malaria in R21/Matrix-M Phase 3 trial control arm, by study site and transmission season



These rates provide context for the VE estimates that follow and demonstrate the marked peaks in the seasonal sites of Nanoro and Bougouni, with markedly less (Nanoro) or relatively little (Bougouni) malaria transmission occurring during the dry season. Notably, transmission at the standard sites, measured during the trial, is low to moderate; this includes Dandé, in Burkina Faso, where unlike the other two standard sites, transmission is highly seasonal and similar to Nanoro and Bougouni. SMC is provided by the government as standard of care at Dandé, Nanoro and Bougouni.

Malaria transmission settings according to the WHO Malaria Guidelines *(1)* and the WHO Malaria surveillance, monitoring, and evaluation reference manual *(39)* are defined as:

- High: ≥ 35% *P. falciparum* parasite rate ($PfPR_{2–10}$) or ~450 per 1000 annual parasite incidence (API)
- Moderate: 10-35% $PfPR_{2-10}$ or 250-450 per 1000 API
- Low: 1-10% $PfPR_{2-10}$ or 100-250 per 1000 API
- Very low: >0 but < 1% $PfPR_{2-10}$ or <100 per 1000 1000 API.

Table 8 indicates the rate of events per 1000 person years at risk (PYAR) in the control arm of the R21/Matrix-M Phase 3 trial, measured over 12 months from the first month of available data in the trial. Baseline annual transmission incidence reported in the protocol is also shown. Notably, the measured transmission intensities during the ongoing Phase 3 trial are higher than the baseline annual malaria incidence rates described in the protocol, which were estimates from the study sites based on the available data at the time of protocol development.

Table 8. Incidence of clinical malaria in R21/Matrix-M Phase 3 trial control arm by study site

Study site	Events, control arm[a]	PYAR, control arm[a]	Events/1000 PYAR, control arm (95% CI)[a] *Transmission intensity based on trial data*	Baseline annual malaria incidence[b] per 1000 PYAR *Transmission intensity based on previously measured incidence*
Seasonal administration				
Nanoro	574	352.3	1629 (1500–1770) *High*	710 *High*
Bougouni	200	348.0	575 (500–660) *High*	450 *Moderate*
Standard administration				
Dandé	133	318.0	418 (350–500) *Moderate*	400 *Moderate*
Bagamoyo	46	147.9	311 (230–410) *Low/moderate*	250 *Low*
Kilifi	57	162.2	351 (270–460) *Moderate*	80 *Very low*

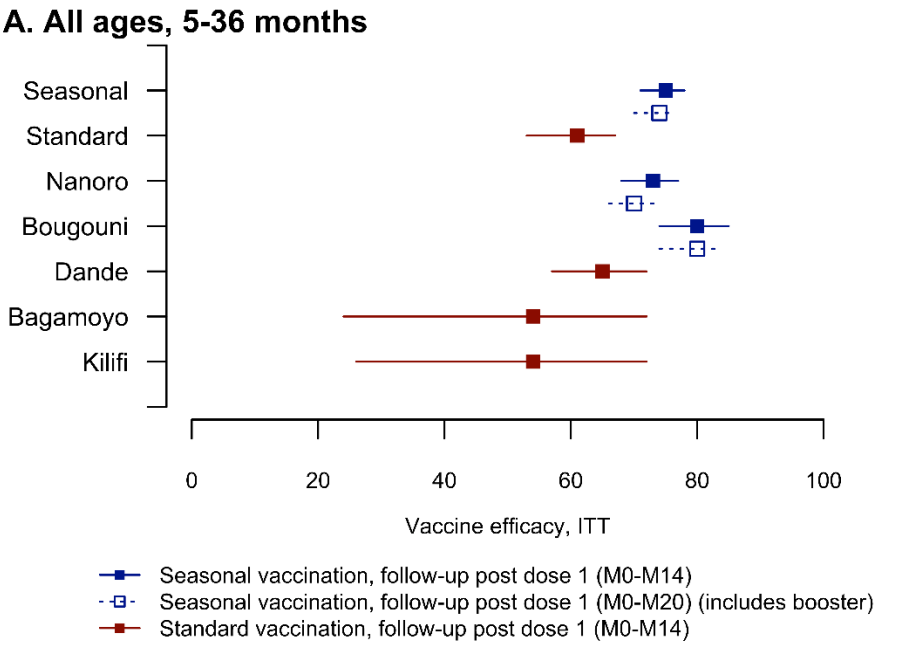
[a] Annual total measured from first month of available data: July 2021–June 2022 in Nanoro and Bougouni, October 2021–September 2022 in Dandé, December 2021–November 2022 in Bagamoyo, and November 2021–October 2022 in Kilifi

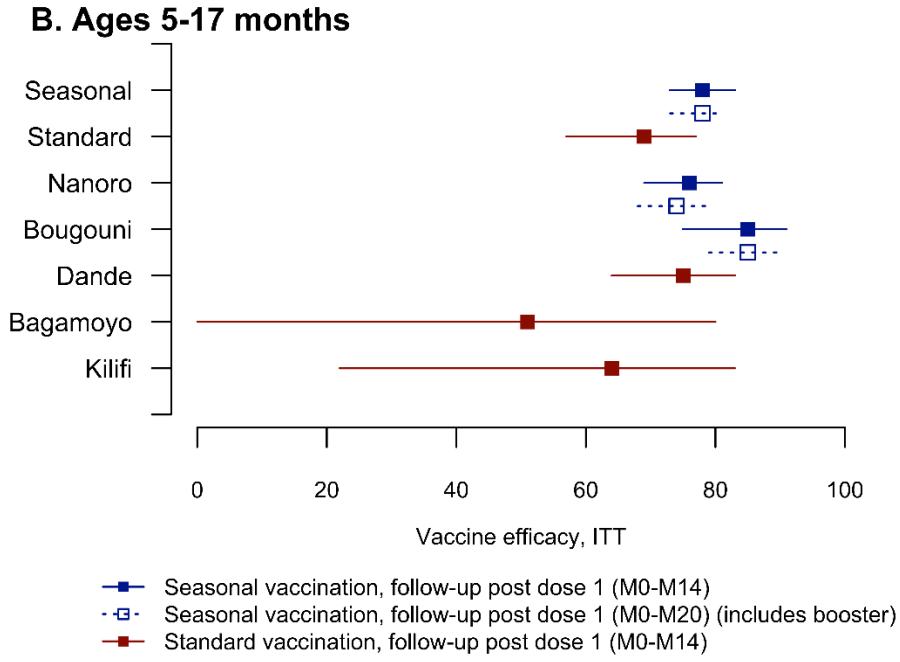
[b] from protocol sample size calculation, estimates by study site using best available data at the time.

6.2. Vaccine efficacy against all episodes of clinical malaria

The VE against all episodes of clinical malaria (primary case definition, see section 5.7) by age and study site is presented graphically in Fig. 9 and in tabular form in Table 9 and Table 10. In Table 10, a separate estimate is also shown for the East African sites (combining estimates from Bagamoyo and Kilifi) to show VE when the vaccine is provided using the age-based administration in areas that are low to moderate transmission, and when excluding the area of highly seasonal transmission (Dandé) which also has SMC administration.

Fig. 9. VE against all episodes of clinical malaria by age at first vaccine dose and study site





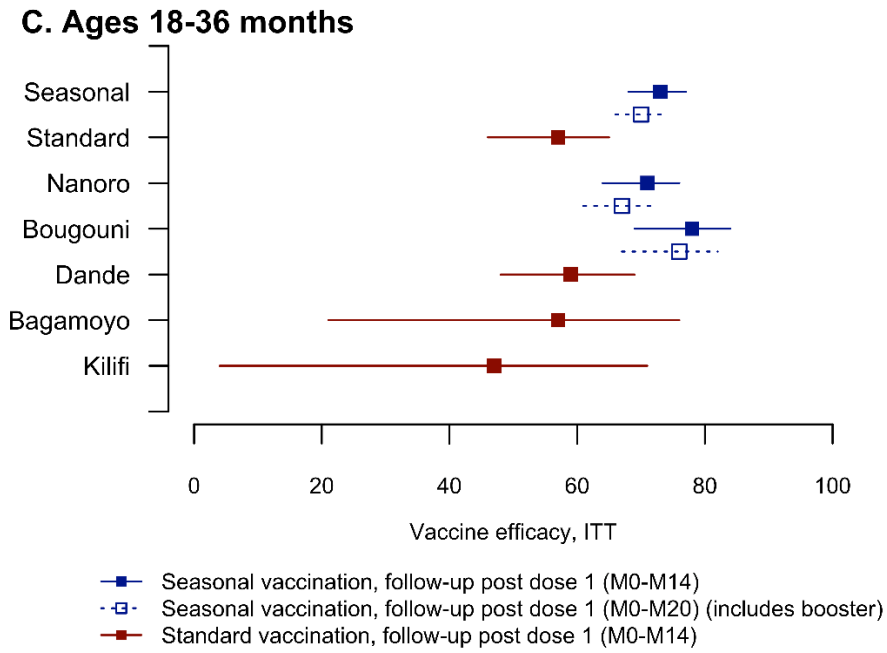

C. Ages 18-36 months
Seasonal
Standard
Nanoro
Bougouni
Dande
Bagamoyo
Kilifi
0
20
40
60
80
100
Vaccine efficacy, ITT
Seasonal vaccination, follow-up post dose 1 (M0-M14)
Seasonal vaccination, follow-up post dose 1 (M0-M20) (includes booster)
Standard vaccination, follow-up post dose 1 (M0-M14)

Table 9. Seasonal administration – VE against all episodes of clinical malaria (primary case definition), all ages (5-36 months at first vaccination), per-protocol and modified intention to treat

Study site	R21/Matrix-M				Control				VE, unadjusted (95%CI)
	N	n	T	n/T	N	n	T	n/T	
12 months post dose 3 (PP) / 14 months post dose 1 (mITT) [a,b]									
Seasonal sites combined									
PP (M2.5–M14)	1514	417	1418.4	0.29	764	820	716.5	1.14	75% (71–78)
mITT (M0–M14)	1613	466	1783.3	0.26	811	920	892.3	1.03	75% (71–78)
Nanoro									
PP (M2.5–M14)	756	342	712.7	0.48	382	610	359.0	1.70	72% (67–76)
mITT (M0–M14)	800	374	905.5	0.41	401	685	452.1	1.52	73% (68–77)
Bougouni									
PP (M2.5–M14)	758	75	705.7	0.11	382	210	357.5	0.59	82% (76–87)
mITT (M0–M14)	813	92	877.8	0.10	410	235	440.2	0.53	80% (74–85)
18 months post dose 3 (PP) / 20 months post dose 1 (mITT) [a]									
Seasonal sites combined									
PP (M2.5–M20)	1453	914	2127.6	0.43	729	1602	1071.0	1.50	73% (69–76)
mITT (M0–M20)	1613	932	2664.6	0.35	811	1688	1334.5	1.26	74% (70–76)
Nanoro									
PP (M2.5–M20)	722	747	1058.7	0.71	360	1189	531.6	2.24	68% (64–72)
mITT (M0–M20)	800	756	1312.5	0.58	401	1255	653.5	1.92	70% (66–74)
Bougouni									
PP (M2.5–M20)	731	167	1068.9	0.16	369	413	539.4	0.77	80% (74–84)
mITT (M0–M20)	813	176	1352.1	0.13	410	433	681.0	0.64	80% (74–84)

N = number of subjects included in each group, n = number of episodes included in each group, T = person years at risk, n/T = Incidence = person year rate in each group, VE(%) = unadjusted VE (negative binomial random-effects model for all clinical and all severe malaria episodes).

[a] For mITT population, time at risk is measured from dose 1 (M0), and for PP population, time at risk is measured from 14 days after dose 3 (M2.5). A participant is classified as completing 12-month or 18-month follow-up at 14 months (M14) or 20 months (M20) after dose 1, respectively. Participants vaccinated at the lower end of the vaccination window received dose 3 less than 2 months after dose 1 and reached 18-month follow-up post dose 3 before 20-month follow-up post dose 1.

[b] If dose 4 given before 365 days after dose 3, follow-up time censored the day before dose 4 given.

Table 10. Standard administration – VE against all episodes of clinical malaria (primary case definition), all ages (5–36 months), PP and mITT

Study site	R21/Matrix-M				Control				VE, unadjusted (95% CI)
	N	n	T	n/T	N	n	T	n/T	
12 months post dose 3 (PP) / 14 months post dose 1 (mITT) [a,b]									
Standard sites combined									
PP (M2.5–M14)	1270	178	1201.9	0.15	615	252	584.7	0.43	66% (56–73)
mITT (M0–M14)	1636	315	1840.8	0.17	815	406	910.8	0.45	61% (53–67)
Dandé, Burkina Faso									
PP (M2.5–M14)	525	68	502.1	0.14	254	126	243.6	0.52	74% (64–81)
mITT (M0–M14)	833	187	947.8	0.20	416	269	474.3	0.57	65% (57–72)
Bagamoyo, Tanzania									
PP (M2.5–M14)	357	53	337.3	0.16	166	57	157.1	0.36	57% (28–74)
mITT (M0–M14)	403	61	444.3	0.14	197	63	209.8	0.30	54% (24–72)
Kilifi, Kenya									
PP (M2.5–M14)	388	57	362.5	0.16	195	69	184.0	0.37	58% (33–74)
mITT (M0–M14)	400	67	448.7	0.15	202	74	226.8	0.33	54% (26–72)
East Africa combined (Bagamoyo and Kilifi)									
PP (M2.5–M14)	745	110	699.8	0.16	361	126	341.1	0.37	58% (40–70)
mITT (M0–M14)	803	128	893.0	0.14	399	137	436.6	0.31	54% (35–67)

N = number of subjects included in each group, n = number of episodes included in each group, T = person years at risk, n/T = Incidence = person year rate in each group, VE(%) = unadjusted VE (negative binomial random-effects model for all clinical and all severe malaria episodes)

[a] For mITT population, time at risk is measured from dose 1 (M0) and a participant is classified as completing 12-month follow-up at 14 months (M14) after dose 1. For PP population, time at risk is measured from 14 days after dose 3 (M2.5) and a participant is classified as completing 12-month follow-up at 12 months (M14) after dose 3 .

[b] If dose 4 given before 365 days after dose 3, follow-up time censored the day before dose 4 given.

Among children of all ages (5–36 months at time of first vaccine dose) and when combining seasonal sites, the VE against all episodes of clinical malaria 14 months following dose 1 (mITT population) was 75% (95% CI: 71–78), and did not differ significantly between Nanoro, VE 73% (68–77) and Bougouni, VE 80% (74–85) (Table 9). At 20 months following dose 1 (6 months following dose 4), the combined and per site VEs remained similar to the 12-month estimates (Table 9). In both seasonal and standard administration sites, PP VE was similar to mITT VE.

When VE was stratified by age at first vaccination at seasonal sites, point estimates tended to be higher in the 5- to 17-month age group compared to the 18- to 36-month age group at both 12- and 18-month follow-up points, but these differences were not statistically different (Annex 3, Table S3 and S4).

Combining data across all standard sites, VE against all episodes of clinical malaria among children of all ages (5–36 months) 12 months following dose 3 was 61% (95% CI: 53–67); the estimate in Dandé was higher than the estimate in the other standard sites, but the difference was not statistically different. As noted, transmission intensity was low to moderate in all standard sites, (Fig. 7C–E), and confidence intervals were wide. In Dandé, transmission was highly seasonal with very few malaria cases until the last half of the 12-month follow-up period, when transmission increased. The measured VE, with most cases

occurring at the end of that 12-month follow-up period, suggests that the vaccine will provide protection through the first 12 months after the primary three-dose vaccination series. One third of the participants in Dandé (256 of 766 in the R21/Matrix-M group; 142 of 388 in the control group) received a delayed dose 3, which was given up to 16 weeks, rather than the planned 4 weeks, after dose 2. In Dandé, 378 participants received dose 3 between 6-12 weeks after dose 2, and 27 participants received dose 3 between 12-16 weeks after dose 2.

VE was higher when the vaccine was provided seasonally in highly seasonal sites [75% (95% CI: 71–78)] than when provided using standard vaccine administration [61% (53–67)], with confidence limits that did not overlap. When VE was stratified by age at first vaccine dose at standard sites (Annex 3, Table S7 and S8), no significant differences were detected between age groups or by study site.

6.3. Vaccine efficacy against severe malaria

Overall, there were few severe malaria events during the trial, as summarized in Table 11. At seasonal sites among all age children through 18 months of follow-up there were 16 cases of severe malaria, with 8 occurring in the R21/Matrix-M arm and 8 in the control arm, resulting in estimates of VE of 50% against severe malaria but with wide confidence intervals that include zero.

Combining seasonal sites, among all ages (5–36 months) at 14-month follow-up post dose 1 (mITT population), there were only 4 cases of severe malaria in the R21/Matrix-M arm (2 each in Nanoro and Bougouni) and 4 cases in the control arm, giving an estimate of VE of 50% (95% CI: –100 to 87); findings at 18-month follow-up post dose 3 were similar (Table 11). Analyses stratified by age at first vaccine dose further reduced the number of severe malaria events in each group, resulting in even wider confidence limits for VE estimates (Annex 3, Table S10 and S11). Point estimates of VE according to PP analysis were 83% (95% CI: –62 to 98) and 58% (95% CI: –37 to 87) at 12-months and 18-months follow-up post dose 3, respectively, also with wide confidence intervals that include zero.

Table 11. Seasonal administration – VE against all episodes of severe malaria, all ages (5–36) months, PP and mITT

Study site	R21/Matrix-M				Control				VE, unadjusted (95% CI)
	N	n	T	n/T	N	n	T	n/T	
12 months post dose 3 (PP) / 14 months post dose 1 (mITT) [a,b]									
Seasonal sites combined									
PP (M2.5–M14)	1514	1	1418.0	0.001	764	3	714.1	0.004	83% (–62 to 98)
mITT (M0–M14)	1613	4	1780.9	0.002	811	4	889.9	0.004	50% (–100 to 87)
Nanoro, Burkina Faso									
PP (M2.5–M14)	756	1	712.2	0.001	382	1	358.0	0.003	50% (–705 to 97)
mITT (M0–M14)	800	2	905.2	0.002	401	2	450.5	0.004	50% (–254 to 93)
Bougouni, Mali									
PP (M2.5–M14)	758	0	705.7	0.000	382	2	356.1	0.006	100% (., 100)
mITT (M0–M14)	813	2	875.7	0.002	410	2	439.4	0.005	50% (–257 to 93)
18 months post dose 3 (PP) / 20 months post dose 1 (mITT) [a]									
Seasonal sites combined									
PP (M2.5–M20)	1453	6	2122.4	0.003	729	6	1062.6	0.006	58% (–37 to 87)
mITT (M0–M20)	1613	8	2562.7	0.003	811	8	1279.2	0.006	50% (–33 to 81)
Nanoro, Burkina Faso									
PP (M2.5–M20)	722	5	1053.9	0.005	360	2	526.1	0.004	0% (–446 to 82)
mITT (M0—M20)	800	5	1293.4	0.004	401	4	643.0	0.006	38% (–130 to 83)
Bougouni, Mali									
PP (M2.5–M20)	731	1	1068.4	0.001	369	4	536.6	0.007	87% (–12 to 99)
mITT (M0–M20)	813	3	1269.3	0.002	410	4	636.2	0.006	62% (–68 to 92)

N = number of subjects included in each group, n = number of episodes included in each group, T = person years at risk n/T = Incidence = person year rate in each group, VE(%) = unadjusted VE (negative binomial random-effects model for all clinical and all severe malaria episodes).

[a] For mITT population, time at risk is measured from dose 1 (M0), and for PP population, time at risk is measured from 14 days after dose 3 (M2.5). A participant is classified as completing 12-month or 18-month follow-up at 14 months (M14) or 20 months (M20) after dose 1, respectively. Participants vaccinated at the lower end of the vaccination window received dose 3 less than 2 months after dose 1 and reached 18-month follow-up post dose 3 before 20-month follow-up post dose 1.

[b] If dose 4 given before 365 days after dose 3, follow-up time censored the day before dose 4 given.

At standard sites, through 14 months of follow-up post dose 1 (mITT population), there were 7 cases of severe malaria in the R21/Matrix-M arm and 3 cases of severe malaria in the control arm (Table 12), giving a negative estimate of VE, but confidence intervals were wide. According to PP analysis at 12-month follow-up post dose 3, VE against severe malaria was 38% (95% CI: –176 to 86), but with wide confidence intervals that include zero. No significant VE was observed, overall or when stratified by age at first vaccine dose (Annex 3, Table S13 and S14).

Table 12. Standard administration — VE against all episodes of severe malaria, all ages (5—36 months), PP and mITT

Study site	R21/Matrix-M				Control				VE, unadjusted (95% CI)
	N	n	T	n/T	N	n	T	n/T	
12 months post dose 3 (PP) / 14 months post dose 1 (mITT) [a,b]									
Standard administration sites combined									
PP (M2.5–M14)	1270	4	1199.7	0.003	615	3	582.5	0.005	38% (–176 to 86)
mITT (M0–M14)	1636	7	1837.0	0.004	815	3	908.7	0.003	–11% (–329 to 71)
Dandé, Burkina Faso									
PP (M2.5–M14)	525	1	501.2	0.002	254	0	243.6	0.00	–
mITT (M0–M14)	833	3	945.7	0.003	416	0	474.3	0.00	–
Bagamoyo, Tanzania									
PP (M2.5–M14)	357	3	336.0	0.009	166	3	154.9	0.019	54% (–128 to 91)
mITT (M0–M14)	403	4	442.6	0.009	197	3	207.6	0.014	38% (–177 to 86)
Kilifi, Kenya									
PP (M2.5–M14)	388	0	362.5	0.00	195	0	184.0	0.00	–
mITT (M0–M14)	400	0	448.7	0.00	202	0	226.8	0.00	–
East Africa combined (Bagamoyo and Kilifi)									
PP (M2.5–M14)	745	3	698.5	0.004	361	3	338.9	0.009	54% (–128 to 91)
mITT (M0–M14)	803	4	891.3	0.004	399	3	434.4	0.007	38% (–177 to 86)

N = number of subjects included in each group, n = number of episodes included in each group, T = person years at risk, n/T = Incidence = person year rate in each group; VE(%) = unadjusted VE (negative binomial random-effects model for all clinical and all severe malaria episodes).

[a] For mITT population, time at risk is measured from dose 1 (M0), and for PP population, time at risk is measured from 14 days after dose 3 (M2.5). A participant is classified as completing 12-month follow-up at 14 months (M14) after dose 1.

[b] If dose 4 given before 365 days after dose 3, follow-up time censored the day before dose 4 given.

Table 13 summarises the cases averted.

Table 13. Cases of clinical malaria averted, 12 months post dose 3

Analysis population	Cases averted per 1000 child years (95% CI)
Seasonal sites combined	
PP (M2.5–M14)	851 (745–957)
mPP (M2.5–M14)	868 (762–974)
mITT (M0–M14)	1235 (1097–1372)
Standard sites combined	
PP (M2.5–M14)	283 (211–355)
mPP (M2.5–M14)	296 (231–361)
mITT (M0–M14)	289 (227–350)

6.4. Vaccine efficacy against malaria hospitalizations and mortality

VE against malaria hospitalizations (defined as hospitalization with confirmed *P. falciparum* parasitaemia > 5000 parasites/µL) is summarized in Table 14. As was observed with severe malaria, overall there were relatively few malaria hospitalizations during the trial. All severe malaria cases were hospitalized and included in the malaria hospitalization analysis. Six children who were hospitalized with malaria parasitaemia were not included in the analysis for the following reasons: 1 participant was hospitalized on the day of screening prior to the first dose (standard site); 5 participants had a parasitaemia <5000 (4 in seasonal sites, 1 in standard site) and therefore did not meet the primary definition for malaria hospitalization.

At seasonal sites through 20 months of follow-up post dose 1 (mITT population) there were 16 cases of malaria hospitalization, with 8 occurring in the R21/Matrix-M and 8 in the control arm, resulting in estimates of VE against malaria hospitalization of 50% with wide confidence intervals, including zero (Table 14). As would be expected, age-stratified analyses further reduced the number of malaria hospitalization events in each group, resulting in even wider confidence limits for VE estimates (Annex 3, Table S16 and S17). At standard sites through 14 months of follow-up post dose 1 (mITT population), there were 9 cases of malaria hospitalization in the R21/Matrix-M arm and 4 cases in the control arm (Table 14), giving a VE estimate just below zero, but confidence intervals were very wide and included over 50% VE. No significant VE was observed, overall or when stratified by age at first vaccine dose (Annex 3, Table S19 and S20).

VE against mortality (excluding deaths due to trauma or injury) is summarized in Table 14. Additional details and information on causes and timing of deaths is presented in section 7.

The trial was not powered to show efficacy against mortality. Overall, according to mITT population with follow-up measured from dose 1, a total of 14 deaths occurred among participants, lower than might have been expected when considering historical mortality rates. An imbalance in number of deaths in vaccination compared to control arm was observed, recognizing the 2:1 randomization, with 12 deaths in the R21/Matrix-M arm and 2 deaths in the control arm. No VE estimates against mortality were statistically significant, overall, by site and or when stratified by age group.

Table 14. VE against malaria hospitalizations and mortality, all ages (5–36 months), mITT

Study site	R21/Matrix-M				Control				VE, unadjusted (95% CI)
	N	N	T	n/T	N	n	T	n/T	
Malaria hospitalizations									
Seasonal administration									
Follow-up post dose 1, M0–M14[a,b]	1613	3	1782.0	0.005	811	4	889.9	0.005	63% (–67 to 92)
Follow-up post dose 1, M0–M20[b]	1613	8	2564.3	0.003	811	8	1279.2	0.01	50% (–32 to 81)
Standard administration									
Follow-up post dose 1, M0–M14[a,b]	1636	9	1836.5	0.005	815	4	907.6	0.004	–8% (–250 to 67)
Mortality (excluding deaths due to trauma or injury)									
Seasonal administration									
Follow-up post dose 1, M0–M14[a,b]	1613	1	1784.2	0.001	811	0	893.1	0.000	–
Follow-up post dose 1, M0–M20[b]	1613	7	2568.5	0.003	811	1	1284.4	0.001	-248 (-2726 to 57)
Standard administration									
Follow-up post dose 1, M0–M20[a,b]	1636	5	2595.7	0.002	815	1	1278.8	0.001	-145 (-1997 to 71)

N = number of subjects included in each group, n = number of episodes included in each group, T = person years at risk, n/T = Incidence = person year rate in each group, VE(%) = unadjusted VE (negative binomial random-effects model for all clinical and all severe malaria episodes).

[a] For mITT population, time at risk is measured from dose1 (M0) and a participant is classified as completing 12-month or 18-month follow-up at 14 months (M14) or 20 months (M20) after dose 1, respectively. Participants vaccinated at the lower end of the vaccination window received dose 3 less than 2 months after dose 1 and reached 18-month follow-up post dose 3 before 20-month follow-up post dose 1.

[b] If dose 4 given before 365 days after dose 3, follow-up time censored the day before dose 4 given.

6.5. Vaccine efficacy by sex against all episodes of clinical malaria (primary case definition)

VE estimates against all episodes of clinical malaria by sex by site are presented in Tables 15–16, based on the mITT population**.** VE estimates against all episodes of clinical malaria did not differ significantly by the sex of the participant, with non-significant p-values for interaction of 0.40 in seasonal sites (at 20 months follow-up post dose 1) and 0.91 in standard sites (at 14 months follow-up post dose 1). VE by sex based on the PP population were similar to mITT (Annex 3, Table S27 and 28).

Table 15. Seasonal administration — VE against clinical malaria (primary case definition), by sex, all ages (5–36 months), mITT

Study site	R21/Matrix-M				Control				VE, unadjusted (95% CI)
	N	n	T	n/T	N	n	T	n/T	
Follow-up post dose 1, M0–M14[a,b]									
Seasonal sites combined									
Male	850	259	935.3	0.28	429	521	468.8	1.11	76% (71–80)
Female	763	207	848	0.24	382	399	423.5	0.94	74% (68–79)
Nanoro, Burkina Faso									
Male	417	205	470.6	0.44	211	373	234.6	1.59	73% (66–78)
Female	383	169	434.8	0.39	190	312	217.5	1.43	73% (65–79)
Bougouni, Mali									
Male	433	54	464.6	0.12	218	148	234.1	0.63	82% (74–87)
Female	380	38	413.2	0.09	192	87	206	0.42	78% (66–86)
Follow-up post dose 1, M0–M20[b]									
Seasonal sites combined									
Male	850	499	1406.5	0.35	429	939	705.1	1.33	74% (70–78)
Female	763	433	1258.1	0.34	382	749	629.4	1.19	72% (67–77)
Nanoro, Burkina Faso									
Male	417	402	686.2	0.59	211	684	343.6	1.99	71% (65–75)
Female	383	354	626.3	0.57	190	571	309.9	1.84	69% (63–75)
Bougouni, Mali									
Male	433	97	720.3	0.13	218	255	361.5	0.71	81% (74–86)
Female	380	354	626.3	0.57	190	571	309.9	1.84	78% (68–84)

N = number of subjects included in each group, n = number of episodes included in each group, T = person years at risk, n/T = Incidence = person year rate in each group, VE(%) = VE (negative binomial random-effects model (adjusted for study site) for all clinical and all severe malaria episodes).

[a] For mITT population, time at risk is measured from dose 1 (M0) and a participant is classified as completing 12-month or 18-month follow-up at 14 months (M14) or 20 months (M20) after dose 1, respectively. Participants vaccinated at the lower end of the vaccination window received dose 3 less than 2 months after dose 1 and reached 12-month follow-up post dose 3 before 14-month follow-up post dose 1 or 18-month follow-up post dose 3 before 20-month follow-up post dose 1.

[b] If dose 4 given before 365 days after dose 3, follow-up time censored the day before dose 4 given.

Table 16. Standard administration – VE against clinical malaria (primary case definition), by sex, all ages (5–36 months at first vaccination), mITT

Study site	R21/Matrix-M				Control				VE, unadjusted (95% CI)
	N	n	T	n/T	N	n	T	n/T	
Follow-up post dose 1, M0–M14[a,b]									
Standard sites combined									
Male	833	173	939	0.18	424	226	474	0.48	61% (50 to 70)
Female	803	142	901.8	0.16	391	180	436.9	0.41	60% (48 to 80)
Dandé, Burkina Faso									
Male	430	109	488.8	0.22	215	138	245.6	0.56	60% (47 to 70)
Female	403	78	458.9	0.17	201	131	228.6	0.57	70% (59 to 78)
Bagamoyo, Tanzania									
Male	202	31	224.5	0.14	107	44	113.8	0.39	64% (30 to 81)
Female	201	30	219.8	0.14	90	19	96	0.2	31% (–49 to 68)
Kilifi, Kenya									
Male	201	33	225.6	0.15	102	44	114.6	0.38	62% (27 to 80)
Female	199	34	223.1	0.15	100	30	112.2	0.27	43% (–15 to 72)
East African sites combined (Bagamoyo and Kilifi)									
Male	403	64	450.2	0.14	209	88	228.3	0.39	63% (41 to 76)
Female	400	64	442.9	0.14	190	49	208.2	0.24	38% (–4 to 63)

N = number of subjects included in each group, n = number of episodes included in each group, T = person years at risk, n/T = Incidence = person year rate in each group, VE(%) = VE (negative binomial random-effects model (adjusted for study site) for all clinical and all severe malaria episodes).

[a] For mITT population, time at risk is measured from dose 1 (M0) and a participant is classified as completing 12-month follow-up at 14 months (M14) after dose 1. Participants vaccinated at the lower end of the vaccination window received dose 3 less than 2 months after dose 1 and reached 12-month follow-up post dose 3 before 14-month follow-up post dose 1.

[b] If dose 4 given before 365 days after dose 3, follow-up time censored the day before dose 4 given.

6.6. Duration of protection against all episodes of clinical malaria

The duration of protection (and waning of VE), pooled by seasonal vaccination sites and standard vaccinations sites, is presented in Fig. 10, Table 17 and Table 18 (and by study site in Annex 3).

At seasonal sites among children of all ages, VE (according to mPP1 population) point estimates remained high for the first 6 months following dose 3 (81% during months 1–3 and 74% during months 4–6), then dropped significantly during months 7–9 (44%), but increased again in months 10–12 (prior to dose 4) to 67% (95% CIs are provided in Table 17). The overall decrease in VE at seasonal sites during months 7–9 was driven largely by a decrease in VE in Nanoro to 42% (95% CI: 16–61). This was due to a large reduction in events during the low transmission season, resulting in an imprecise estimate for VE during this study interval that may not be indicative of overall trends over time. Estimated VE in Bougouni at 7–9 months was imprecise – 80% (–70 to 98), due to only 1 event in the R21/Matrix-M arm and 3 events in the control arm (Annex 3, Table S29C).

After dose 4, protective efficacy was maintained during the 6 months post dose 4 follow-up, with point estimates of 70% (13–15 months) and 69% (16–18 months). At standard sites among children of all ages, VE point estimates declined slowly over time (test for trend was not conducted), with point estimates decreasing from 79%, during 1–3 months post dose 3, to 68% during 4–6 months, 64% during 7–9 months, and 63% during 10–12 months (95% CIs are provided in Table 18). This pattern did not differ significantly by site. All enrolled children received dose 4 at 12 months after dose 3, so further assessment of duration of protection following only three vaccine doses is not available.

Fig. 10. VE against all clinical episodes in 3-month intervals, all ages 5–36 months

Data shown are for (a) seasonal sites pooled, excluding participants who received dose 4 outside the specific time window, and (b) standard sites pooled. VE estimates for months 1–12 are after receiving three doses, and VE estimates for months 13–18 are after receiving four doses.

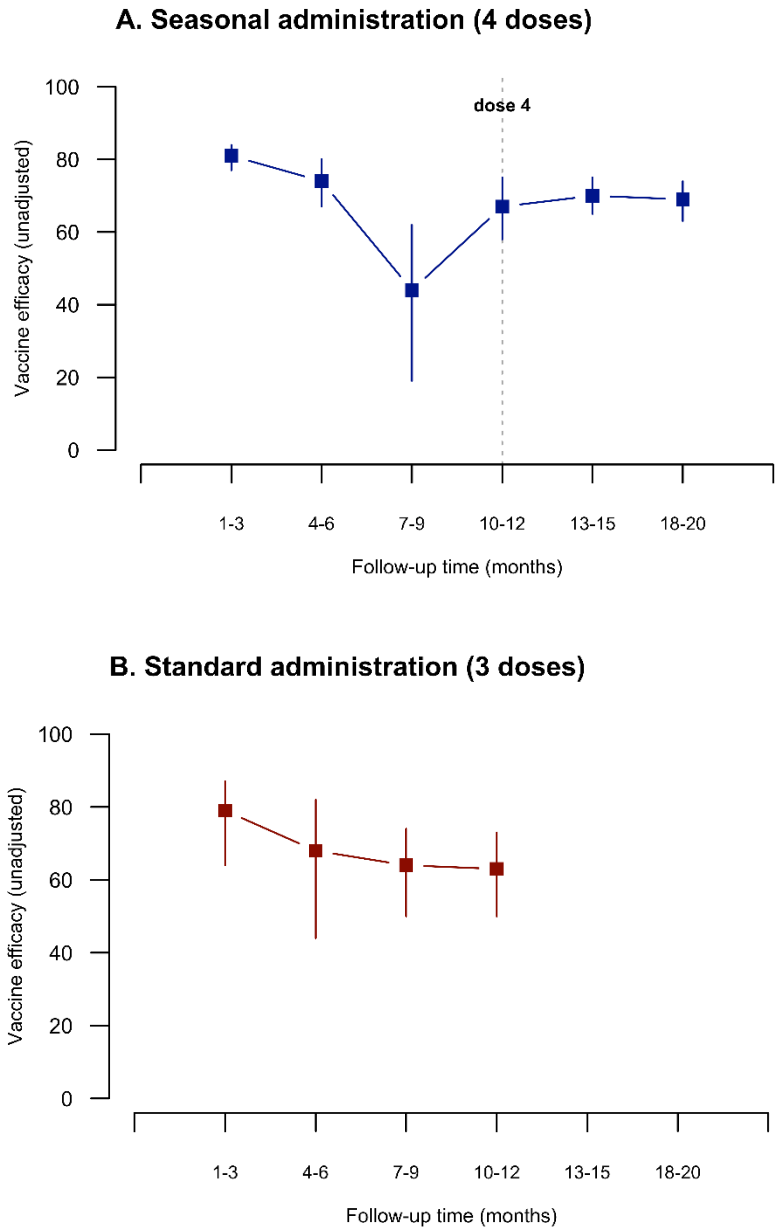


Table 17. Seasonal administration – VE against all episodes of clinical malaria (primary case definition) by 3-month study period, mPP1

Study period[a]	Incidence clinical malaria (events/PYAR)		VE, unadjusted (95% CI)
	R21/Matrix-M	Control	
Seasonal sites combined (Nanoro and Bougouni)			
1–3 months	0.45 (169/373.5)	2.38 (444/186.2)	81% (77–84)
4–6 months	0.31 (117/373.5)	1.20 (224/186.3)	74% (67–80)
7–9 months	0.19 (72/373.5)	0.34 (64/186.3)	44% (19–62)
10–12 months	0.23 (87/373.5)	0.71 (132/186.3)	67% (58–75)
13–15 months (post dose 4)	0.71 (264/373.5)	2.38 (443/186.3)	70% (65–75)
16–18 months (post dose 4)	0.51 (190/373.4)	1.64 (306/186.2)	69% (63–74)

PYAR = person year at risk

[a] Data shown are for all seasonal sites pooled, excluding participants who received dose 4 outside the specific time window. VE estimates for months 1–12 are after receiving three doses, and VE estimates for months 13–18 are after receiving four doses.

Table 18. Standard administration — VE against of all episodes of clinical malaria (primary case definition) by 3-month study period, mPP1

Study period[a]	Incidence clinical malaria (events/PYAR)		VE, unadjusted (95% CI)
	R21/Matrix-M	Control	
Standard sites combined (Dandé, Bagamoyo and Kilifi)			
1–3 months	0.06 (24/384.4)	0.29 (55/189.8)	79% (64–87)
4–6 months	0.06 (23/382.8)	0.18 (35/189.3)	68% (44–82)
7–9 months	0.21 (80/378.1)	0.59 (111/188.0)	64% (50–74)
10–12 months	0.28 (90/317.0)	0.77 (121/156.5)	63% (50–73)

PYAR = person year at risk

[a] Data shown are for all standard sites pooled. VE estimates for months 1–12 are after receiving 3 doses.
VE estimates post dose 4 are not yet available in standard administration sites.

6.7. Vaccine efficacy among children receiving a delayed dose 3

Receipt of dose 3 was delayed among some children due to various factors including those posed by the COVID-19 pandemic; this delayed dosing occurred mostly at the Dandé site, where approximately one third of enrolled children received a delayed dose 3. The impact of this delayed dose 3 was further assessed by defining two study populations for VE analysis as noted in section 5.7:

- Study population modified per protocol 1 (mPP1) was defined as the same as the PP population but, allowing the interval between doses 2 and 3 to be between 3 and 16 weeks.

- Study populations modified per protocol 2 (mPP2) was defined as the same as the primary PP, but only including participants with the interval between doses 2 and 3 to be between 6 and 16 weeks (i.e. participants who were delayed in receiving dose 3).

The VE against all episodes of clinical malaria comparing mPP1 and mPP2 is shown in Table 19 for all standard sites combined and for Dandé alone. VE estimates did not differ significantly among mPP1 and mPP2 study populations, suggesting that VE was not affected significantly by the delayed dose 3.

Table 19. VE against all clinical episodes, mPP2 compared to mPP1, all ages (5–36 months)

Study site	R21/Matrix-M				Control				VE, unadjusted (95% CI)
	N	n	T	n/T	N	n	T	n/T	
12 months follow-up post dose 3[a]									
Standard sites combined									
mPP1 (M2.5–M14)	1543	217	1462.4	0.15	761	322	723.5	0.45	66% (59–73)
mPP2 (M2.5–M14)	283	40	269.7	0.15	156	77	148.5	0.52	71% (54–81)
Dandé, Burkina Faso									
mPP1 (M2.5–M14)	766	103	742.0	0.14	388	195	371.3	0.53	74% (65–80)
mPP2 (M2.5–M14)	256	36	244.8	0.15	142	76	135.4	0.56	74% (58–83)

N = number of subjects included in each group, n = number of episodes included in each group, T = person years at risk, n/T = Incidence = person year rate in each group, VE(%) = VE (negative binomial random-effects model (adjusted for study site) for all clinical and all severe malaria episodes).

[a] If dose 4 given before 365 days after dose 3, follow-up time censored the day before dose 4 given

6.8. Vaccine efficacy stratified by seasonal malaria chemoprevention

The clinical trial was not designed to measure the effect of SMC on VE. SMC was provided through the routine system with varying uptake, and ascertainment of SMC use was through the review of child home health cards, with no data on the card interpreted as no SMC administered. Noting these limitations, there was no synergistic or other effect of SMC observed on VE against all clinical episodes when stratified by participants receiving zero SMC rounds compared to participants receiving 3 or 4 SMC rounds (Table 20), with p-values for interaction effect of 0.38 and 0.91 at 14- and 20-months follow-up pose dose 1. VE stratified by SMC and study site is included in Annex 3, Table S33.

Table 20. VE stratified by SMC, against all episodes of clinical malaria, all ages (5–36 months at first vaccination), mITT

SMC rounds received 2021	R21/Matrix-M		Control		VE, unadjusted (95%CI)	p-value, interaction
	N	Incidence (n/T)	N	Incidence (n/T)		
14-months follow-up post dose 1 (M0–M14)[a,b]						
Seasonal sites combined (Nanoro and Bougouni)[c]						
0	115	0.41 (34/82.2)	65	1.24 (55/44.4)	71% (50–83)	0.38
3–4	730	0.28 (237/836.1)	390	1.14 (504/444.1)	76% (71–80)	
20-months follow-up post dose 1 (M0–M20)[a]						
Seasonal sites combined (Nanoro and Bougouni)[c]						
0	115	0.36 (68/189.7)	65	0.89 (96/107.6)	69% (43–83)	0.91
3–4	730	0.41 (499/1212.1)	390	1.52 (976/642.4)	74% (70–78)	

N = number of subjects included in each group, n = number of episodes included in each group, T = person years at risk, n/T = Incidence = person year rate in each group, VE(%) = VE (negative binomial random-effects model (adjusted for study site) for all clinical and all severe malaria episodes).

[a] For mITT population, time at risk is measured from dose 1 (M0) and a participant is classified as completing 12-month or 18-month follow-up at 14 months (M14) or 20 months (M20) after dose 1, respectively. Participants vaccinated at the lower end of the vaccination window received dose 3 less than 2 months after dose 1 and reached 12-month follow-up post dose 3 before 14-month follow-up post dose 1 or 18-month follow-up post dose 3 before 20-month follow-up post dose 1.

[b] If dose 4 given before 365 days after dose 3, follow-up time censored the day before dose 4 given.

[c] Dandé is not included in this analysis because all participants in the study site received ≥ 1 round of SMC and comparison against zero SMC as a reference group was not possible. VE by SMC rounds received for Dandé is included in Annex 3, Table S34.

6.9. Overall assessment of R21/Matrix-M efficacy

VE against all episodes of clinical malaria

- Among children of all ages (5–36 months at first vaccine dose) and when combining the data from the two sites, where R21/Matrix-M was provided seasonally in areas of highly seasonal malaria transmission, VE against all episodes of clinical malaria 14 months following dose 1 (mITT population) was 75% (95% CI: 71–78), and did not differ significantly by site. In the 20 months following dose 1 (6 months following dose 4), the combined and per site VEs remained similar to the 14-month estimates. VE did not differ significantly between younger (5–17 months at dose 1) and older (18–36 months at dose 1) children.
- Among children of all ages (5–36 months at dose 1) and when combining the data from sites where R21/Matrix-M was given in an age-based "standard" vaccination in areas of low to moderate or highly seasonal moderate transmission, VE against all episodes of clinical malaria 14 months following dose 1 was 61% (95% CI: 53–67). As observed in seasonal sites, VE was not significantly different when dose 1 was given in the younger or older age group.
- VE was reasonably high after 12 months in settings of low to moderate transmission and showed good durability over 12 months (pre-dose 4). In areas of highly seasonal transmission, VE also showed good durability over 6 months post-dose 4. VE and durability of protection at sites with high perennial transmission was not assessed in the Phase 3 trial and should be assessed as part of the post-introduction risk management activities.
- VE estimates against all episodes of clinical malaria did not differ by the sex of the participant.

VE against severe malaria

- Few cases of severe malaria were observed in the trial and the power to assess VE against severe malaria was low.
- At seasonal sites, among all age children (5–36 months at first vaccine dose) through 18 months of follow-up, there were 16 cases of severe malaria, with 8 occurring in the R21/Matrix-M and 8 in the control arm, resulting in a VE estimate of 50% but with confidence intervals that included zero.
- At standard sites, through 12 months of follow-up, there were slightly more cases of severe malaria in the R21/Matrix-M arm (7 cases of severe malaria in the R21/Matrix-M arm and 3 in the control arm). Confidence intervals were wide and were consistent with both no effect and with the effect seen against clinical malaria.

VE against malaria hospitalization or mortality

- Like severe malaria, malaria hospitalization or participant death were relatively infrequent events compared to clinical malaria.
- At seasonal sites, among all age children (5–36 months) through 18 months of follow-up, 16 cases of malaria hospitalization were recorded, with 8 occurring in the R21/Matrix-M and 8 in the control arm, resulting in estimates of VE against malaria hospitalization of 50%, but with wide confidence intervals. At standard sites, there were 9 cases of malaria hospitalization in the R21/Matrix-M arm and 4 cases in the control arm); no significant VE against malaria hospitalization was observed, but again the confidence intervals were very wide.
- A statistically non-significant imbalance in number of deaths was observed, with 12 deaths in

the R21/Matrix-M and 2 deaths in the control arm (noting the 2:1 randomization). No VE estimates against mortality were statistically significant by site r when stratified by age group at which the first vaccine dose was given.

- VE estimates against all episodes of clinical malaria did not differ by the sex of the participant.

Duration of protection against all episodes of clinical malaria

- At sites with highly seasonal malaria and receiving seasonal vaccination, among children of all ages (5–36 months at dose 1), VE point estimates remained high for the first 6 months following dose 3 (81% during months 1–3 and 74% during months 4–6), then dropped significantly during months 7–9 (44%), but increased again in months 10–12 (prior to dose 4) to 67%. After dose 4, protective efficacy was maintained with point estimates of 79% (13–15 months) and 69% (16–18 months).
- At standard administration sites among children of all ages (5–36 months at dose 1), VE point estimates declined slowly over time (test for trend was not conducted), with point estimates decreasing from 79% during months 1–3 post dose 3, to 68% during months 4–6, 64% during months 7–9, and 63% during months 10–12 (confidence limits overlap). This pattern did not differ significantly by site. Of interest is that the efficacy observed in Dandé, during the first year of follow-up after the primary 3-dose series, was similar to that seen in the sites where the vaccine was given just prior to the high transmission season, even though vaccination in Dandé was administered about 6 months before the high transmission season. This finding is consistent with durability of protection during the 12-month follow-up period.

VE with a delayed dose 3

- VE estimates did not differ significantly among children whose dose 3 was delayed (received 6–16 weeks after dose 2). However, it should be noted that the trial was not designed or powered to address the effect of a delay in dose 3.

7. R21/Matrix-M safety

R21/Matrix-M safety data are available from both early clinical studies (Phase 1 and 2) and the ongoing Phase 3 trial. The safety data from the Phase 1 and 2 studies are summarized briefly in section 7.1.

The safety data have been reviewed by the R21/Matrix-M Safety Working Group, composed of members of the WHO Global Advisory Committee on Vaccine Safety (GACVS) and the SAGE/MPAG Working Group on Malaria Vaccines, and then subsequently by the full GACVS.

7.1. Overview of early-stage R21/Matrix-M clinical studies

The safety data from early-stage clinical studies are summarized below.

- **Phase 1a UK and 1b Burkina Faso *(32)* (VAC053, see section 4.2.2).** Vaccinations were well tolerated, and most local and systemic adverse events were mild. No serious adverse reactions or suspected unexpected serious adverse reactions (SUSARs) occurred. Two serious adverse events (SAEs) occurred; the first was deemed unlikely and the second not related to vaccination. Overall reactogenicity was significantly lower in Burkina Faso as compared to UK volunteers receiving the same dose.
- **Phase 1 and 2a (VAC072, see section 4.2.2).** No SUSARs or SAEs were observed related to vaccination. For the standard dose of 10 µg R21/50 µg Matrix-M, most adverse events were mild with very few graded as severe. A total of eight participants experienced fever, all receiving the standard dose of 10µg R21/50µg Matrix-M. For the higher dose of 50 µg R21/50 µg Matrix-M, most adverse events were also mild.
- **Phase 1 and 2a (VAC073, see section 4.2.2).** No SUSARs or SAEs related to vaccination were reported. At all doses, the majority of adverse events were mild with very few severe adverse events.
- **Phase 2b (VAC076), see section 4.2.3).** R21/Matrix-M had a favourable safety profile and was well tolerated. No SUSARs/SAEs (n = 13) were assessed as related to vaccination, and no febrile convulsions were assessed as related to vaccination. Most adverse events were mild, with the most common event being fever. Fever occurred in 19–30% during the primary series of vaccinations across all vaccine doses. The percentage of children with fever following each booster dose was: dose 4, 25%; dose 5, 41%; and dose 6, 18%. Pain/swelling at the injection site was the most common solicited local adverse event. During the primary series of vaccinations (doses 1, 2 and 3) pain occurred among 2–6% of vaccinees and swelling in 4–16% across all vaccine doses. With booster doses, the occurrences of pain and swelling were: dose 4, pain 0%, swelling 0%; dose 5, pain 20%, swelling 17%; dose 6, pain 20%, swelling 23%.

7.2. Phase 3 trial safety data

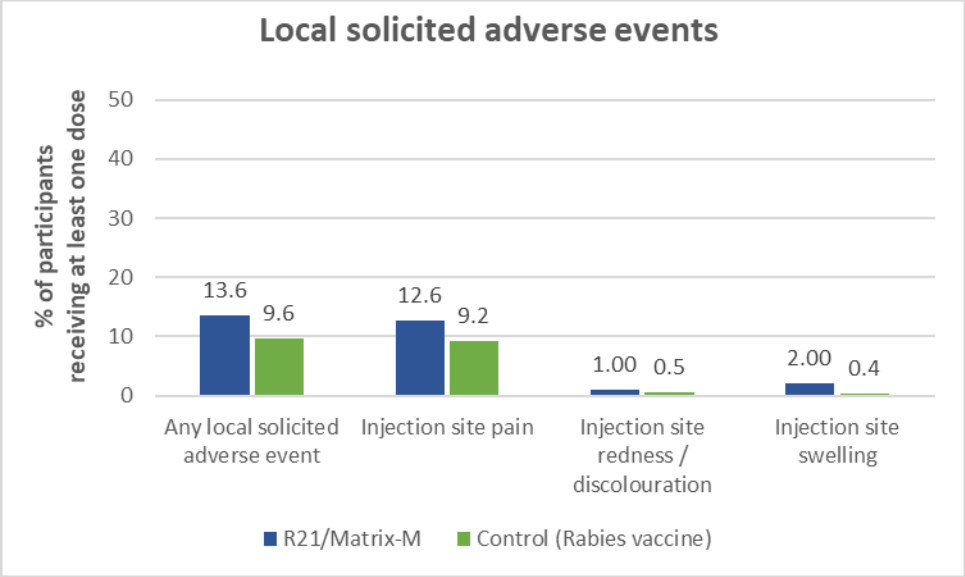
The R21/Matrix-M Phase 3 trial enrolled over 4800 children aged 5–36 months at both seasonal and standard sites in similar numbers in four sub-Saharan African countries. Children were randomized 2:1 to malaria vaccine or control (rabies vaccine) at each site. The CONSORT diagrams are included as Annex 3, Figures S1-6. The safety analysis for the Phase 3 study was based on a modified intention-to-treat (mITT) population, which included randomized children who received at least one dose of study vaccine. Of note, the Phase 2b study analyses, including safety, included only participants who received three vaccinations, and thus are not strictly comparable to the Phase 3 trial.

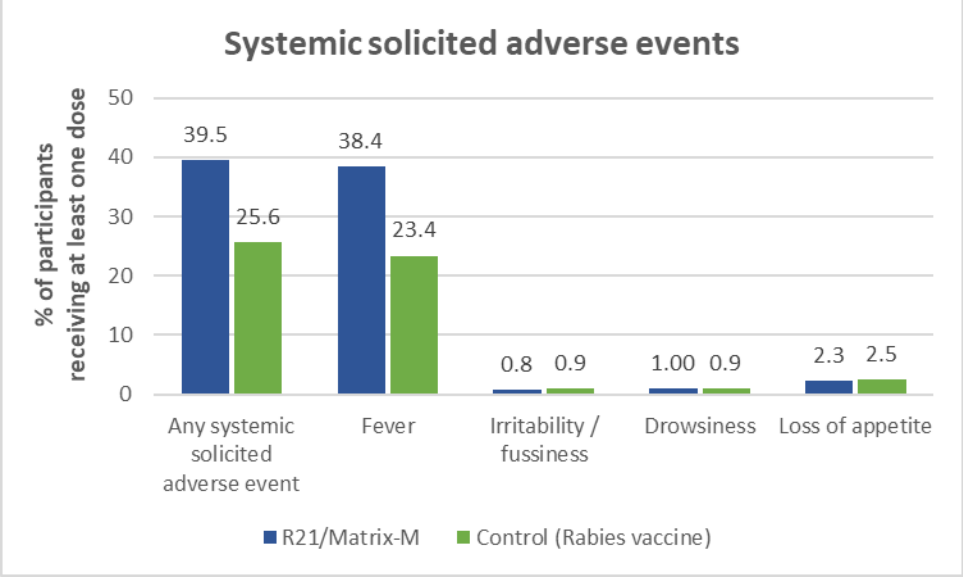
7.2.1. Reactogenicity

Solicited adverse events were recorded over a 7-day follow-up period (day of vaccination and 6 subsequent days) after each vaccination for the first 50% of participants randomized at each site. Unsolicited adverse events were collected for all participants over a 28-day follow-up period (day of vaccination and 27 subsequent days) and recorded at 14 days and 28 days following each vaccination. All unsolicited adverse events were assessed as not, unlikely, possibly, probably, or definitely related to vaccination.

Local and systemic solicited adverse events are presented in Fig. 11.

Fig. 11. Percentage of participants with solicited adverse events following the primary series of vaccinations (doses 1, 2 and 3), Phase 3 trial R21/Matrix-M





Among R21/Matrix-M recipients, 38.4% had fever as a solicited adverse event, compared to 23.4% of control (rabies vaccine) recipients.

7.2.2. Serious adverse events (SAEs)

Overall, in the Phase 3 trial, as of 31 March 2023, there were 142 SAEs reported; 64 at seasonal administration sites and 69 at standard sites. Of these, 95 SAEs were reported in 88 (2.7%) of 3252 participants in the R21/Matrix-M vaccine arm, as compared with 47 SAEs reported in 41 (2.5%) of 1626 participants in the control arm, thus the frequency of SAEs was balanced between the study arms.

The most common seriousness criterion in both vaccination arms was hospitalization.

Six SAEs were considered related to vaccination (all febrile convulsions – 5 in the R21/Matrix-M vaccine arm and 1 in the rabies vaccine arm); all resolved without sequelae.

SAEs by gender and dosing regimen are presented in Table 21.

Table 21. SAEs by gender and dosing regimen, Phase 3 trial R21/Matrix-M

	Seasonal		Standard		Total	
	R21/Matrix-M n (%), E	**Control n (%), E**	**R21/Matrix-M n (%), E**	**Control n (%), E**	**R21/Matrix-M n (%), E**	**Control n (%), E**
mITT population	1 614	811	1 638	815	3 252	1 626
Any SAE (Male)	25 (2.9), 27	10 (2.3), 12	26 (3.1), 27	12 (2.8), 12	51 (3.0), 54	22 (2.6), 24
Any SAE (Female)	14 (1.8), 16	9 (2.4), 11	23 (2.9), 25	10 (2.6), 12	37 (2.4), 41	19 (2.5), 23
Any SAE (Total)	39 (2.4), 43	19 (2.3), 23	49 (3.0), 52	22 (2.7), 24	88 (2.7), 95	41 (2.5), 47
Relationship with study vaccine						
No relationship	38 (2.4), 42	19 (2.3), 23	41 (2.5), 44	20 (2.5), 21	79 (2.4), 86	39 (2.4), 44
Unlikely	0	0	4 (0.2), 4	2 (0.2), 2	4 (0.1), 4	2 (0.1), 2
Possible	1 (0.1), 1[a]	0	2 (0.1), 2[a]	0	3 (0.1), 3[a]	0
Probably	0	0	2 (0.1), 2[a]	0	2 (0.0), 2[a]	0
Definite	0	0	0	1 (0.1), 1	0	1 (0.1), 1
Number of participants with any SAE that led to death[b]	8 (0.5)	2 (0.2)	7 (0.4)	2 (0.2)	**15 (0.5)**	**4 (0.2)**

n = number of participants, E = events

[a] Possibly and probably related events were the events of febrile convulsion

[b] No deaths were considered to be related to the study vaccine

An imbalance was noted in number of fatal SAEs in the R21/Matrix-M vaccination arm compared to the control arm. Overall, 19 events of fatal outcome were reported: 15 subjects (0.5%) in the R21/Matrix-M arm, compared to 4 subjects (0.2%) in the control arm, noting 2:1 randomization. An imbalance was seen in both seasonal and standard vaccination sites. At seasonal sites, there were 10 deaths: 8 subjects (0.5%) in the R21/Matrix-M arm, and 2 subjects (0.2%) in the control arm. At standard sites, there were 9 deaths: 7 subjects (0.4%) in the R21/Matrix-M arm, and 2 subjects (0.2%) in the control arm. The causes of death are listed in Table 24.

Fatal SAEs by gender and dosing regimen are summarized in Table 22. Combining seasonal and standard vaccination sites, there were 11 deaths in males: 10 subjects (0.6%) in the R21/Matrix-M arm and 1 subject (0.1%) in the control arm. This imbalance in deaths was not seen with females: 5 subjects (0.3%) in the R21/Matrix-M arm and 3 subjects (0.4%) in the control arm.

Table 22. Fatal SAEs leading to death by sex and vaccine administration approach, Phase 3 trial R21/Matrix-M

	Seasonal		Standard		Total	
	R21/Matrix-M n (%)	**Control n (%)**	**R21/Matrix-M n (%)**	**Control n (%)**	**R21/Matrix-M n (%)**	**Control n (%)**
mITT population	1614	811	1638	815	3252	1626
mITT population (male)	810	429	834	474	1684	853
SAEs leading to death (male)	4 (0.5) 4 (0.5)	1 (0.2) 1 (0.1)	6 (0.7) 4 (0.5)	0 –	10 (0.6) 8 (0.5)	1 (0.1) 1 (0.1)
mITT population (female)	704	382	804	391	2273	773
SAEs leading to death (female)	4 (0.5) 3 (0.5)	1 (0.3) 1 (0.3)	1 (0.1) 1 (0.1)	2 (0.5) 1 (0.3)	5 (0.3) 4 (0.2)	3 (0.4) 2 (0.3)
SAEs leading to death (total)	8 (0.5) 7 (0.4)	2 (0.2) 2 (0.2)	7 (0.4) 5 (0.3)	2 (0.2) 1 (0.1)	15 (0.5) 12 (0.4)	4 (0.2) 3 (0.2)

n = number of participants, E = events

Red: excluding SAEs leading to death which were due to trauma or injury as described in the Council for International Organization of Medical Science (CIOMS) narratives of fatal cases

The imbalance in mortality was further explored; no imbalance was observed in SAEs for severe malaria, including severe malarial anaemia and cerebral malaria (Table 23).

Table 23. SAEs for severe malaria (including severe malarial anaemia and cerebral malaria), by vaccine administration approach and study arm

	Seasonal sites		Standard sites		Total	
Serious adverse event term	**R21/ Matrix-M n**	**Control n (E)**	**R21/ Matrix-M n**	**Control n (E)**	**R21/ Matrix-M n (%), E**	**Control n (%), E**
mITT population	1614	811	1638	815	3252	1626
Severe malaria	7	3	4	3	11	6
Febrile convulsions, secondary to severe malaria	0	0	1	0	1	0
Severe malarial anaemia	4	2 (3)	3	1	7	3 (4)
Severe anaemia, secondary to severe malaria	0	2	3	3	3	5
Malaria	0	0	1	0	1	0
Malarial anaemia	0	1	1	0	1	1
Cerebral malaria	0	0	0	1	0	1
Convulsions, secondary to cerebral malaria	1	0	0	0	1	0
Total of selected SAEs	**12**	**8 (9)**	**13**	**8**	**25 (0.77), 25**	**16 (0.98), 17**
Fatal cases among selected SAEs	**4**	**1**	**1**	**1**	**5 (0.15), 5**	**2 (0.12), 2**

Excluding the four accidental/trauma-related deaths, the imbalance in deaths remained, with a total 16 fatal SAEs in 15 subjects (2 events, severe malaria and sepsis, were marked as resulting in death in a single child): 13 in 12 subjects (0.4%) in the R21/Matrix-M arm, and 3 in 3 subjects (0.2%) in the control

arm (Table 22). Further analysis of deaths did not reveal any clustering in time of deaths related to vaccination, or pattern of cause of death (Table 24 and Fig. 12). The proportionate mortality in the R21/Matrix-M arm compared to the control arm was not statistically significant; nor was the difference between males and females statistically significant. A number of children who died were noted to have suffered from malnutrition, and this variable was explored. There was no imbalance in nutritional status at enrollment and no excess in malnutrition in the R21/Matrix-M arm 12 months after dose 3. Furthermore, vaccine efficacy (VE) was similar among undernourished and well-nourished children (Annex 3, Table S35 and Table S36).

Table 24 Listing of fatal SAEs by vaccination strategy, study arm and cause of death

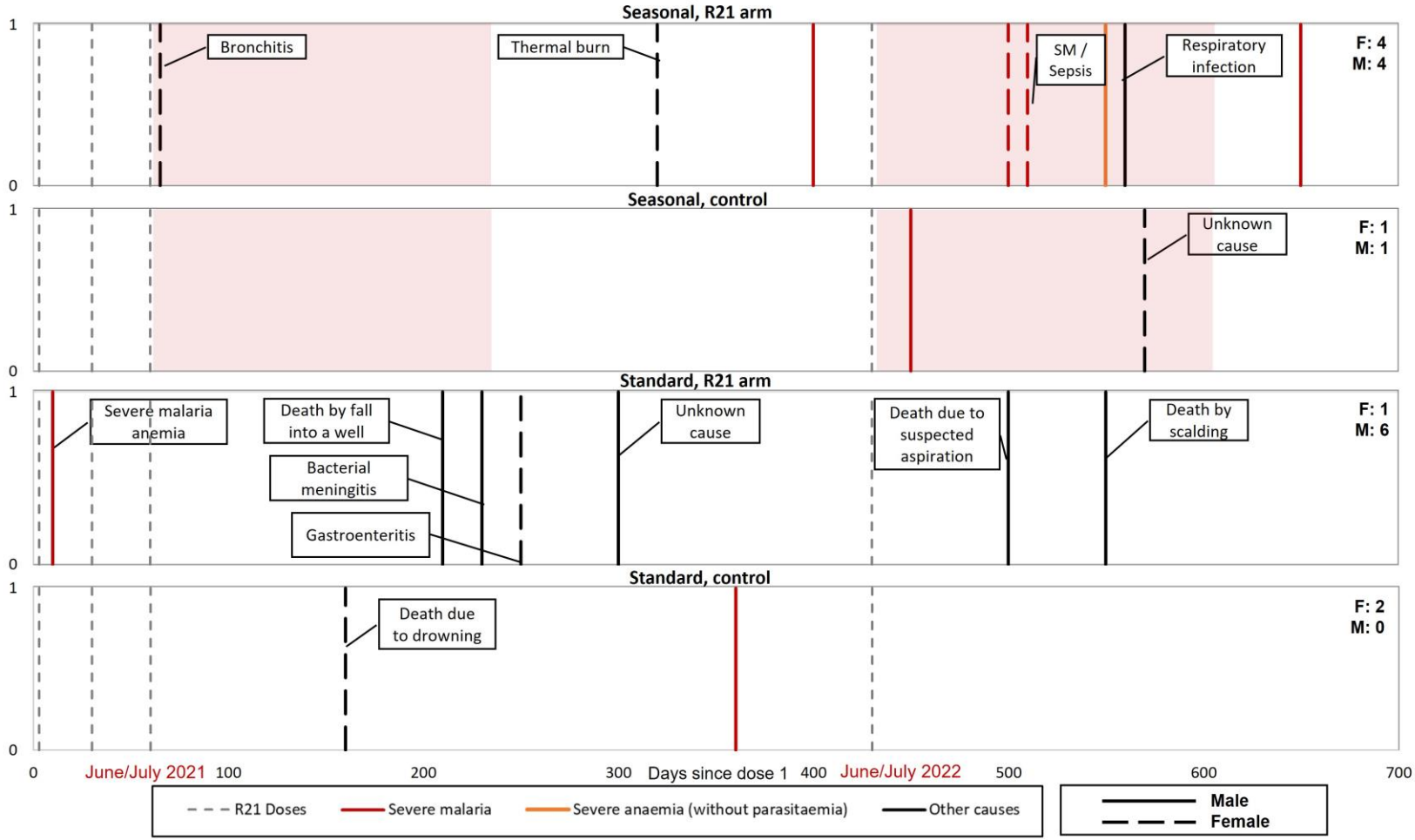
SAEs leading to death are ordered by vaccination strategy (seasonal and standard), study arm (R21/Matrix-M and control), cause of death – severe malaria (highlighted in grey) vs. other causes – and time since last dose at SAE onset (days in ascending order).

Vaccination strategy	Study arm	Cause of death (as reported in the study)	Gender	Age (in months)	Last dose given prior to SAE	Time since last dose at SAE onset (days)	Death associated with vaccine?
Seasonal	R21/Matrix-M	Severe malaria	Female	13	Dose 4	73	No relationship
Seasonal	R21/Matrix-M	Severe malaria or septicaemia	Female	9	Dose 4	85	No relationship
Seasonal	R21/Matrix-M	Severe malaria	Male	5	Dose 4	223	No relationship
Seasonal	R21/Matrix-M	Severe malaria	Male	9	Dose 3	346	No relationship
Seasonal	R21/Matrix-M	Bronchitis	Female	5	Dose 3	8	No relationship
Seasonal	R21/Matrix-M	Severe anaemia[a]	Male	6	Dose 4	126	No relationship
Seasonal	R21/Matrix-M	Respiratory infection	Male	28	Dose 4	126	No relationship
Seasonal	R21/Matrix-M	Superficial dermal burn of the neck and face	Female	6	Dose 3	258	No relationship
Seasonal	Control	Severe malaria	Male	5	Dose 4	36	No relationship
Seasonal	Control	Death due to unknown cause	Female	14	Dose 4	119	No relationship
Standard	R21/Matrix-M	Severe malarial anaemia	Male	12	Dose 1	13	No relationship
Standard	R21/Matrix-M	Suspected aspiration	Male	5	Dose 4	84	No relationship
Standard	R21/Matrix-M	Scalding	Male	28	Dose 4	103	No relationship
Standard	R21/Matrix-M	Fall into a well	Male	6	Dose 3	156	No relationship
Standard	R21/Matrix-M	Bacterial meningitis	Male	9	Dose 3	177	No relationship
Standard	R21/Matrix-M	Acute gastroenteritis with severe dehydration and subsequent hypovolemic shock	Female	6	Dose 3	190	No relationship
Standard	R21/Matrix-M	Unknown cause	Male	9	Dose 3	244	No relationship
Standard	Control	Severe malaria	Female	17	Dose 3	250	No relationship
Standard	Control	Drowning	Female	10	Dose 3	102	No relationship

[a] severe anaemia without parasitaemia

Fig. 12. Timing and cause of deaths from day of first vaccination, by vaccine administration strategy, study arm, cause of death and sex

Malaria transmission season is indicated by pink shaded period.



7.2.3. Adverse events of special interest (AESIs)

As per the trial protocol, AESIs are being collected for the duration of the Phase 3 trial and are reported as SAEs. AESIs reported for the Phase 3 trial include febrile convulsions, meningitis, and cerebral malaria.

Febrile convulsions

The frequency of febrile convulsions was higher in the R21/Matrix-M arm than in the control arm. Overall, there were 14 cases of febrile convulsions: 11 (0.3%) of these occurred in the R21/Matrix-M arm, with 5 assessed as probably or possibly related to vaccination (reported within 3 days of vaccination). There were 3 (0.2%) cases of febrile convulsions in the control arm, with one assessed as definitely related (reported within 3 days of vaccination) and one not related. No childhood immunization vaccines had been administered within 2 weeks of study vaccine for these participants with febrile convulsions. Based on the Phase 3 data, the attributable risk of febrile convulsions is 1 per 2800 R21/Matrix-M doses administered.

Meningitis

Two cases of meningitis were reported in the R21/Matrix-M arm and none in the rabies vaccine arm. Both cases of meningitis were assessed as not related to the study vaccine.

Cerebral malaria

One cerebral malaria case was reported in each treatment arm, and both were assessed as not related to the study vaccines.

7.2.4. Populations of special interest

As described in section 8.2, a trial is currently ongoing in HIV-positive Ugandan children to assess safety and immunogenicity.

7.3. Safety review by GACVS

A review of the safety data was performed by the R21/Matrix-M Safety Working Group on 20 June 2023, who shared their findings with GACVS. The documents provided as part of the R21/Matrix-M Safety Working Group review included:

- WHO Prequalification Dossier (Modules 1-5) in September 2022 (including an update submitted in February 2023)
- Data from the Phase 3 trial provided by the developer in May 2023
- Reports of the Data Safety and Monitoring Board (DSMB) up to March 2023
- Council for International Organization of Medical Sciences (CIOMS) narratives of fatal cases
- Further data and analysis provided by the developers in response to specific questions from the R21/Matrix-M Safety Working Group and GACVS

The R21/Matrix-M Safety Working Group and GACVS reviewed additional data analysis by the vaccine developers to address questions raised regarding potential confounders that may help explain the imbalance in deaths between the R21/Matrix-M and the control arms. Specifically, the Working Group questioned whether differences were observed at randomization, by study arms, in the coverage of SMC or ITNs, or in the nutritional status of participants. They also questioned whether mortality rates among children who participated in the Phase 3 trial were lower than expected mortality rates for the study sites.

GACVS reviewed these findings and available safety data on 30 June 2023, and concluded the following:

- GACVS endorsed the summary reports and conclusions from the meeting of the R21/Matrix-M Safety Working Group and agreed there were no major safety concerns that would warrant a delay in recommendation of the R21/Matrix-M vaccine for public health use.
- GACVS agrees with the questions raised by the R21/Matrix-M Safety Working Group regarding the imbalance of deaths between the two study arms, with a non-statistically significant higher number of deaths in the R21/Matrix-M arm than in the control arm, recognizing the limited study power for this outcome. Furthermore, the imbalance in deaths (excluding deaths caused by injury) by study arm, in addition to being statistically non-significant, showed no clustering of deaths around timing of vaccination or by dose, and there was no pattern or consistency in the causes of death.
- GACVS noted the reactogenicity of this vaccine, which includes a higher number and clustering of febrile convulsions within 3 days after vaccination among children in the R21/Matrix-M arm: 5 (0.15%) compared to 1 (0.062%) in the control group, noting 2:1 randomization.
- GACVS noted that the attributable risk for febrile convulsions for R21/Matrix-M was 1/2800 doses (calculation from the R21/Matrix-M Safety Working Group), also noting that the attributable risk for febrile convulsions with RTS,S/AS01 is 2.5/1000, and for measles-containing vaccine is 1/2000–3000. GACVS requested additional information, such as specifics about fever gradients, to understand this further. The R21/Matrix-M Safety Working Group also noted that the manufacturer is conducting a small co-administration study with measles-rubella vaccine, but the sample size is limited and therefore will provide limited data on safety. Febrile convulsions have been included as an important identified risk associated with R21/Matrix-M vaccination in the risk management plan.
- GACVS noted the limited number of young children who have received the Matrix-M adjuvant to date, compared to adults, although no specific issues or concerns (other than the previously noted reactogenicity) have been identified.
- GACVS recommended close monitoring of AESIs, including deaths, seizures, febrile convulsions within 7 days, and severe fever (which can lead to febrile convulsions), especially if the vaccine is co-administered with other vaccines, and attention to conducting timely causality assessment and analysis, including the analysis of gender difference and nutritional status in fatal outcomes. GACVS will further review the need to recommend more specific post-marketing surveillance or studies (e.g. cohort event monitoring or other active surveillance) as appropriate once additional data are presented to GACVS, including the safety data related to the co-administration of other vaccines.
- GACVS recommended that rebound malaria be assessed during the ongoing clinical trial in alignment with recommendations from the WHO Technical consultation on the malaria rebound phenomenon, and noted that a WHO recommendation for vaccine use does not need to wait for such an assessment.
- As with all new vaccines with limited experience, GACVS recommends overall adequate pharmacovigilance for post-introduction safety monitoring of the new R21/Matrix-M vaccine should WHO issue a policy recommendation approving its use.

7.4. Overall assessment of R21/Matrix-M safety

- No major safety concerns were noted that would warrant a delay in recommendation of R21/Matrix-M for public health use.
- Overall the frequency of SAEs was balanced among children randomized to receive the R21/Matrix-M vaccine and those who received the control (rabies) vaccine.
- There was a higher number and clustering of febrile convulsions within 3 days after vaccination among children in the R21/Matrix-M arm (5 [0.15%] versus 1 [0.062%] in the control group, noting 2:1 randomization). A post-hoc analysis of the attributable risk of febrile convulsions within 0–3 days of vaccination compared to within 4–27 days of vaccination showed that the risk difference for the R21/Matrix-M arm is 0.000 36 (95% CI: 0.000 008 to 0.000 71, *P* = 0.004) and the risk difference for the control is 0.000 16 (95% CI: –0.000 15 to 0.000 47, *P* = 0.28). The risk difference of 0.000 36 translates to an attributable risk of 1/2800 doses administered. This shows evidence of clustering in the R21/Matrix-M arm (*P* = 0.004) but not in the control arm (*P* = 0.28). This is comparable to the attributable risk for febrile convulsions with RTS,S/AS01, which was 2.5/1000 doses, and for measles-containing vaccine, which was 1/2000–3000 doses. GACVS noted the limited number of young children who have received Matrix-M in other vaccines to date compared with adults, although no specific issues or concerns (other than the previously noted reactogenicity) have been identified.
- An imbalance in deaths was noted; excluding trauma or accidents, and noting 2:1 randomization, there were 12 deaths (0.4%) in the R21/Matrix-M arm and 3 (0.2%) in the control arm. However, the overall numbers were small, the imbalance was not statistically significant, there was no pattern among deaths in relation to timing of vaccination, and there were no observed patterns or consistency among causes of death.
- Meningitis and cerebral malaria were uncommon, and no imbalance was noted between the R21/Matrix-M and control arms.
- GACVS recommended post-introduction safety monitoring for AESIs, including deaths, seizures, febrile convulsions within 7 days, and severe fever (which can lead to febrile convulsions), especially in the context of co-administration with other vaccines.
- The need for additional areas of post-marketing surveillance or studies will be considered once additional data are presented to GACVS, including the safety data related to the co-administration of other vaccines.
- Rebound malaria should be assessed during the ongoing clinical trial in alignment with recommendations from the WHO Technical consultation on malaria rebound phenomenon, and noted that a WHO recommendation for vaccine use does not need to wait for such an assessment.
- As with all new vaccines, GACVS recommends overall adequate pharmacovigilance for post-introduction safety monitoring of the new R21/Matrix-M vaccine should WHO issue a policy recommendation approving its use.

8. Other ongoing R21/Matrix-M studies

8.1. Single-vial presentation and co-administration study

In a Phase 1b trial (VAC088 – NCT05155579), 120 Malian children aged 5–36 months were immunized with a new single-vial presentation of R21/Matrix-M. Groups were stratified by age and randomized to receive the single-vial presentation (*n* = 60) or the original two-vial presentation (*n* = 60). Three doses were delivered 1 month apart (at months 0, 1 and 2). These study arms are listed as groups 3a-b in Table 25. As of August 2023, 117 participants in these study groups have received dose 4 at 12 months following the primary series and will be followed for up to 12 months post dose 4.

A comparison of the single-vial presentation with the two-presentation is also being assessed as dose 4 in VAC078 at standard sites. Approximately 1500 children receiving dose 4 of R21/Matrix-M 12 months after dose 3 were randomized to receive either the single-vial or two-vial formulation of the vaccine and data will be available in Q3 2023.

In addition, a fourth group (*n* = 150) has been enrolled to assess the safety and immunogenicity of co-administration of R21/Matrix-M administered as a third dose at approximately 9 months of age with yellow fever and measles-rubella vaccines. Vaccinations (for groups 4a-c listed in Table 25) began in early 2023; all participants recruited have reached 6 months follow-up in the trial and will be followed up for 12 months post dose 3 of R21/Matrix-M.

This study will also assess the co-administration of R21/Matrix-M with pentavalent (diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b), rotavirus, pneumococcal, and oral polio vaccines (OPV) at 6, 10 and 14 weeks of age (*n* = 30); children will also receive inactivated polio vaccine (IPV) 2 weeks following dose 3 of R21/Matrix-M. Vaccinations (for groups 5a-b listed in Table 25) began in June 2023 and will be followed up for 12 months post dose 3 of R21/Matrix-M.

Table 25. VAC088 dosing regimen

Study arm	**Intervention**		
Safety and immunogenicity of 2-vial vs. single-vial formulation			
Dosing schedule	**Month 0[a]**	**Month 1**	**Month 2**
1a, 2a, 3a[b] **(*n* = 60)** **age 5–36 months at time of first vaccination**	5 µg R21/50 µg Matrix-M (2-vial formulation)	5 µg R21/50 µg Matrix-M (2-vial formulation)	5 µg R21/50 µg Matrix-M (2-vial formulation)
1b, 2b, 3b[b] **(*n* = 60)** **age 5–36 months at time of first vaccination**	5 µg R21/50 µg Matrix-M (single-vial formulation)	5 µg R21/50 µg Matrix-M (single-vial formulation)	5 µg R21/50 µg Matrix-M (single-vial formulation)
Safety and immunogenicity of co-administration of R21/Matrix-M with other childhood vaccines			
Dosing schedule	**Month 0[a]**	**Month 1**	**Month 2**
Group 4a **(*n* = 150)** **age 6–7 months at time of randomization**	5 µg R21/50 µg Matrix-M (single-vial)	5 µg R21/50 µg Matrix-M (single-vial)	5 µg R21/50 µg Matrix-M (single-vial) + Measles-rubella Yellow fever
Group 4b (active comparator) **(*n* = 150)** **age 6–7 months at time of**			Measles-rubella Yellow fever

Study arm	Intervention		
randomization			
Group 4c (*n* = 50) age 6–7 months at time of randomization	5 µg R21/50 µg Matrix-M (single-vial)	5 µg R21/50 µg Matrix-M (single-vial)	5 µg R21/50 µg Matrix-M (single-vial)
Dosing schedule	**6 weeks**	**10 weeks**	**14 weeks** [c]
Group 5a (*n* = 30) age 6 weeks at time of randomization	5 µg R21/50 µg Matrix-M (single-vial) + Pentavalent Rotavirus Pneumococcal Oral polio vaccine	5 µg R21/50 µg Matrix-M (single-vial) + Pentavalent Rotavirus Pneumococcal Oral polio vaccine	5 µg R21/50 µg Matrix-M (single-vial) + Pentavalent Rotavirus Pneumococcal Oral polio vaccine
Group 5b (active comparator) (*n* = 30) age 6 weeks at time of randomization	Pentavalent Rotavirus Pneumococcal Oral polio vaccine	Pentavalent Rotavirus Pneumococcal Oral polio vaccine	Pentavalent Rotavirus Pneumococcal Oral polio vaccine
Safety and immunogenicity of delayed dose 3 of R21/Matrix-M			
Dosing schedule	**Month 0**	**Month 1**	**Month 6**
Group 6a (*n* = 30) age 5—36 months at time of first vaccination	5 µg R21/50 µg Matrix-M (single-vial)	5 µg R21/50 µg Matrix-M (single-vial)	5 µg R21/50 µg Matrix-M (single-vial) (delayed dose 3)
Dosing schedule	**Month 0**	**Month 1**	**Month 12**
Group 6b (*n* = 30) age 5—36 months at time of first vaccination	5 µg R21/50 µg Matrix-M (single-vial)	5 µg R21/50 µg Matrix-M (single-vial)	5 µg R21/50 µg Matrix-M (single-vial) (delayed dose 3)

[a] First vaccine doses were administered at 7 months of age

[b] Group 1a/1b is ages 5—11 months (*n* = 20), Group 2a/2b is ages 12–23 months (*n* = 20), Group 3a/3b is ages 24—36 months (*n* = 20)

[c] IPV will be administered 2 weeks following dose 3; this is not a co-administration with R21/Matrix-M vaccine

8.2. Safety and immunogenicity of R21/Matrix-M in African children living with HIV

In a Phase 1b trial (VAC092 – NCT05385510) 100 HIV-positive (WHO HIV stage 1 or 2 disease) Ugandan children aged 5—36 months have been enrolled to receive R21/Matrix-M vaccine to assess safety and immunogenicity. The dosing regimen is shown in Table 26. Immunizations with R21/Matrix-M began in mid-January 2023. Initial safety and immunogenicity data should be available in 2023.

Table 26. VAC092 dosing regimen

Month	0	1	2	14 (boost)
Group 1 (HIV+) (*n* = 100)	5 µg R21/50 µg Matrix-M	5 µg R21/50 µg Matrix-M	5 µg R21/50 µg Matrix-M	5 µg R21/50 µg Matrix-M
Group 2 (HIV–) (*n* = 20)	5 µg R21/50 µg Matrix-M	5 µg R21/50 µg Matrix-M	5 µg R21/50 µg Matrix-M	5 µg R21/50 µg Matrix-M

9. Programmatic considerations

The 2021 malaria vaccine recommendation was based on the high, equitable vaccine coverage achieved during the pilot introductions of RTS,S/AS01. This section presents programmatic considerations specific to R21/Matrix-M as well as global malaria vaccine evidence assumed to be applicable if R21/Matrix-M is included under the current WHO recommendation for malaria vaccines (section 3.3.1), including with similar target populations, delivery strategies and schedules:

The following programmatic considerations are discussed below:

- vaccine schedule
- vaccine formulation and presentation
- feasibility
- acceptability
- economic and financial attributes
- equity
- vaccine co-administration
- evaluation and management of malaria rebound within the public health system.

9.1. Vaccine schedule

Current WHO guidance *(1) (2)* recommend the following delivery strategies and schedules for the malaria vaccine:

- An **age-based schedule of four doses** starting from 5 months of age in areas of moderate to high malaria transmission with year-round delivery. There should be a minimum interval of 4 weeks between doses. The vaccine should be administered in a 3-dose primary schedule, with dose 4 provided approximately 12–18 months after the third dose to prolong the duration of protection.
- An **optional schedule of five doses with seasonal delivery of vaccination** from 5 months of age in areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks. This approach maximizes impact by ensuring that the period of highest vaccine efficacy (just after vaccination) coincides with the period of highest malaria transmission.
- WHO's recommendation allows for flexibility in the dosing schedule in order to optimize uptake. There is no maximum child age recommended by WHO for dose 1, however the age of clinical malaria illness and the development of acquired immunity should be considered in determining at what age the vaccine is likely to be most effective and cost-effective. Similarly, there is no maximum age for dose 4 (a child may receive at any age). In practice, immunization programmes may choose to offer late vaccination until 5 years of age.

The R21/Matrix-M Phase 3 trial enrolled children at 5—36 months of age at time of first vaccination. The dosing schedules used during the trial are in general alignment with the current WHO recommendation:

- An **age-based schedule** of four doses ("standard administration") where a child receives doses 1, 2, and 3 at 4-week intervals and a dose 4 is administered 12 months after dose 3.
- A **seasonal schedule** of four doses ("seasonal administration") where a child receives seasonally timed doses 1, 2, and 3 at 4-week intervals just prior to the peak malaria season, and a dose 4 administered 12 months after dose 3 (just prior to the subsequent peak season). A Phase 2b trial

(VAC076) (N=450 equally randomized to three study arms) evaluated a dose 5 administered 12 months after dose 4 (Section 4.2.2), although numbers were small (n ≤ 50).

9.2. Vaccine formulation and presentation

R21/Matrix-M is available in a two-vial presentation, presented in a Combi-pack format containing one vial of R21 antigen at 20 µg/mL and one vial of Matrix-M adjuvant at 200 µg/mL. The storage temperature of the vaccine and adjuvant is 2–8 °C. Mixing prior to administration involves withdrawal of 0.5 mL of antigen from the R21 vial and addition to the Matrix-M vial (containing 0.5 mL adjuvant). A 0.5 mL volume of the mixture is administered to recipients, such that each dose will contain 5 µg of R21 and 50 µg of Matrix-M.

In one arm of an ongoing clinical trial (VAC088, see section 8.1), Serum Institute of India Pvt Ltd (SIIPL) is evaluating a single vial presentation that contains 0.65 mL of formulate drug product, with a composition of 10 µg/mL of R21 and 100 µg/mL of Matrix-M. Children are randomized (60 children per arm) to receive all vaccines doses from a 2-vial vaccine presentation or from a single-vial vaccine presentation. With the single-vial formulation, a 0.5 mL volume of drug product is administered to recipients, with each 0.5 mL dose containing 5 µg of R21 and 50 µg of Matrix-M. This single-vial presentation would not require reconstitution, thus simplifying delivery, reducing the need for ancillary supplies. One of the target presentations for commercialization is expected to have a lower cold chain volume requirement per dose than required for the current WHO-recommended malaria vaccine. In the study results to date, no differences in safety profile were identified among children receiving the single- or two-vial presentations. One month after dose 3, there was no difference in immunogenicity between the two presentations. The study is still ongoing to evaluate the efficacy of the single-vial presentation.

9.3. Feasibility

The Malaria Vaccine Implementation Programme (MVIP) demonstrated high community demand for a malaria vaccine, strong health worker acceptability, and the capacity of countries to effectively deliver the vaccine – despite the novel schedule beginning from 5 or 6 months of age – through the childhood immunization platform. It is expected that the R21/Matrix-M vaccine will similarly be feasible to deliver.

Ministries of health in the pilot countries have been delivering the RTS,S/AS01 malaria vaccine since 2019 through their national immunization programmes through phased introductions. National malaria control programmes facilitated integration of the vaccine into their national strategic plans (alongside other malaria control interventions) and actively participated in introduction planning and implementation activities. Malaria vaccine coverage estimates in the pilot introductions are meeting or exceeding expectations for a new vaccine. As of August 2023, over 5.4 million vaccine doses have been administered across Ghana, Kenya and Malawi, more than 1.8 million children have received at least one dose of the RTS,S/AS01 vaccine, and over 650 000 children have received their fourth and final dose. While there has been variation in performance observed across and within the three countries, according to administrative data, since start of vaccination, all three countries have reached at least 80% of their target populations with dose 1 of RTS,S/AS01 and at least 70% with dose 3 (Table 27 and Fig. 13). Furthermore, the global COVID-19 pandemic, natural disasters and occasional health worker strikes disrupted stocks and/or access to vaccines at various time points in each of the three countries, but uptake in all countries returned to prior levels once the disruption was resolved, demonstrating the resilience of the immunization programmes, the high demand for malaria vaccine from the community, and acceptability by the health workers.

Uptake of dose 4 continues to be lower than doses 1, 2 and 3.[3] A similar trend of lower coverage is observed for other vaccines administered in the second year of a child's life, pointing to general (rather than vaccine-specific) challenges of reaching children at an older age. Overall, coverage of the fourth RTS,S/AS01 dose has increased. Large increases were noted in Ghana after the immunization schedule was changed in early 2023 to administer dose 4 at 18 months of age rather than 24 months of age; dose 4 administration now coincides with administration of the meningococcal A vaccine and dose 2 of the measles-rubella vaccine and falls within the second year of life platform.

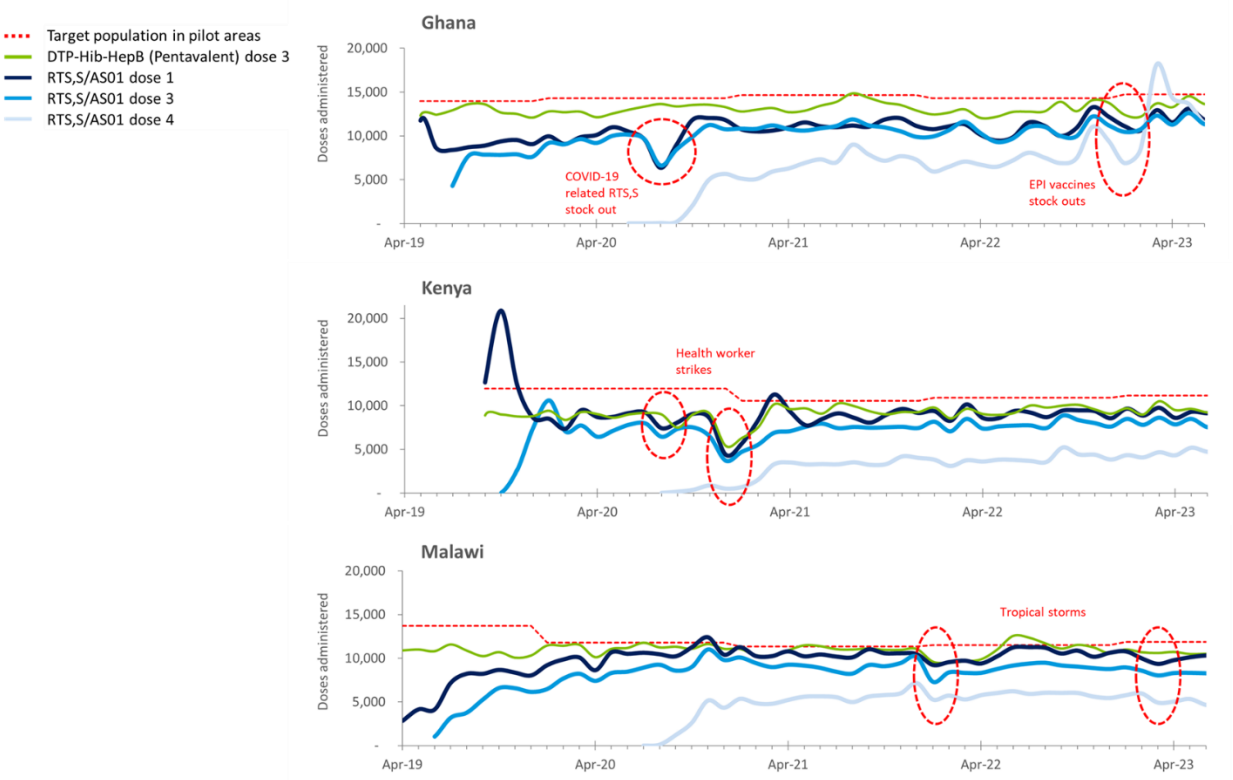
Table 27. Vaccine coverage estimates based on administrative data reports from the pilot countries (estimates for Ghana (G); Kenya (K); Malawi (M))

Vaccine[1]	**2020**			**2021**			**2022**			**H1 2023[2]**		
	G	**K**	**M**	**G**	**K**	**M**	**G**	**K**	**M**	**G**	**K**	**M**
RTS,S/AS01 dose 1	71%	69%	88%	76%	82%	93%	77%	83%	90%	81%	83%	85%
RTS,S/AS01 dose 2	67%	64%	79%	73%	75%	84%	73%	77%	80%	76%	76%	75%
RTS,S/AS01 dose 3	66%	60%	73%	74%	67%	81%	74%	72%	76%	78%	73%	71%
RTS,S/AS01 dose 4	-	-	-	47%	29%	49%	53%	36%	50%	82%	41%	45%
Pentavalent dose 3	92%	72%	95%	92%	87%	97%	91%	87%	95%	90%	86%	90%
Measles-rubella dose 1	85%	73%	90%	86%	86%	94%	88%	88%	87%	72%	89%	87%
Measles-rubella dose 2	-	-	-	78%	52%	77%	79%	53%	67%	66%	60%	64%

Notes: [1] Schedule for RTS,S/AS01 (dose 1, 2, 3, 4) in Ghana (6, 7, 9, 24 months; dose 4 changed to 18 months since early 2023), in Kenya (6, 7, 9, 24 months) and Malawi (5, 6, 7, 22 months); pentavalent (DTP-Hib-HepB containing) vaccine is administered at 14 weeks of age, measles-rubella containing vaccine dose 1 at 9 months, dose 2 at 15-18 months. [2] Preliminary estimates.

[3] Dose 4 coverage trends require careful interpretation: as there is a 15-month time lag between administration of dose 3 and dose 4, the scope of possible improvements in today's dose 4 coverage (when measured with the target population denominator) is confined by the primary series' performance more than a year ago.

Fig. 13. Vaccine implementation in pilot countries: administrative data reports (through June 2023)



A seasonal vaccination delivery strategy with a malaria vaccine has not been implemented outside trial settings, and WHO encourages countries who implement this strategy to document their experience. R21/Matrix-M product characteristics, combined with an expected lower vaccine price (section 9.5) and fewer limits on vaccine supply capacity, may increase feasibility of implementation, including seasonal delivery and the implementation of a five-dose schedule.

There is no experience with R21/Matrix-M malaria vaccine implementation outside of the trial setting; however, the MVIP has demonstrated high uptake of the four-dose age-based strategy even in the period of a global pandemic, and there is no indication that the age-based four-dose R21/Matrix-M vaccine introduction and uptake would differ from that of RTS,S/AS01.

9.4. Acceptability

The MVIP generated evidence on the acceptability of a malaria vaccine through a series of cross-sectional household surveys, post-introduction evaluations, and qualitative health utilization studies. The findings from these evaluations are assumed to be applicable to R21/Matrix-M, which has similar vaccine product characteristics, efficacy (in general terms), and safety profile, as well as its alignment with the WHO recommendations for delivery strategies, target population and schedule.

Survey results were consistent with coverage estimates from the administrative data and suggest acceptability by the target population, caregivers and health workers administering the vaccine.

Other key findings from the household surveys include:[4]

- **Impact on childhood vaccination coverage:** In all countries, there was no impact of RTS,S/AS01

[4] Further details can be found in the RTS,S, Full evidence report *(9)*

introduction on the uptake of other childhood vaccines. Coverage of dose 3 of pentavalent (diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b) vaccine remained high – over 90% – in all three countries. Similarly, coverage of dose 1 of measles-rubella vaccine remained over 85% in all three countries. Administration of the malaria vaccine as part of the immunization programmes has continued despite the challenges and effects of the COVID-19 pandemic. The ability of the national immunization programmes to maintain or improve upon performance, and to quickly recover from COVID-19-related and other disruptions, is a testament to their resilience. It also demonstrates the demand for the vaccine by parents and the acceptance by health workers who provide the vaccine.

- **Use of malaria prevention and control:** In all countries, there was no impact on the use of ITNs among children following the introduction of the malaria vaccine and no impact on health seeking behaviour. ITN use among children aged 5–48 months was over 80% in Malawi, over 60% in Ghana and over 90% in Kenya, with no significant differences between vaccine implementation and control arms or over time. In each country, over 60% sought advice or treatment for fever in the past 2 weeks, and of those who sought treatment, there was no impact on use of malaria diagnostic testing or receiving antimalarials for treatment. Results were comparable between baseline and endline surveys in Ghana, Malawi and Kenya, and between implementation and comparison areas.
- **Impact of RTS,S/AS01 on other child health activities or indices:** Overall, there was no impact on the uptake of vitamin A or anthelminthics (deworming).

Post-introduction evaluation (PIE)

A PIE for the malaria vaccine was conducted in each pilot country to systematically assess the overall impact of malaria vaccine introduction on the existing immunization system (national, subnational, health facility), with a focus on documenting best practices and lessons learned, and developing recommendations for improvement. Based on a variety of data collection efforts and a nonrepresentative sample, the PIE results indicated general acceptance of the malaria vaccine by health workers, reported positive benefit of the malaria vaccine introduction on the overall immunization programme by health workers and national immunization programme respondents, and understanding of the malaria vaccine's partial protection by health workers. Other positive benefits reported by respondents included increase in detection and reporting of adverse events following immunization and in opportunities to screen children for missed or delayed vaccination. Areas identified for improvement included caregiver understanding of the malaria vaccine schedule with emphasis that four doses are needed.

Health utilization study

The health utilization study, a qualitative longitudinal study in the MVIP, evaluated provider perceptions of the RTS,S/AS01 malaria vaccine, primary caregiver perceptions, the impact of RTS,S/AS01 uptake on malaria treatment seeking and other preventive behaviours, and health provider perceptions of acceptability and feasibility of providing RTS,S/AS01 *(49)*. Positive attitudes and trust in the malaria vaccine among primary caregivers increased substantially over time, driven mainly by the perception of the health benefits of the vaccine in their own children and the broader community. While there were early concerns about safety, these were replaced by widespread perception that adverse events following immunization were normal and similar to other vaccines. There was perception from primary caregivers and health workers that the vaccine results in less frequent and less severe malaria (resulting in fewer children reporting to the facilities with malaria). Key concerns among health providers were the operational challenges faced in introducing and delivering the vaccine (increased workloads, and lack of adequate training and supportive supervision), lack of clarity about missed or delayed vaccination, and

lack of community sensitization on key messages.

9.5. Economic and financial attributes

Cost, affordability, and cost-effectiveness (see section 10) are key issues for country decisions whether to introduce a vaccine and how to incorporate the vaccine into national strategies and budgets. In addition to any country-specific estimates and local data, global estimates on the malaria vaccine economic and financial attributes are available for adaptation/application to country contexts. Global estimates should be regularly refined based on emerging data and information available.

9.5.1. Vaccine price

Based on the first supply agreement between GSK and UNICEF, the RTS,S/AS01 malaria vaccine will cost EUR 9.30 per dose for supply during 2023-2025 *(12)*. This price reflects the anticipated cost of manufacturing and GSK's agreement to supply the vaccine in 2023 without a financial return (and a return of no more than five percent in subsequent years). Like with many other vaccines with a relatively high initial price, the price reflects the fact that vaccine production is still scaling up and supply is not yet in a steady state or benefitting from economies of scale.

The manufacturer of R21/Matrix-M, Serum Institute of India Pvt Ltd (SIIPL), has publicly stated that the vaccine can be manufactured at mass scale and modest cost *(46)*. The price for doses procured through UNICEF is not yet known as finalization of the supply agreement is dependent on the outcome of the WHO review. The cost-effectiveness estimates by Imperial College (see section 10) assume a vaccine purchase price of US$ 3 (range US$ 2-4) per dose.

With the transfer of production of RTS,S/AS01 to BBIL and the potential entry of R21/Matrix-M into the market, the average price per dose is expected to decrease over time.

To make the new vaccine more affordable for eligible countries, in December 2022, Gavi approved an exceptional and time-limited co-financing modality for malaria vaccines. Under the revised policy, the lowest income countries contribute US$ 0.20 per dose, while countries in the accelerated transition phase will co-finance an increasing proportion of the price over a period of eight years.

9.5.2. Cost of delivery

Costing analyses conducted to date on RTS,S/AS01 malaria vaccine have estimated the incremental non-vaccine financial costs (actual financial outlays) and economic costs (financial costs plus opportunity cost of existing resources including labor) per dose for vaccine introduction and delivery from a provider perspective (e.g. government). To the extent R21/Matrix-M is expected to have similar delivery strategies, schedule, and target population as RTS,S/AS01, two of the currently available cost of delivery estimates available on RTS,S/AS01 (Table 28 and Table 29) are assumed to be the most applicable to the R21/Matrix-M malaria vaccine:

1. A retrospective cost of delivery study to evaluate the cost of phased subnational introduction and delivery of the RTS,S/AS01 malaria vaccine in each of the pilot countries (Ghana, Kenya and Malawi) using a four-dose age-based schedule (year-round delivery with vaccine administration based on the child's age) *(41)*. The reported estimates were based on target populations and coverage levels from administrative data in the three pilot countries for dose 1 (72, 75, 93%), dose 2 (66, 73, 84%), dose 3 (58, 75, 80%) and dose 4 (46, 57, 54%) after approximately one year of dose 4 administration.

Table 28. Incremental cost of phased subnational introduction and delivery per dose of RTS,S/AS01 malaria vaccine in pilot countries using a four-dose age-based schedule (2020 US$)

Non-vaccine costs (commodities excluded)	Financial cost	Economic cost
Age-based delivery strategy		
Cost of delivery per dose[a]	US$ 1.04–2.46	US$ 1.52–4.62
Cost of delivery per dose, recurring only[b]	US$ 0.29–0.86	US$ 0.59–2.29

[a] Excludes cost of vaccine and immunization supplies as well as the procurement add-on costs. Includes only the non-vaccine costs of vaccine introduction and delivery.

[b] Recurrent costs exclude the initial set-up costs related to RTS,S/AS01 introduction and delivery and are expected to be more representative of the programme costs in the long run.

2. A prospective cost of delivery study to estimate the cost of nationwide introduction and delivery of RTS,S/AS01 seasonally timed doses (with or without mass campaigns) in Mali and Burkina Faso *(40)*. The seven-dose regimen used in the costing study is based on the Phase 3b RTS,S/AS01 seasonal malaria vaccination trial *(25)* in these countries. Three different seasonal delivery strategies were estimated:
    - **Seasonal schedule with mass campaigns:** first three doses are given with a mass campaign just prior to first peak transmission season, and subsequent annual doses (doses 4–7) are given with mass campaigns just prior to peak transmission seasons.
    - **Hybrid schedule with mass campaigns**: first 3 doses are age-based (delivered through childhood immunization visits), and subsequent annual doses are given with mass campaigns just prior to peak transmission seasons.
    - **Hybrid schedule without mass campaigns**: first 3 doses are age-based, and subsequent annual doses are given prior to the peak transmission seasons (without mass campaigns).

The prospective cost of delivery study findings suggest that vaccine delivery using the seasonal schedule with mass campaigns approach is the costliest option and the hybrid schedule without mass campaigns is the least costly option. Across the two countries included in the study, the non-vaccine financial cost per dose delivered ranges across US$ 0.99 and US$ 1.99 (seasonal schedule with mass campaigns), US$ 0.58 and US$ 1.28 (hybrid schedule with mass campaigns), and US$ 0.39 and US$ 0.76 (hybrid schedule without mass campaigns). The economic cost per dose delivered ranges across US$ 1.17 and US$ 2.12 (seasonal schedule with mass campaigns), US$ 0.70 and US$ 1.37 (hybrid schedule with mass campaigns), and US$ 0.48 and US$ 0.82 (hybrid schedule without mass campaigns) (Table 29).

Table 29. Incremental cost of nationwide introduction and delivery per dose of RTS,S/AS01 malaria vaccine (Burkina Faso and Mali) using different seasonal delivery strategies (2021 US$) (40)

Non-vaccine costs (commodities excluded)	Financial cost	Economic cost
Seasonal schedule with mass campaigns	US$ 0.99–1.99	US$ 1.17–2.12
Hybrid schedule with mass campaigns	US$ 0.58–1.28	US$ 0.70–1.37
Hybrid schedule without mass campaigns	US$ 0.39–0.76	US$ 0.48–0.82

Note: the costing study refers to the delivery strategies as “mass campaign” (seasonal schedule), “routine EPI” (hybrid schedule without mass campaigns), and “mixed delivery” (hybrid schedule with mass campaigns); however, they have been updated for alignment with the current WHO recommendations and guidance (see section 3.3.1 for more information on malaria vaccine schedules and delivery approaches).

Taken together, these malaria vaccine cost of delivery estimates suggest a cost range that varies both by country and delivery strategy. This range is indicative of the varied resource requirements for malaria vaccines across countries in sub-Saharan Africa, and the cost of delivery for R21/Matrix-M is expected to be similar.

The resources required for malaria vaccine delivery are comparable to those needed for other new vaccine introductions. For example, the costs per dose for the newly introduced pneumococcal conjugate vaccine or rotavirus vaccine are estimated at US$ 0.84 (range: US$ 0.48–1.38, economic) *(42)*. The cost estimates from the RTS,S/AS01 pilot countries drawn from phased subnational introduction (rather than full national introduction) were comparable to human papillomavirus costs per dose delivered under a pilot implementation setting at US$ 1.74–2.24 (financial) and US$ 2.22–4.29 (economic) *(42)*.

However, direct comparisons of the results across vaccine delivery costing studies should be made with caution, as the methods, delivery strategies and schedules, settings and context can vary widely.

9.6. Equity considerations

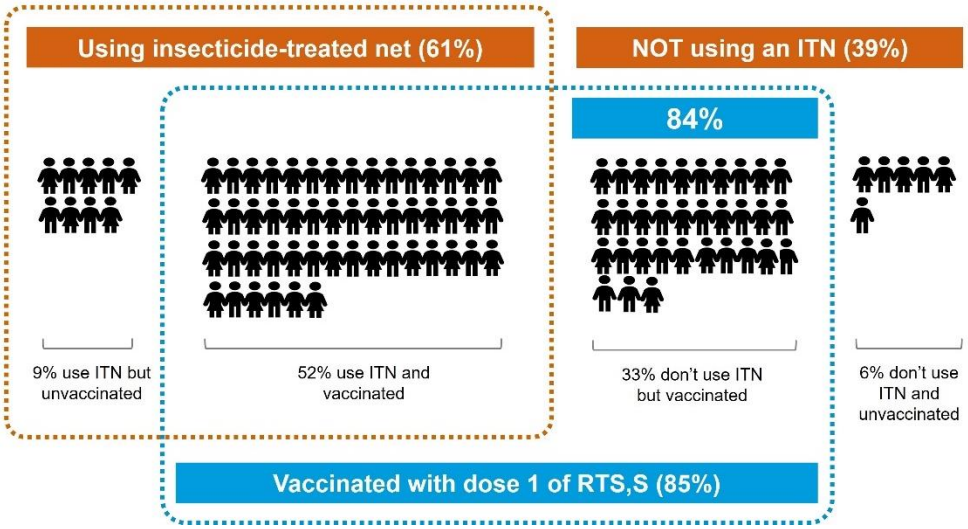
The vast majority of malaria illness and death occurs in Africa and in children under 5 years of age. Malaria disproportionately affects the poor and those living in rural areas. HIV exposure, HIV infection or chronic malnutrition, all of which frequently overlap geographically with areas of malaria endemicity, are additional risk factors for malaria illness or death *(43,44)*. Although progress has been made in improving equity for malaria control interventions, in some countries, access to malaria control measures differ by socioeconomic status and rural/urban settings *(1)*. The R21/Matrix-M malaria vaccine is efficacious in undernourished children and is being tested in children with HIV infection; results are expected in late 2023 or early 2024 (see section 8).

To the extent that R21/Matrix-M has a similar target population, delivery strategy and schedule as current malaria vaccine recommendation, evidence from the endline household surveys conducted in the three pilot countries can be considered applicable. Endline household surveys show that a malaria vaccine was delivered equitably by sex and by socioeconomic status (across rural and urban residences in Kenya and Ghana; higher coverage was observed among rural residences in Malawi compared to urban residences).

Immunization programmes have frequently been shown to reach higher coverage than is achieved by many existing approaches to malaria control; the potential to reach high coverage with a malaria vaccine could help reduce inequities in access to malaria control interventions. Because of the broad reach of the vaccine, and relatively rapid uptake to reach a high proportion of age-eligible children, layering of the malaria vaccine and ITNs has increased access to at least one malaria prevention tool (ITN or malaria vaccine) among vulnerable children. A 2020 analysis of Demographic and Health Survey (DHS) and Malaria Indicator Survey (MIS) data from 20 African countries showed that among the 33 million children who do not use ITNs, 23 million (70%) are reached by childhood immunization programmes. Malaria vaccination for children not using ITNs could avert an estimated 9.7 million clinical malaria cases per year and an additional 10.8 million cases among children already using an ITN *(45)*.

These findings are supported by data from the MVIP household surveys, reflecting the first 30–-36 months of RTS,S/AS01 malaria vaccine introduction. In Ghana, 61% of children reportedly slept under an ITN the night prior to the survey, 85% had received dose 1 of RTS,S/AS01, and 84% of children who did not sleep under an ITN had received dose 1 of the malaria vaccine. The introduction of the malaria vaccine expanded the percentage of children accessing at least one malaria prevention measure – an ITN or the malaria vaccine – with coverage increasing from 61% to 94%, while 52% of children benefitted from both an ITN and the vaccine (see Fig. 14).

Fig. 14. Adding malaria vaccine to current interventions increases access and reduces gaps in malaria prevention tools



Ghana Endline Feasibility Household Survey, children 12–23 months (conducted 30–36 months after introduction). Household survey data from KHRC Ghana

9.7. Co-administration with other vaccines

As described in section 8.1, an ongoing study in Mali (VAC088) will assess the safety and immunogenicity of co-administration of R21/Matrix-M dose 3 with yellow fever and measles-rubella vaccine at 9 months of age (*n* = 150). This study will also assess the co-administration of R21/Matrix-M with pentavalent (diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b), rotavirus, pneumococcal, and oral polio vaccines at 6, 10 and 14 weeks of age (*n* = 30); children will receive inactivated polio vaccine 2 weeks following dose 3 of R21/Matrix-M. This study is expected to be completed in August 2024.

Data on the co-administration of R21/Matrix-M with other childhood vaccines are currently limited, which could lead to missed opportunities for vaccination and lower vaccine coverage. No co-administration studies are currently planned with R21/Matrix-M and meningococcus A, typhoid conjugate, cholera, Japanese encephalitis, tick-borne encephalitis, rabies, mumps, influenza or varicella vaccines.

9.8. Evaluation and management of malaria rebound within the public health system

As discussed in section 3.3.2, although the available evidence suggests that rebound[5] is a real, measurable phenomenon, it has been shown to occur infrequently and, when present, does not appear to have a measurable cumulative negative impact. Deployment of highly effective interventions should not be delayed to measure rebound, however, it is useful to assess rebound over longer periods of follow-up. In the context of vaccines with gradually waning protection, rebound could be assessed through continued follow-up of clinical trial participants following a policy recommendation.

[5] Defined as a period of increased malaria risk after time-limited protection from malaria (i.e. after chemoprevention, vaccination or vector control), relative to individuals of the same age from the same population who did not receive the intervention

If evidence of rebound is identified, programmatic measures should be taken to ameliorate risk. Such measures will need to be tailored to the local programmatic context, and could include enhanced awareness of new vulnerabilities arising from a rebound effect, the delivery of additional annual (or later) doses, improved access to and delivery of prompt testing and treatment of fever, increased or targeted vector control measures, improved coverage with other malaria control interventions (e.g. ITNs to those at risk), and heightening surveillance in groups at greatest risk.

9.9. Regulatory review

As of July 2023, R21/Matrix-M has been approved by several national regulatory authorities. In September 2022, the Drugs Controller General of India granted SIIPL a license for export of R21/Matrix-M to the United Kingdom. Countries that have granted authorization for in-country use of R21/Matrix-M include the Ghana Food and Drugs Authority (FDA) *(7)* (March 2023), the Nigerian National Agency for Food and Drug Administration and Control (NAFDAC) *(8)* (April 2023) and the Agence Nationale de la Règulation Pharmaceutique (ANRP) in Burkina Faso (July 2023).

R21/Matrix-M is produced by SIIPL. The adjuvant Matrix-M is produced and provided to SIIPL by Novavax. SIIPL has stated publicly that it has established capacity to manufacture more than 200 million doses annually *(46)*. Notably, if the vaccine is recommended and prequalified by WHO under the current recommendation, it will be supported by Gavi, the Vaccine Alliance, so that countries could ultimately receive either RTS,S/AS01 or R21/Matrix-M with Gavi support, via UNICEF procurement.

As outlined in section 3.3.3, the availability of a second malaria vaccine would improve the health of the malaria vaccine market by increasing supply availability and supply security, and fostering a competitive environment with expected vaccine price reductions and product innovations. Current projections suggest that, if R21/Matrix-M was recommended and prequalified by WHO by the end of 2023, the combined availability of RTS,S/AS01 and R21/Matrix-M would greatly improve the supply situation and could result in sufficient supply to meet demand in the first half of 2024.

10. Modelled public health impact and cost-effectiveness estimates of R21/Matrix-M

10.1. Overview and prior evidence on malaria vaccines

The 2019 Framework for Policy Decision on RTS,S/AS01 *(50)* recommended that cost-effectiveness estimates be regularly refined as data become available in order to remain valid and accurate. Cost-effectiveness analyses are informative to WHO, partners and countries. Cost-effectiveness is highly context-specific and estimates could differ considerably depending on the country-specific inputs. Nonetheless, cost-effectiveness can be used as one factor to guide decision-making by countries, which should assess affordability and/or cost-effectiveness using locally relevant data. Furthermore, the results of cost-effectiveness analyses are not fixed, and inputs and assumptions may evolve. Notably, costs of new interventions, including vaccines, are expected to reduce over time, which can markedly impact cost-effectiveness estimates.

Mathematical models were first developed in 2015 examining the addition of the RTS,S/AS01 malaria vaccine to existing malaria control interventions and treatment, following the conclusion of the Phase 3 trial. These models were developed by multiple groups and used harmonized inputs drawing on data from the RTS,S/AS01 Phase 3 clinical trials and malaria disease burden studies. All models predicted a substantial additional public health impact and high cost-effectiveness of RTS,S/AS01 across a wide range of transmission settings (results are summarized in Penny et al.) *(23)*. Subsequently, these modelling analyses were updated in 2021 by two of the groups (Swiss TPH and Imperial College) to estimate impact and cost-effectiveness using data from the RTS,S/AS01 Phase 3 clinical trials, as well as additional evidence from the Malaria Vaccine Implementation Programme (MVIP). The models included previously modelled and validated disease and vaccine parameters (from the 2015 analysis), with assumptions and cost of delivery estimates from the MVIP.

Consistent with previous estimates from 2015, the updated Imperial and Swiss TPH models predict a positive health impact, suggesting that all RTS,S/AS01 delivery strategies (age-based, seasonal and hybrid) are cost-effective at an assumed vaccine price of US$ 5 per dose (range: US$ 2–10) in settings which broadly equate to areas of moderate to high malaria transmission ($PfPR_{2–10}$ 10–50%) over a 15-year time horizon (Table 30) *(48)*. Both models estimate that three doses of RTS,S/AS01, delivered on an age-based schedule, can avert over 400 malaria deaths (417 [205–540] estimated by the Swiss TPH model and 448 [315–534] estimated by the Imperial model) and over 100 000 clinical malaria cases (108 824 [46 978–121 182] in the Swiss TPH model and 101 413 [57 839–145 301] in the Imperial model) per 100 000 vaccinated children. At an assumed cost of US$ 5 per vaccine dose, incremental cost-effectiveness ratios (ICERs) were estimated to be US$ 59 and US$ 28 per clinical case averted by the Swiss TPH and Imperial models, respectively.

The cost-effectiveness of RTS,S/AS01 seasonal vaccination strategies was estimated using data from the Phase 3b clinical trial assessing RTS,S/AS01 seasonal vaccination when combined with seasonal malaria chemoprevention (SMC); the Imperial College transmission model was used to estimate the population level impact of a seasonally targeted RTS,S/AS01 schedule. Overall, the model estimated that incremental cost-effectiveness ratios were only marginally lower for the seasonal vaccination strategies (i.e. more cost-effective) compared to age-based delivery schedules, despite the higher number of overall doses delivered. At an assumed vaccine price of US$ 5 per dose (range 2—10) in seasonal settings with SMC, the Imperial model estimated incremental cost-effectiveness ratios to be US$ 93 (47—169) per disability-adjusted life year (DALY) averted for seasonal strategy, US$ 112 (58—204) for age-based strategy, and

US$ 157 (81—285) for hybrid strategy. The cost per clinical case averted was US$ 27 (14—50), US$ 34 (18—62), and US$ 51 (26—92), respectively.

Further details on RTS,S/AS01 cost-effectiveness modelling are described in the 2021 RTS,S/AS01 full evidence report *(9)* and its Annex 9 *(48)*.

Table 30. Public health impact of RTS,S/AS01 and incremental cost-effectiveness ratio (ICER) for four-dose schedule over a 15-year time horizon in regions with 10–50% $PfPR_{2–10}$ (2021 updated estimates)

RTS,S/AS01 malaria vaccine	**Median estimate (range)**	
*For children who receive at least 3 doses	**Swiss TPH model**	**Imperial College model**
Percentage of malaria deaths averted in children younger than 5 years of age	9.2% (9.7–10.1)	18.6% (13.6–20.8)
Percentage of malaria cases averted in children younger than 5 years of age	13.2% (11.2–14.6)	20.9% (20.1–23.6)
Malaria deaths averted per 100 000 fully vaccinated children[a]	417 (205–540)	448 (315–534)
Malaria clinical cases averted per 100 000 fully vaccinated children*	108 824 (46 978–121 182)	101 413 (57 839–145 301)
ICER (US$) per DALY averted		
$2 per dose	$50 (42–120)	$52 (43-78)
$5 per dose	$97 (81–230)	$103 (86–151)
$10 per dose	$175 (146–412)	$187 (157–274)
ICER (US$) per clinical case averted		
$2 per dose	$31 (25–46)	$14 (10–26)
$5 per dose	$59 (48–89)	$28 (19–50)
$10 per dose	$105 (87–160)	$52 (35–91)

[a] The Swiss TPH model deaths include those directly attributable to the disease and those caused by comorbidities. The absolute number of deaths (and how RTS,S/AS01 impacts them) can differ between models, which can result in similar deaths averted per 100 000, despite there being a different percentage of deaths averted.

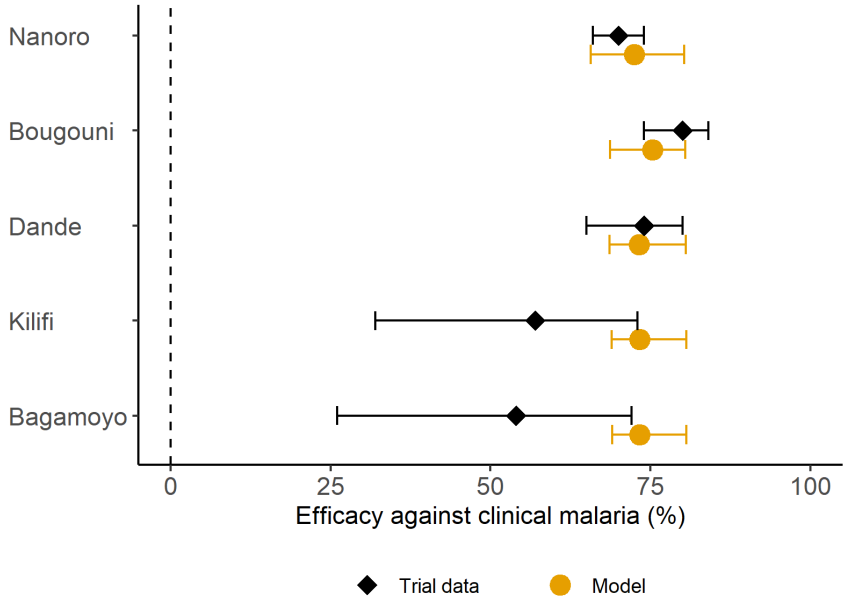
10.2. R21/Matrix-M model inputs and data sources

Mathematical modelling of the public health impact and cost-effectiveness of R21/Matrix-M has been performed by Imperial College for 1) perennial settings using an age-based ("standard") delivery strategy, and 2) seasonal settings using age-based ("standard") delivery, seasonal delivery or a hybrid of the two strategies. The draft manuscript is available in Annex 6. Model inputs and assumptions are summarized in Table 31. Estimated malaria cases, malaria deaths and DALYs averted are based on a modelled relationship between anti-CSP antibody titres and vaccine efficacy against clinical malaria, using data measured during 3 years of follow-up from the R21/Matrix-M Phase 2b study in Burkina Faso that evaluated seasonal vaccine administration in a highly seasonal transmission setting in children ages 5–17 months. The model was validated by comparing the model-predicted to the observed vaccine efficacy in the R21/Matrix-M Phase 3 trial sites over 18 months follow-up after dose 3 in a seasonal regimen (Nanoro and Bougini) and over 12 months follow-up after dose 3 in a standard regimen (Dandé, Kilifi, and Bagamoyo) (Fig. 15). In all sites, the model-predicted credible intervals overlapped with the observed confidence intervals in the trial. Modelled estimates were found to be more consistent with the vaccine efficacy observed in the Phase 3 study sites with seasonal and higher transmission settings (Nanoro, Bougouni, and Dandé), than the standard administration sites with low to moderate perennial transmission settings (Bagamoyo and Kilifi), where median model estimates of vaccine efficacy were higher than the 95% CI of the observed vaccine efficacy, indicating more uncertainty.

Subsequently, the validated model was used to estimate the malaria cases, malaria deaths and DALYs averted, and cost-effectiveness of R21/Matrix-M introduction across a range of transmission settings over a 15-year time horizon.

Fig. 15. Model validation against Phase 3 R21/Matrix-M trial data

Median model estimates and 95% credible intervals for the fitted model (yellow points and error bars) are shown in relation to trial estimates of vaccine efficacy against clinical malaria with 95% confidence intervals (black diamonds and error bars). In Nanoro and Bougouni, participants received the seasonal regimen and had a follow-up of 18 months. In Dandé, Kilifi and Bagamoyo, participants received the standard regimen and had a follow-up of 12 months.



Where applicable, ranges shown in parentheses in Table 31 were explored in sensitivity analysis. Fully vaccinated children were defined as those who received 3 doses of a primary series via age-based, hybrid or seasonal delivery strategies (with optional dose 5 for hybrid or seasonal delivery strategies).

Table 31. R21/Matrix-M public health impact and cost-effectiveness model assumptions

	Model assumptions	Data source
Demographics	2020 sub-Saharan Africa age structure	United Nations World Population Prospects
Transmission intensity	Parasite prevalence in 2–10 year old children between 1% and 65%, representing current levels in Africa	Malaria Atlas Project
Transmission settings	Perennial (non-seasonal) and seasonal	Climate Hazards Group InfraRed Precipitation with Station data (CHIRPS)
Case management	Effective coverage (i.e treatment with parasitological cure) for clinical malaria is 45%	Penny et al., *(23)*
Other interventions	Predictions assume that current interventions in place at the start of vaccination remain at static levels	Penny et al., *(23)*
Vaccine efficacy	Model estimates of R21 efficacy against infection profiles based on fitting to phase 2 trial data	Datoo et al., *(13) (14)*
Vaccine schedule	4 or 5 doses via age-based, seasonal, or hybrid delivery strategies	
Fully vaccinated child	Defined as a child who has received the first 3 doses of the primary series	
Vaccine coverage	Doses 1, 2, and 3: 80% Doses 4, 5: 64%	MVIP
Cost of R21/Matrix-M vaccination	Consumables (per dose): US$ 0.69, US$ 0.79, US$ 1.24 Delivery (per dose): US$ 1.33 (age-base), US$ 3.35 (seasonal), US$ 2.09 (hybrid)	Baral et al., *(41)* Diawara et al., *(40)*
Vaccine price	US$ 2.00, US$ 3.00 or US$ 4.00 per dose (excluding cost of consumables and delivery)	R21/Matrix-M Phase 3 trial; American Society of Tropical Medicine and Hygiene (ASTMH) Annual Meeting – 2022
Cost of malaria case management	US$ 6.00 (child) and US$ 9.60 (adult) per clinical case treated and US$ 12.84 (child) and US$ 16.44 (adult) per severe case treated.	WHO Choosing Interventions that are Cost-Effective (WHO-CHOICE); The Global Fund Pooled Procurement Mechanism Reference Pricing

10.3. Results

The impact and cost-effectiveness estimates from the introduction of R21/Matrix-M vaccine into childhood immunization schedules over a 15-year time horizon are summarized across vaccine delivery strategies (age-based, seasonal or hybrid), transmission settings (perennial or seasonal) and a range of transmission intensities (Table 32, Fig. 16 and Fig. 17).

In settings representative of *P. falciparum* transmission of 20% $PfPR_{2–10}$ (approximately corresponding to the mean 2019 value across areas in sub-Saharan Africa with >1% $PfPR_{2–10}$), the median estimated incremental cost-effectiveness ratios are US$ 5—13 per case averted and US$ 23—69 per DALY averted.

The model estimates that introduction of a four-dose malaria vaccine schedule using an age-based, seasonal or hybrid strategy could avert between 32 324 and 398 726 clinical malaria cases and between 216 and 733 malaria deaths for every 100 000 fully vaccinated children in settings with 3% $PfPR_{2–10}$ and 65% $PfPR_{2–10}$ respectively. Assuming an R21/Matrix-M vaccine price of US$ 3 per dose, the model estimates a median incremental cost effectiveness ratio of US$ 3–69 per clinical case averted and US$ 27–202 per DALY averted in the same settings.

In seasonal settings, the inclusion of a fifth dose (delivered annually, 12 months after dose 4) is estimated to avert more cases and deaths but is estimated to be slightly less cost-effective than a four-dose regimen because of the increased cost of the extra dose.

Table 32. Public health impact and cost-effectiveness of R21/Matrix-M as a four-dose or five-dose schedule over a 15-year time horizon

Point estimates represent median values at 20% $PfPR_{2–10}$ (median 2019 value across areas in sub-Saharan Africa with >1% $PfPR_{2–10}$) and intervals represent median values at 3% and 65% $PfPR_{2–10}$

Setting	**Perennial**		**Seasonal**					
Delivery strategy	Age-based		Age-based		Seasonal		Hybrid	
Regimen	4-dose	5-dose	4-dose	5-dose	4-dose	5-dose	4-dose	5-dose
Proportion of clinical malaria cases averted in children younger than 5 years	41.6% [46.0, 30.6]	42.2% [47.1, 31.3]	41.4% [47.2, 29.3]	42.1% [48.0, 29.9]	43.4% [49.8, 29.4]	43.8% [51.0, 29.8]	41.8% [47.4, 29.4]	42.3% [48.2, 30.1]
Proportion of malaria deaths averted in children younger than 5 years	34.3% [44.6, 21·4]	34.7% [44.6, 21.1]	34.4% [45.3, 20.2]	34.5% [46.7, 20.4]	35.0% [47.8, 18.9]	35.1% [49.3, 19.0]	33.6% [45.9, 20.3]	34.9% [48.1, 21.0]
Clinical malaria cases averted per 100 000 fully vaccinated children[a]	190 602 [42 236, 330 866]	197 826 [42 436, 335 796]	210 616 [32 428, 398 620]	219 324 [34 081, 408 221]	225 428 [37 117, 391 277]	232 586 [38 228, 402 365]	211 369 [32 324, 398 726]	220 540 [33 645, 410 641]
Malaria deaths averted per 100 000 fully vaccinated children[a]	632 [268, 633]	645 [269, 657]	663 [216, 719]	702 [239, 724]	689 [236, 709]	714 [254, 691]	672 [217, 733]	696 [225, 724]
Cost per clinical malaria case averted								
US$ 2 per dose	$5 [33, 3]	$6 [37, 3]	$5 [43, 2]	$5 [47, 2]	$7 [58, 4]	$8 [64, 5]	$6 [52, 3]	$7 [57, 3]
US$ 3 per dose	$7 [42, 4]	$8 [48, 5]	$6 [56, 3]	$7 [61, 4]	$9 [69, 5]	$10 [76, 6]	$8 [65, 4]	$9 [71, 4]
US$ 4 per dose	$10 [55, 6]	$12 [63, 7]	$9 [73, 4]	$10 [79, 5]	$12 [83, 6]	$13 [93, 7]	$10 [82, 5]	$12 [90, 6]
Cost per DALY averted								
US$ 2 per dose	$25 [97, 23]	$30 [109, 30]	$23 [122, 17]	$26 [126, 21]	$38 [169, 38]	$45 [186, 44]	$29 [146, 23]	$34 [157, 28]
US$ 3 per dose	$36 [126, 34]	$41 [141, 42]	$33 [158, 27]	$36 [163, 31]	$48 [202, 47]	$55 [221, 55]	$40 [181, 32]	$45 [196, 39]
US$ 4 per dose	$50 [165, 48]	$57 [183, 58]	$46 [205, 40]	$51 [212, 45]	$61 [246, 59]	$69 [268, 69]	$53 [228, 43]	$59 [247, 52]

[a] fully vaccinated child defined as receiving at least three doses

In settings representative of current levels of low *P. falciparum* transmission, the model estimates that introduction of a four-dose schedule of R21/Matrix-M could avert between 1 870 and 48 413 cases for every 100 000 fully vaccinated children, in settings of 1% and 10% $PfPR_{2–10}$ respectively, over a 15-year time horizon (Table 33). Assuming a vaccine price of US$ 3 per dose, the model estimates an incremental cost effectiveness ratio of US$ 13–324 per case averted and US$ 52–697 per DALY averted in settings of prevalence between 1% and 10%. The modelled public health impact and cost-effectiveness of R21/Matrix-M at 1%, 3%, 5% and 10% $PfPR_{2–10}$ is shown in Table 33, estimated for perennial settings (age-based delivery) and seasonal settings (age-based, seasonal and hybrid delivery).

Table 33. Public health impact and cost-effectiveness of R21/Matrix-M in low transmission settings (1–10% $PfPR_{2–10}$) over a 15-year time horizon – for all current WHO-recommended delivery strategies, *four*-dose schedule

Median (2.5th to 97.5th percentile) over 50 parameter draws; negative cost per case averted or cost per DALY averted are a result of negative cases or DALYs averted.

	1% $PfPR_{2–10}$	**3% $PfPR_{2–10}$**	**5% $PfPR_{2–10}$**	**10% $PfPR_{2–10}$**
Perennial settings – age-based delivery				
Malaria clinical cases averted per 100 000 population	4 950 (1 669—8 121)	16 411 (8758–23 831)	27 651 (16 886—43 137)	46 760 (28 859—67 297)
Malaria deaths averted per 100 000 population	49 (11—122)	104 (39—191)	134 (70—312)	187 (90—382)
Cost per clinical case averted (US$ 3 per dose)	$147 (89—446)	$42 (28—82)	$24 (14—41)	$13 (8—23)
Cost per DALY averted (US$ 3 per dose)	$307 (129—1143)	$126 (64—323)	$86 (36—167)	$55 (26—120)
Seasonal settings – age-based delivery				
Malaria clinical cases averted per 100 000 population	1 930 (-1 206—6 667)	12 601 (7 375—18 694)	27 859 (14 607—43 837)	46 484 (29 920—72 515)
Malaria deaths averted per 100 000 population	21 (-16—68)	84 (37—183)	138 (61—274)	196 (94—371)
Cost per clinical case averted (US$ 3 per dose)	$233 (-21 954—3 540)	$56 (37—98)	$24 (14—48)	$13 (7—22)
Cost per DALY averted (US$ 3 per dose)	$560 (-1 503—5 647)	$158 (69—372)	$82 (42—189)	$52 (25—115)
Seasonal settings – seasonal delivery				
Malaria clinical cases averted per 100 000 population	2 334 (-1 113—6 237)	14 432 (8 858—21 537)	31 055 (17 125—49 116)	52 354 (32 359—77 491)
Malaria deaths averted per 100 000 population	27 (-14—68)	92 (40—203)	153 (61—310)	196 (106—387)
Cost per clinical case averted (US$ 3 per dose)	$293 (-3 915—3 404)	$69 (45—114)	$30 (18—57)	$17 (10—29)
Cost per DALY averted (US$ 3 per dose)	$652 (-2 514—6 367)	$202 (91—503)	$108 (54—278)	$73 (35—147)
Seasonal settings – hybrid delivery				
Malaria clinical cases averted per 100 000 children	1 870 (-1 100—5 305)	12 550 (6 908—19 110)	27 769 (14 725—43 410)	48 413 (28 891—74 239)
Malaria deaths averted per 100 000 children	22 (-15—63)	84 (37—194)	145 (66—290)	188 (99—379)
Cost per clinical case averted (US$ 3 per dose)	$324 (-1 467—3 096)	$65 (41—121)	$28 (17—55)	$15 (9—27)
Cost per DALY averted (US$ 3 per dose)	$697 (-2 729—6 493)	$181 (76—411)	$96 (47—213)	$62 (29—129)

Fig. 16. Summary of impact and cost-effectiveness for R21/Matrix-M across vaccine delivery strategies and transmission settings of $PfPR_{2–10}$ 1–65%

A) Cases and B) deaths averted per 100 000 fully vaccinated children, 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.

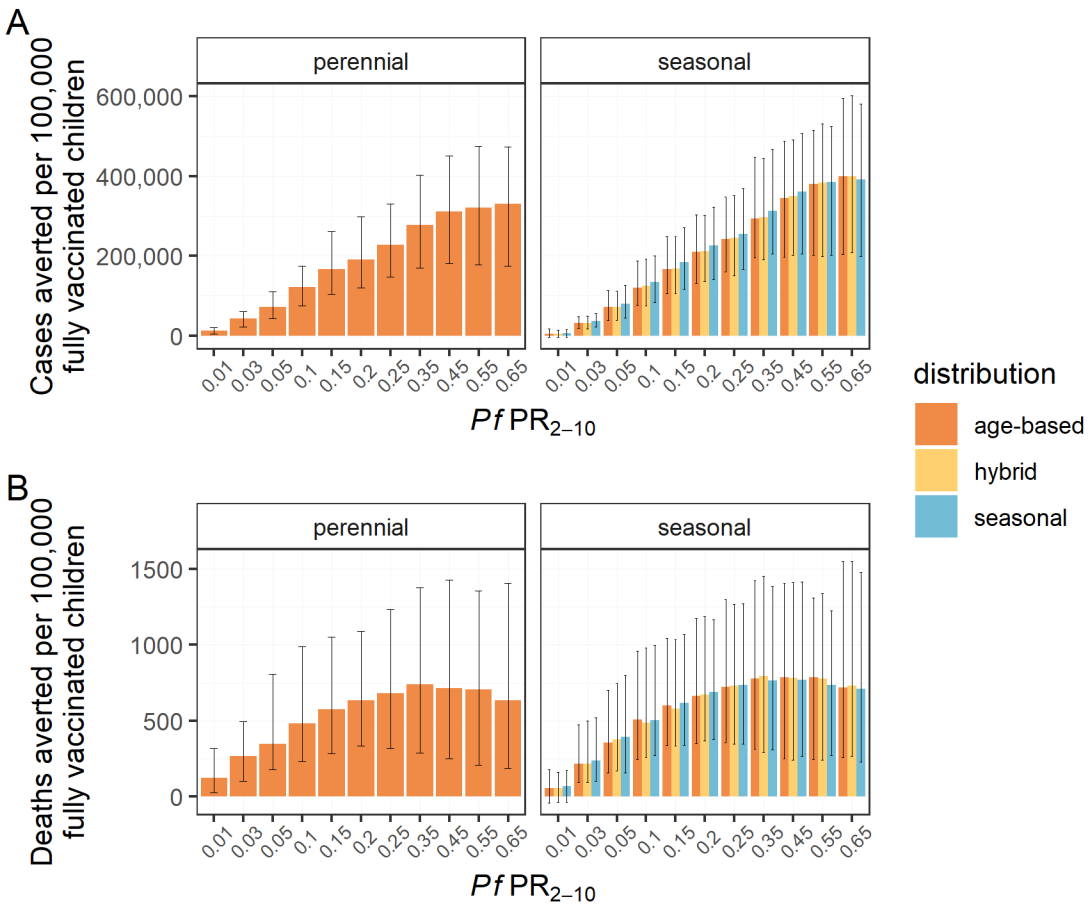
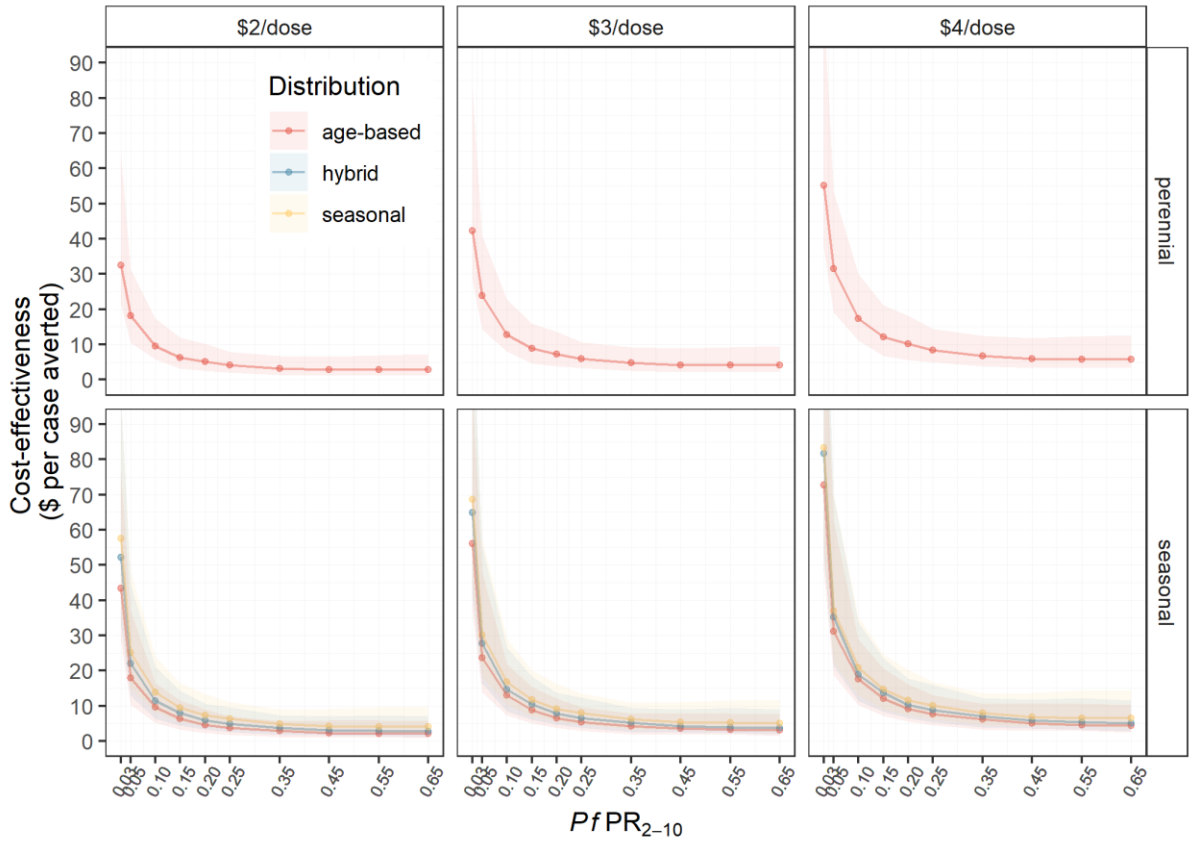


Fig. 17. Estimated cost-effectiveness of R21/Matrix-M as a four-dose regimen

As summarized by cost (US dollars) per case averted, stratified by 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 parameter draw uncertainty runs. In seasonal settings, the age-based and hybrid implementations nearly completely overlap.



10.4. Interpretation of modelled public health impact and cost-effectiveness

Modelling results suggest that the introduction of R21/Matrix-M into childhood immunization programmes could have a substantial impact on reducing malaria cases and malaria deaths in children living in settings with endemic malaria in Africa.

Estimates of R21/Matrix-M cost-effectiveness are comparable with other malaria interventions and other childhood vaccines across a range of transmission settings in sub-Saharan Africa, with $PfPR_{2–10}$ between 3 to 65%. The Imperial model estimates that the R21/Matrix-M vaccine becomes more cost-effective with increasing $PfPR_{2–10}$. In lower transmission settings (estimated at 1% to 10% $PfPR_{2–10}$), the vaccine still provided comparable cost effectiveness to other interventions however the cost effectiveness ratios were considerably higher and more uncertain in the lowest transmission setting (1% $PfPR_{2–10}$).

The estimated cost per case and DALY averted from the Imperial model of R21/Matrix-M is lower than previously estimated for RTS,S/AS01 across a harmonized comparison of multiple models (Imperial College, Swiss TPH, Institute for Disease Modeling, and GSK Vaccines); however, there are methodological differences in the models and differences in the trial sites, transmission intensities, dosing schedules and trial methods from which the estimates that informed the models are derived, and therefore direct

comparison of these estimates cannot be made. While the anticipated cost per dose of R21/Matrix-M (US$ 3; US$ 2–4) is a major driver of the modelled estimates, it is possible the public health impact and cost-effectiveness of R21/Matrix-M once broadly introduced may be different than these estimates.

Overall, the model estimated that costs per clinical malaria case or DALY averted were similar or slightly lower for four-dose age-based strategies when compared to five-dose seasonal or hybrid delivery strategies. Interpretation of impact and cost-effectiveness of a five-dose schedule in seasonal settings should be made with caution given the limited Phase 2b follow-up data available in a very small subset of trial participants (~122 total, randomized to receive either 3, 4 or 5 doses).

Among the limitations of this first modelled impact and cost-effectiveness analysis for R21/Matrix-M are reliance on data from a single Phase 2b study site to model the relationship between anti-CSP antibody titres and vaccine efficacy, the limited follow-up time resulting in large uncertainty bounds of projected efficacy beyond 3 years, the limited evidence regarding efficacy and duration of protection following administration of dose 5, and limited reflection of the variation of seasonality patterns across sub-Saharan Africa. Additional follow-up time anticipated in the Phase 3 trial will contribute to refined estimates over time; country-specific or sub-national modelling making use of local data will be important in tailoring these results to specific settings.

11. SAGE/MPAG Working Group on Malaria Vaccines assessment and summary of key recommendations for SAGE and MPAG consideration

11.1. Assessment of vaccine efficacy

The R21/Matrix-M vaccine has been shown to reduce clinical malaria cases by 75% (modified intention-to-treat [mITT] or per protocol [PP]) during the 12 months following a three-dose primary series when the vaccine was provided seasonally in areas of highly seasonal transmission. This high vaccine efficacy (VE) was maintained during the 6 months following the administration of dose 4, given 12 months after dose 3. The vaccine likewise showed good VE when given as age-based ("standard") vaccine administration to children living in areas of low to moderate malaria transmission, reducing clinical malaria cases by 61% (mITT; 66% PP) during 12 months following dose 3. VE declined slowly over the 12 months following dose 3 in both seasonal and standard administration sites. Data are not yet available on VE following dose 4, given 1 year after dose 3, in the standard administration sites. These data will become available in the next 12 months, as follow-up of children enrolled in the clinical trial continues. However, the high VE observed after dose 4 when given seasonally (Fig. 5) is reassuring, and it seems likely that children receiving the vaccine in standard administration sites will have a similar good clinical response to dose 4, with good VE and an extended period of protection.

Estimates of public health impact in the clinical trial are high, with an estimated 837 and 279 cases averted per 1000 child years during 12 months follow-up in seasonal and standard administration sites, respectively (Table 13). A mathematical model also estimates high impact, with approximately 689 and 632 malaria deaths averted per 100 000 children fully vaccinated in a four-dose schedule in seasonal and standard administration, respectively. High impact has likewise been demonstrated with the pilot introduction of the first malaria vaccine, even in areas of high insecticide-treated net (ITN) use and good access to care. Of note, modelling indicates that both the R21/Matrix-M and RTS,S/AS01 vaccines would have important impact even in areas of low transmission.

The R21/Matrix-M vaccine and the first WHO-recommended malaria vaccine, RTS,S/AS01, are similar in vaccine construct, antigenic target and mechanism of action. Both vaccines show efficacy in seasonal and standard administration sites. There are currently no data on the VE of R21/Matrix-M in high perennial transmission settings and data from low transmission settings are limited. However, given the similarity of the vaccines and the observation that RTS,S/AS01 has been shown to be efficacious in areas of high, moderate and low malaria transmission, as well as in highly seasonal malaria settings, it is reasonable to assume that R21/Matrix-M will be efficacious in all malaria endemic settings. Nonetheless, it will be important to collect post-licensure data on the public health impact of R21/Matrix-M in settings of high perennial transmission and low transmission.

During 12 months of follow-up after dose 3 in standard administration sites and 18 months of follow-up in seasonal administration sites, there were a relatively small number of cases of severe disease secondary end-points – severe malaria, malaria hospitalization and all-cause mortality – and the trial had insufficient power to conclude on VE against these end-points. However, given the high efficacy against clinical malaria, the efficacy against severe malaria is also expected to be high. This was demonstrated for RTS,S/AS01 in the Malaria Vaccine Implementation Programme (MVIP), where programmatic introduction of RTS,S/AS01 resulted in important impact on severe malaria hospitalization and all-cause mortality. Given that severe disease outcomes are rare and challenging to measure with precision in Phase 3 trials, these end-points are not required for a WHO recommendation for use *(37),* but effectiveness against these end-points should be monitored in some settings post-licensure.

11.2. Assessment of vaccine safety

Safety data on the R21/Matrix-M vaccine were reviewed by an R21/Matrix-M Safety Working Group and the Global Vaccine Advisory Group on Vaccine Safety (GACVS), whose assessments are incorporated into this report.

No major safety concerns were noted that would warrant a delay in recommendation of R21/Matrix-M for public health use.

Overall, the frequency of SAEs was balanced among children randomized to receive the R21/Matrix-M vaccine and those who received the control (rabies) vaccine.

There was a higher number and clustering of febrile convulsions within 3 days after vaccination among children in the R21/Matrix-M arm (5 subjects [0.15%]) compared with the control arm (1 subject [0.062%]), with an attributable risk of 1/2800 doses administered. In all cases, the children recovered without sequelae. Febrile convulsions are associated with other childhood vaccines, including RTS,S/AS01 (attributable risk 2.5/1000 doses) and measles vaccine (attributable risk 1/2000–3000 doses).

In the setting of a small number of deaths among participants in the trial, an imbalance was observed, with more deaths in the R21/Matrix-M arm than in the control arm. Excluding trauma or accidents, and noting the 2:1 randomization, there were 12 deaths (0.4%) in the R21/Matrix-M arm and 3 (0.2%) in the control arm. The imbalance was not statistically significant and may have been a chance finding, no deaths were assessed as causally related to vaccination, there was no pattern among deaths in relation to timing of vaccination, and there were no observed patterns or consistency among causes of death.

GACVS noted the limited number of young children who have received Matrix-M globally in other vaccines to date compared with adults, although no specific issues or concerns (other than the previously noted reactogenicity) have been identified in adults or children.

The SAGE/MPAG Working Group on Malaria Vaccines agrees with GACVS' recommendations for post-introduction safety monitoring for adverse events of special interest (AESIs) including deaths, seizures, febrile convulsions within 7 days, and severe fever (which can lead to febrile convulsions), especially in the context of co-administration with other vaccines.

Rebound malaria should be assessed during the ongoing clinical trial in alignment with recommendations from the WHO Technical consultation on malaria rebound phenomenon *(31)*. The SAGE/MPAG Working Group on Malaria Vaccines agrees that a WHO recommendation for vaccine use should not wait for such an assessment, noting that the trial will continue for 4 years following dose 3, sufficient to detect any rebound, should it occur, and to propose mitigating measures for those who may be at risk.

11.3. Malaria vaccines in the context of other malaria control interventions

The malaria vaccine should be provided as part of a comprehensive malaria control strategy. All malaria control interventions, including currently available malaria vaccines, provide only partial protection, and the highest impact is achieved when multiple interventions are used concomitantly. Appropriate mixes of interventions should be identified for different subnational settings. These mixes are defined by national malaria control programmes on the basis of the local malaria epidemiology (e.g. transmission intensity, age pattern of severe disease, vector species and insecticide-resistance patterns) and contextual factors (e.g. structure and functioning of the formal health system).

The SAGE/MPAG Working Group on Malaria Vaccines notes that R21/Matrix-M demonstrated substantial added protection against clinical malaria even when provided in the setting of other efficacious interventions, including long-lasting insecticidal nets (LLINs), distributed to all participants at enrollment,

and seasonal malaria chemoprevention (treatment regimens of sulfadoxine-pyrimethamine plus amodiaquine monthly for 4 months delivered as part of the malaria programme during the malaria transmission season as per national guidelines) in the two seasonal delivery sites and one of the three standard delivery sites. This finding again underscores the benefit of layering effective malaria preventive interventions to optimize impact.

11.4. Assessment of feasibility

The R21/Matrix-M vaccine has not been implemented by national immunization programmes; however, it is very similar to the currently recommended malaria vaccine with regards to the indication for use and target population, schedule, route of administration and delivery strategies. The MVIP has provided robust evidence on the feasibility and acceptability of a malaria vaccine as an additional intervention to reduce malaria. Based on lessons learned from the MVIP, and the similar characteristics of RTS,S/AS01 and the R21/Matrix-M vaccines, the vaccine is considered feasible to implement.

As of August 2023, more than 5.4 million doses of the RTS,S/AS01 malaria vaccine have been administered, and more than 1.8 million children have received dose 1 (over 600 000 children have received dose 4) through the national immunization programmes of Ghana, Kenya and Malawi as part of the pilot introductions, noting strong uptake of doses 1–3 but lower uptake of dose 4. These findings support the feasibility to achieve similar coverage and uptake for R21/Matrix-M vaccine.

The MVIP found no impact on the use of ITNs or overall health seeking behaviour for febrile illnesses following malaria vaccine introduction. Qualitative data and the high demand for a malaria vaccine show that malaria is seen by both caregivers and health workers as a significant health risk and the malaria vaccine, together with other malaria prevention measures, are seen as desirable interventions.

R21/Matrix-M has strong thermostability (2 weeks at 24 °C and 48 °C and shelf-life of 24 months at 2–8 °C), and an all-liquid single-vial presentation is under development, which, if approved for use, would require no reconstitution, thereby simplifying processes and reducing the need for reconstitution supplies. The expected high volume of R21/Matrix-M supply increases feasibility of implementation, reducing the need for a phased introduction because of the current limited supply of malaria vaccine, and increasing the likelihood a country could opt for a 5-dose strategy, whether as a seasonal or age-based approach, to optimize impact.

There is currently limited evidence on co-administration of R21/Matrix-M with other childhood vaccines. Studies are ongoing and post-licensure data are expected on the co-administration of R21/Matrix-M with measles-rubella and yellow fever vaccines as well as pentavalent (diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b), rotavirus, pneumococcal and oral polio vaccines.

11.5. Conclusions and recommendations for SAGE and MPAG consideration

The SAGE/MPAG Working Group on Malaria Vaccines recommends the programmatic use of R21/Matrix-M for the prevention of *P. falciparum* malaria in children living in malaria endemic areas, prioritizing areas of moderate and high transmission. Thus, the R21/Matrix-M vaccine would be recommended as a second pre-erythrocytic malaria vaccine to be included under the current WHO recommendations for malaria vaccines.

The vaccine should be provided in a schedule of four doses in children from around 5 months of age[vi] for the reduction of *P. falciparum* malaria disease and burden.

A 5th dose, given 1 year after dose 4, may be considered in areas where there is a significant malaria risk remaining in children a year after receiving dose 4. More details on implementation considerations are provided in section 11.5.2.

Countries may consider providing the vaccine using an age-based administration, seasonal administration, or hybrid of these approaches in areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks.

Countries should prioritize vaccination in areas of moderate and high transmission, but may also consider providing the vaccine in low transmission settings. Both R21/Matrix-M and RTS,S/AS01 are efficacious in areas of low malaria transmission, and clinical trial data and mathematical modelling estimate considerable impact, including in areas of low malaria transmission. With a second vaccine coming to market and other market shaping efforts, there is a high potential for lower vaccine cost and improved vaccine cost-effectiveness. Decisions on expanding to low transmission settings should be considered at a country level, based on the overall malaria control strategy, cost-effectiveness, affordability and programmatic considerations, such as whether including such areas will simplify delivery.

The SAGE/MPAG Working Group on Malaria Vaccines notes that the standard sites in the Phase 3 trial are areas of low to moderate transmission, and information on VE and duration of protection with R21/Matrix-M in high transmission perennial sites is currently lacking. The SAGE/MPAG Working Group on Malaria Vaccines recommends that as the vaccine is deployed under programmatic conditions in high burden areas with perennial transmission, post-licensure monitoring of impact should be undertaken to provide this information.

Evidence to date shows that the R21/Matrix-M has an acceptable safety profile. However, the SAGE/MPAG Working Group on Malaria Vaccines and GACVS note that, although the Matrix-M adjuvant has been widely used in other vaccines, the available safety data are primarily in adults. Because young children are the main target population for R21/Matrix-M, post-licensure monitoring in children receiving R21/Matrix-M is recommended to obtain additional safety information in this age group, including monitoring the frequency of febrile convulsions. As included in section 11.2, the SAGE/MPAG Working Group on Malaria Vaccines also agrees with the GACVS recommendations for post-authorization monitoring of AESIs, including monitoring of deaths, and continued follow-up of trial participants to measure duration of protection and assessment of potential rebound.

The availability of a second malaria vaccine is welcome at a time when progress in malaria control has stalled in recent years, and other current malaria control tools face challenges in terms of biological

[vi] Vaccination programmes may choose to give dose 1 at a later age based on operational consideration. Studies with RTS,S/AS01 indicated lower efficacy if dose 1 was given around 6 weeks of age. However, it seems unlikely that efficacy would be substantially reduced if some children received the dose 1 at 4 rather than 5 months, and providing vaccination at an age younger than 5 months may increase coverage or impact.

threats such as drug and insecticide resistance, and in the context of continuing and unacceptably high levels of malaria illness and death. Demand for a malaria vaccine is very high, and supply of the first malaria vaccine is currently not able to meet demand. A second malaria vaccine, in addition to RTS,S/AS01, could help close the gap between supply and demand, enabling broader access and saving tens of thousands of lives each year. A second vaccine would also create a healthier malaria vaccine market that is not reliant on a single product.

11.5.1.Product choice

Currently, two malaria vaccines have undergone WHO policy review (RTS,S/AS01 and R21/Matrix-M) and available evidence indicates they are both safe and effective. RTS,S/AS01 received WHO prequalification in July 2022, and R21/Matrix-M is currently undergoing prequalification review. Both products are pre-erythrocytic vaccines using a similar vaccine construct (virus-like particle), saponin-based adjuvants, and have the same target antigen, target population and mechanism of action.

There are no data directly comparing VE between the products, and the clinical trials of each vaccine were conducted in different transmission settings and contexts. The relative efficacy of the two vaccines is therefore unclear based on currently available data. The choice of product to be used in a country should be based on programmatic characteristics, vaccine supply and vaccine affordability.

11.5.2. Implementation considerations

The SAGE/MPAG Working Group on Malaria Vaccines made the following recommendations for implementation, monitoring and evaluation, and further research. Some of the recommendations will result in modifications to the current WHO malaria vaccine recommendations and guidelines, and apply to both malaria vaccines.

- In areas of perennial malaria transmission, the vaccine should be provided as a three-dose primary series, starting from around 5 months of age[vi], with a minimum interval of 4 weeks between doses.
    - Data from the Phase 3 trial indicate that the R21/Matrix-M vaccine is safe and efficacious when dose 1 is delivered up to 36 months of age. A fourth dose should be given to prolong protection. The R21/Matrix-M Phase 3 trial showed there was VE when dose 4 was provided 12 months after dose 3 in highly seasonal areas. However, there can be flexibility to optimize delivery, including by aligning dose 4 with other vaccines given in the second year of life or prior to seasonal peaks in malaria transmission.
    - If malaria remains a significant public health problem in children a year after dose 4, then a 5th dose might be considered, depending on a local assessment of feasibility and cost-effectiveness.
    - The optimal interval between doses 3 and 4 has not been established.
- Overall, flexibility in vaccine schedule and delivery options is supported, with an aim to optimize uptake. Countries may consider how to achieve highest impact in their local context when considering dosing intervals, potential for catch-up vaccination, delivery through childhood immunization, periodic intensification of routine immunization (PIRI), or campaigns. When novel approaches or schedules are used, countries are encouraged to document and evaluate their experience.
- Although clinical trial data show that high impact can be achieved when malaria vaccine doses are provided just prior to the high transmission season using a seasonal delivery strategy, the

optimal dosing schedule in such settings remains uncertain, and studies comparing the effectiveness, feasibility and cost of different strategies are encouraged. Countries considering seasonal or hybrid approaches are strongly encouraged to evaluate their experience, including costs of implementation.

- Countries are encouraged to consider strategies to improve coverage in populations with high need and at high risk of malaria burden and disease (e.g. hard to reach or marginalized populations, areas of conflict or emergency, displaced populations, or other areas with poor access to health services). Some populations, including those in areas of conflict, that are hard to reach, and/or have poor access to health services, may benefit from delivery through campaigns. Additionally, as observed in the MVIP, dose 4 coverage has been relatively low, with modest improvement through PIRI. Exploration and documentation of other programme strategies, such as campaigns, to improve dose 4 or 5 coverage are encouraged.
- Malaria vaccines may be administered simultaneously with other childhood vaccines if programmatically efficient. Studies are ongoing to evaluate the co-administration of R21/Matrix-M with measles-rubella and yellow fever vaccines as well as pentavalent (diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b), rotavirus, pneumococcal and oral polio vaccines. As there is no evidence of vaccine interference to date, absence of data should not discourage co-administration and its related further evaluation. This recommendation is further supported by the findings from several trials showing that RTS,S/AS01 can safely be given in conjunction with other childhood vaccines.[vii]
- In the absence of interchangeability studies and in the event that countries may need to use heterologous schedules with RTS,S/AS01 and R21/Matrix-M, mixed vaccine use can be considered. Monitoring and evaluation of immunogenicity and reactogenicity of mixed vaccine use should be documented where feasible.
    - The malaria vaccination series for each child should be completed with the same product whenever feasible. However, if the product used for a prior dose is unavailable or unknown, the series should be completed with any available WHO-recommended malaria vaccine. Restarting the vaccine series is not recommended. Children who have an incomplete series should complete the series with a different vaccine.
- Catch-up vaccination can be considered at the start of vaccine introduction in children up to 3 or 5 years of age, subject to local epidemiology, feasibility, affordability and vaccine availability. Countries are encouraged to document and evaluate their experience with catch-up vaccination.

11.5.3. Monitoring and evaluation

High priority monitoring and evaluation recommendations for R21/Matrix-M vaccine

- Post-licensure monitoring of R21/Matrix-M safety in infants and young children, including the occurrence of febrile convulsions and mortality. Monitoring mortality may be most easily achieved in areas where there is a demographic surveillance system in place.

[vii] Co-administration studies with RTS,S/AS01 show that it can safely be given concomitantly with any of the following monovalent or combination vaccines: diphtheria, tetanus, whole-cell pertussis, acellular pertussis, hepatitis B, Haemophilus influenzae type b, oral polio, measles-rubella, yellow fever, rotavirus and pneumococcal conjugate vaccines. No co-administration studies have been conducted with RTS,S/AS01 and meningococcal A, typhoid conjugate, cholera, Japanese encephalitis, tick-borne encephalitis, rabies, mumps, influenza or varicella vaccines.

- Monitoring the duration of protection following dose 4 and the benefit of additional doses beyond dose 4.
- Monitoring for risk of malaria rebound and collecting further data on severe malaria and mortality as part of the ongoing Phase 3 trial and 4 years of follow-up.
- Observational clinical and immunological co-administration studies post-licensure with other relevant infant vaccines such as pneumococcal conjugate vaccines, rotavirus, pentavalent vaccines (diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b), inactivated polio vaccine, typhoid conjugate vaccine, meningococcal vaccine, hexavalent (diphtheria, tetanus, whole-cell pertussis, hepatitis B, inactivated polio vaccine and Haemophilus influenzae type b).
- Post-licensure evaluation of vaccine effectiveness in high perennial transmission settings, a setting which is not represented in the Phase 3 trial.

Other monitoring and evaluation recommendations

- Post-licensure evaluation on vaccine effectiveness in low transmission settings.

11.5.4. Research recommendations

High priority research recommendations for R21/Matrix-M vaccine

- Evaluation of VE against severe malaria (e.g. case-control study).
- Evaluation of vaccine impact on mortality using available systems (e.g. health and demographic surveillance system, community mortality surveillance and case-control study).
- Interchangeability studies on heterologous schedule with RTS,S/AS01 and R21/Matrix-M.

Other research recommendations

- Effectiveness of additional annual doses up to 6 or 7 doses (i.e. up to 5 years of age) if and where epidemiologically appropriate, including in areas of highly seasonal malaria or areas of perennial transmission.
- Evaluation of relative effectiveness of seasonal vaccine delivery, including comparison of age-based, seasonal, or hybrid vaccine administration approaches in high burden settings and areas with perennial transmission with seasonal peaks.
- Evaluation of the comparative feasibility and costs of implementing the vaccine in an age-based, seasonal, or hybrid approaches.
- Combined impact of vaccination with or without seasonal malaria chemoprevention (SMC) or perennial malaria chemoprevention (PMC) (or vice versa).
    - These studies could be done in areas eligible for SMC but where SMC has not yet been implemented, to study the added effect of SMC where the vaccine has been introduced.
    - This could also include a head-to-head comparison of age-based and seasonal approaches or age-based (0, 1, 2, 14 month schedule) and hybrid approaches.
- Comparison of RTS,S/AS01 and R21/Matrix-M antibody responses using standardized immunological assay.
- Safety and immunogenicity in HIV-positive children (ongoing Phase 1b trial in Uganda, VAC092 –

NCT05385510)

- Efficacy of vaccination in age groups older than 36 months at first vaccination in areas of low transmission or in non-immune populations, to understand potential vaccine use in situations of mass population movement.
- VE, duration of protection, and cost-effectiveness of a 3-dose R21/Matrix-M schedule (with no dose 4), in areas of low to moderate perennial transmission.
- Assessment of cell-mediated immune responses to R21/Matrix-M in vaccinees
- Safety and efficacy in pregnant women or women planning to become pregnant.

12. Acknowledgements

The R21/Matrix-M evidence report was submitted by the SAGE/MPAG Working Group on Malaria Vaccines to SAGE and MPAG prior to their convening on 27 September 2023. The SAGE/MPAG Working Group members who contributed to the development of this report are listed in Section 14. In addition, the WHO secretariat from the Department of Immunization and Biologicals (IVB) and the Global Malaria Programme (GMP) provided technical input and coordination.

The SAGE/MPAG Working Group gratefully acknowledges the following experts who contributed to their evidence review: Prof Faith Osier and Dr Nelli Westercamp. The R21/Matrix-M Safety Working Group reviewed the available safety data and provided expert advice on the vaccine's safety profile. Imperial College generated the R21/Matrix-M modelled public health impact and cost effectiveness estimates. PATH provided the malaria vaccine cost of delivery estimates most applicable to the R21/Matrix-M.

The Phase 3 evidence generated on the R21/Matrix-M malaria vaccine described in this report would not have been possible without financial support and vaccine doses from Serum Institute of India Private Ltd (SIIPL) or without the trial design, execution, and analysis by the study investigators, statistical teams, and collaborators: Jenner Institute - University of Oxford (United Kingdom), London School of Hygiene & Tropical Medicine (United Kingdom), Institut des Sciences et Techniques (Burkina Faso), Unité de Recherche Clinique de Nanoro - Institut de Recherche en Sciences de la Santé (Burkina Faso), Malaria Research & Training Center - University of Sciences Techniques and Technologies of Bamako (Mali), Ifakara Health Institute – Bagamoyo Research and Training Centre (Tanzania), KEMRI – CGMRC (Kenya). R21/Matrix-M is expected to have similar delivery strategies, schedule, and target population as the first malaria vaccine recommended, RTS,S/AS01. Additional data and evidence on these aspects for RTS,S/AS01 are included in this report and derived from the Malaria Vaccine Implementation Programme (MVIP) implemented by the Ministries of Health in Ghana, Kenya, and Malawi, and financially supported by Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid.

Gemma Villanueva, Katrin Probyn and Nicholas Henschke from the Cochrane Response supported the systematic review of evidence and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) used to inform the recommendations. Finally, Dr Laurence Slutsker had a crucial role in consolidating the evidence and drafting this report.

13. List of supportive materials and annexes

Supportive materials – via links

Malaria vaccine: WHO position paper – March 2022

- https://apps.who.int/iris/handle/10665/352337

WHO guidelines for malaria (section 4.3 Vaccine), 14 March 2023

- https://apps.who.int/iris/handle/10665/366432

Full Evidence Report on the RTS,S/AS01 Malaria Vaccine, September 2021

- https://zenodo.org/record/6394605

WHO Technical consultation on malaria rebound phenomenon, 2022

- https://apps.who.int/iris/handle/10665/361710

Malaria vaccines: preferred product characteristics and clinical development considerations, 2022

- https://apps.who.int/iris/handle/10665/362694

Annexes

Annex 1: VAC078 Phase 3 trial of R21/Matrix-M protocol, version 5.0, 20 May 2022

Annex 2: VAC078 Statistical analysis plan, version 3.0, 5 December 2022

Annex 3: R21/Matrix-M Supplementary tables and figures

Annex 4: Grading of recommendations, assessment, development and evaluations (GRADE) review of malaria vaccine evidence

Annex 5: Evidence to Recommendation framework table for use of the R21/Matrix-M malaria vaccine

Annex 6: The public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine: a mathematical modelling study (draft manuscript, September 2023)

14. SAGE/MPAG Working Group on Malaria Vaccines membership and Terms of Reference

Members of the SAGE/MPAG Working Group on Malaria Vaccines include:

- Professor Peter Smith, London School of Hygiene & Tropical Medicine, United Kingdom (Chair)
- Dr Eusébio Macete, Centro de Investigação em Saúde de Manhiça, Mozambique (Co-Chair)
- Professor Nick Andrews, Public Health England, United Kingdom
- Professor Graham Brown, University of Melbourne, Australia
- Dr Dafrossa Cyrily Lyimo, Independent consultant (and former National Immunization and Vaccine Development Programme Manager, Tanzania
- Dr Corine Karema, Independent consultant (and former Director of the Rwanda National Malaria Control Programme, Rwanda)
- Professor Kim Mulholland, Murdoch Children's Research Institute, Australia
- Professor Kathleen Neuzil, Center for Vaccine Development and Global Health (CVD), University of Maryland School of Medicine, USA
- Professor S. Patrick Kachur, Mailman School of Public Health, Columbia University, USA

Terms of Reference are accessible here: https://www.who.int/initiatives/malaria-vaccine-implementation-programme/sage-mpag-working-group

15. References

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