Strategic Advisory Group of Experts (SAGE) on Immunization Evidence to recommendations framework[1]

Question: Should a malaria vaccine be provided to reduce malaria disease burden in children ≥ 5 months of age living in regions with endemic malaria transmission?
Population: Children ≥ 5 months of age
Intervention: Malaria vaccination according to recommended schedule
Comparison: Malaria prevention interventions currently in place without malaria vaccination
Setting: regions with endemic high, moderate, or low malaria transmission (as defined by WHO[2])

Background: Malaria is one of the leading causes of childhood illness and deaths in Africa. All malaria control interventions provide only partial protection against malaria and the highest impact is achieved when interventions are strategically used together. The RTS,S/AS01 malaria vaccine was recommended by WHO in 2021 to prevent malaria in children living in regions with moderate-to-high *P. falciparum* malaria transmission. As of August 2023, over 1.8 million children have received at least 1 dose of the RTS,S/AS01 vaccine through phased introductions that began in 2019 in Ghana, Kenya, and Malawi. Results from pilot evaluations in those three countries (recommended by WHO in 2015) affirm the malaria vaccine is feasible to deliver, is safe and reduces childhood malaria, hospitalizations, and deaths.

Demand for a malaria vaccine is very high, estimated to reach 40—60 million doses by 2026 and growing to 80—100 million doses per year or more each year by 2030. However, the initial supply of RTS,S/AS01 is insufficient 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.

This Evidence to recommendations framework summarizes evidence available on the **R21/Matrix-M malaria vaccine** for potential inclusion within the current WHO malaria vaccine recommendation (see 2021 Evidence to recommendations framework on RTS,S/AS01 for more details on the global malaria vaccine evidence available).[3]

A Phase 3 clinical trial began in late April 2021 to assess the safety and protective efficacy of the R21/Matrix-M malaria vaccine against clinical malaria caused by *P. falciparum* in children 5—36 months of age at first vaccination using a seasonal administration approach in sites with highly

[1] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework

[2] HIGH: ≥ 35% PfPR or ~ 450 per 1000 API; MODERATE: 10–35% PfPR or 250–450 per 1000 API; LOW: 1–10% PfPR or 100–250 per 1000 API; VERY LOW: > 0 but < 1% PfPR or < 100 per 1000 API. https://www.who.int/publications/i/item/guidelines-for-malaria

[3] GRADE and Evidence to Recommendation tables on RTS,S/AS01 malaria vaccine (2021). https://zenodo.org/record/6395853

seasonal transmission or an age-based ("standard") administration approach in sites with low to moderate perennial transmission or highly seasonal moderate transmission.[4]

Like RTS,S/AS01, R21/Matrix-M is a pre-erythrocytic stage vaccine and targets the circumsporozoite protein (CSP) of *P. falciparum*, using a virus-like particle construct and a saponin-based adjuvant. Both vaccines can be given in a minimum four-dose schedule to children from 5 months of age with doses implemented through age-based and/or seasonal delivery strategies (vaccination just prior to the start of peak transmission season). As of 31 March 2023, the Phase 3 trial of R21/Matrix-M had completed the planned follow-up time for its primary outcomes measures of 12 months of follow-up following administration of vaccine dose 3 for both seasonal and standard administration sites.

[4] In the R21/Matrix-M Phase 3 trial, the age based (or "standard") schedule comprises the administration of 4 vaccine doses given at months 0,1,2, and 14. Seasonal administration in highly seasonal areas comprises 4 doses at months 0,1,2, and 14; the first 3 doses are provided at monthly intervals just prior to the start of the peak transmission season and dose 4 is provided 12 months after dose 3, just prior to the start of the next peak season.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	Despite considerable efforts to scale up and increase the use of WHO recommended interventions, malaria continues as a major public health problem. WHO estimates that in 2021 there were approximately 247 million malaria cases and 619 000 malaria deaths. Over 95% of all malaria deaths occur in sub-Saharan Africa, with most malaria deaths in Africa occurring in children younger than 5 years (470 000 deaths). Within a country, malaria transmission may be heterogeneous, for example, comprised of areas ranging from very high transmission to areas with variable transmission in which sporadic epidemics can affect all age groups, as well as areas with little or no malaria transmission. In areas of moderate or high transmission, malaria remains a major cause of child morbidity and mortality, even where insecticide treated net (ITN) coverage and other malaria preventive interventions, such as chemoprevention, is high. This includes areas of highly seasonal transmission, where transmission may be limited to several months per year (influenced largely by rainfall patterns) and where seasonal malaria chemoprevention (SMC) is provided monthly through the peak transmission season. Since 2015, the rate of progress in reducing both malaria cases and deaths has slowed, and in some countries with the highest burden, the annual number of malaria cases has risen.	Projections from the WHO Global Malaria Programme estimate that in 2024, there will be 25.4 million children under the age of 1 year living in areas of moderate and high transmission in sub-Saharan Africa (>10% *Pf*PR_{2-10}) and 12.1 million children under the age of 1 year are living in areas of low transmission (1-10% *Pf*PR_{2-10}). Areas of highly seasonal malaria, where the majority of clinical malaria cases and deaths occur over a several month period, continue to be areas of high burden; nearly half of childhood malaria deaths in sub-Saharan Africa occur in areas of highly seasonal transmission.

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BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No*	*Un-certain*	*Yes*	*Varies*	In Phase 3 standard administration sites, vaccine efficacy (VE) against all episodes of clinical malaria during 12-months follow-up after dose 3 was 61% (95%CI 53,67). This VE was observed in sites of low/moderate transmission with high ITN coverage (2 sites with a combined VE 54%; 95%CI 0.35,0.67) and in a study site with highly seasonal moderate transmission and high ITN and SMC coverage (VE 65%; 95%CI 0.57,0.72). VE point estimates declined slowly over time, 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. This pattern did not differ significantly among the standard administration sites. Data are not yet available on VE following dose 4, given one-year after dose 3 in standard vaccination sites. The Phase 3 trial will continue for 4 years following dose 3. Unlike the RTS,S/AS01 Phase 3 trial, the R21/Matrix-M Phase 3 trial was not designed to compare the VE of a 3-dose schedule to a 4-dose (or 5-dose) schedule; all children received a 4-dose schedule. Therefore, it is not possible to conclude on the additional benefit of dose 4 or dose 5 over a 3-dose schedule. In seasonal administration sites, VE against all episodes of clinical malaria during 18 months follow-up after dose 3 (and 6 months after dose 4/booster) was 74% (95%CI 70,76). This VE was observed on top of existing interventions (high ITN coverage and SMC implementation during the peak transmission period). Point estimates of VE against clinical malaria remained high for the first 6 months following dose 3 (81% during months 1-3 and VE 74% during months 4-6), dropped during months 7-9 (VE 44%), but increased again in months 10-12 (prior to booster) to 67%. During the 6 months follow-up after the dose 4 (booster dose), VE was maintained with point	Even a modest VE has the potential to translate into significant public health impact on morbidity and mortality for a common and serious disease such as malaria. Considerable evidence is available on the recommended malaria vaccine, RTS,S/AS01, and the following findings on the RTS,S/AS01 vaccine are assumed applicable to R21/Matrix-M due to similar vaccine construct and VE against clinical malaria: • Vaccination just prior to peak transmission is shown to maximize vaccine impact • When provided in an age-based vaccination approach across a broad range of transmission intensities, including high perennial transmission, low transmission, and highly seasonal transmission, at 0,1,2, 20 months, VE for RTS,S/AS01 against clinical malaria and severe malaria after 12 months follow-up was approximately 50% in the Phase 3 clinical trial. • In pilot introductions through the MVIP, high impact was shown when the vaccine was delivered by the Ministry of Health (MoH) through the childhood immunization programme. During 24 months after vaccine introduction, an approximate 30%
		☐	☐	☒	☐		

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			estimates of 70% (13-15 months) and 69% (16-18 months). The high VE observed for R21/Matrix-M is similar to the high VE of the currently recommended malaria vaccine, RTS,S/AS01. The R21/Matrix-M vaccine and the 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, medium 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 follow-up after dose 3 in standard administration sites and 18 months follow-up in seasonal administration sites, there were a relatively small number of cases of severe disease secondary endpoints - severe malaria, malaria hospitalizations and all-cause mortality - and the trial had insufficient power to conclude on VE against these end points.[5] Likewise, there is no evidence on R21/Matrix-M VE against blood transfusions as this was not an endpoint in the Phase 3 trial.	reduction in hospitalized severe malaria was observed, and although not yet powered to show impact on mortality, a 9% (not statistically significant) reduction in all-cause mortality in children age-eligible for vaccination was observed. This level of effectiveness was achieved during the first 24 months after vaccine introduction, when 3-dose coverage was 65-70%.

[5] As outlined in the WHO Preferred Product Characteristics for Malaria Vaccines, while end-points on severe malaria may provide important information on public health impact, they would require considerably larger sample sizes in a Phase 3 trial due to very low incidence and their evaluation may be more feasible in post-licensure studies. Measurements of impact on mortality would not be expected during a clinical trial given that the number of events expected would be very low. https://apps.who.int/iris/handle/10665/362694

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						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 MVIP, where the programmatic introductions of RTS,S/AS01 resulted in an 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 endpoints are not required for a WHO recommendation for use[5], but effectiveness against these endpoints should be monitored in some settings post-licensure.	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No*	*Un-certain*	*Yes*	*Varies*	No major safety concerns were noted in the ongoing R21/Matrix-M Phase 3 trial that would warrant a delay in recommendation for public health use. In the R21/Matrix-M Phase 3 trial (ongoing since 2021), febrile convulsions within 3 days of vaccination were the most reported adverse event of special interest (AESI)— 5 events were observed in the R21/Matrix-M group and 1 event in the control group – with an attributable risk of 1 per 2,800 doses administered. In all cases, the children recovered without sequelae. An imbalance in deaths was noted, however, the overall numbers were small. The imbalance was not statistically significant. There was no pattern among deaths in relation to timing of vaccination. There were no observed patterns or consistency among causes of death. The R21/Matrix-M Phase 3 trial included meningitis and cerebral malaria as adverse events of special interest (AESIs). Meningitis and cerebral malaria were uncommon, and no imbalance was noted between the R21/Matrix-M and control arms.	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).
		☐	☐	☒	☐		

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			The Matrix-M adjuvant has had limited use in young children. Although no specific issues or concerns have been identified (other than reactogenicity), there should be post-licensure monitoring because young children are the main target population. The risk of malaria rebound is unknown but can be monitored post-licensure during the planned 4-year follow-up of participants in the Phase 3 trial.	
	Balance between benefits and harms	*Favours intervention* ☒ / *Favours comparison* ☐ / ~~*Favours both*~~ ☐ / *Favours neither* ☐ / Unclear ☐	In the ongoing Phase 3 trial, the R21/Matrix-M vaccine was shown to significantly reduce clinical malaria, demonstrating substantial added protection to that already provided by existing malaria preventive measures (i.e., ITNs provided at enrollment, and/or SMC, implemented through the MoH per national guidelines). Given the high burden of malaria, the level of VE measured has potential to translate into significant public health impact whether delivered in areas of seasonal or perennial transmission. When R21/Matrix-M was provided via seasonal administration in sites with highly seasonal malaria transmission, the benefits against clinical malaria after 4 doses are substantial. When provided via standard administration, the benefits against clinical malaria after 3 doses is high, but the benefits after 4 doses will not be known until further follow-up is completed in the Phase 3 trial. The Phase 3 trial was not powered to assess VE against less common severe endpoints; therefore, the benefits are unknown against severe malaria, hospitalization due to malaria, malaria-related mortality, and all-cause mortality after 3 or 4 doses.	Judgment options defined as: - "Intervention:" Malaria vaccination plus other malaria control interventions is an acceptable option - "Comparison" other malaria control interventions is only acceptable option - "Neither" intervention nor the control are acceptable - "Unclear" if either intervention or control are acceptable - Note: "Both" removed due to lack of clarity in meaning

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			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, medium 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. The vaccine was associated with febrile convulsions at a rate of approximately 1/2500 doses administered; all resolved without sequelae. Overall, the benefit/risk balance for R21/Matrix-M is positive.	
	What is the overall certainty of this evidence for the critical outcomes?	Efficacy of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Mod-erate* ☐ *High* ☒ Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Mod-erate* ☒ *High* ☐	The certainty of evidence ranged from **moderate** to **high** based on VE against clinical malaria as a critical outcome. The main reason for downgrading was due to lack of data in high transmission settings for the age-based ("standard") administration sites. The certainty of evidence ranged from **low** to **moderate** for the safety of the intervention. The reasons for downgrading include few or no events, wide confidence intervals, and small sample size. While the vaccine was associated with febrile seizures at a rate of approximately 1/2500 vaccinations, all febrile seizures resolved without sequelae. There was no imbalance in other SAEs among children vaccinated with R21/Matrix-M or with the control (rabies) vaccine in the Phase 3 trial.	The overall assessment on the certainty of evidence takes into account all of the data reviewed in the GRADE and the expert opinions of the SAGE/MPAG Working Group and Malaria Vaccines. The GRADE tables are published in an accompanying appendix to the R21/Matrix-M full evidence report. It is noted that the evidence of VE for important (but not critical) outcomes, including severe malaria, hospitalisations and mortality has low certainty due to the low number of events and relatively small trial size. However, severe outcomes are rare and difficult to measure in Phase 3 trials for

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							There was no excess in the R21/Matrix-M arm of the AEs of special interest (cerebral malaria, meningitis). Notably, the MVIP was designed to identify an excess in these outcomes or causal association with RTS,S/AS01; results after 24 months of vaccine introduction indicate no causal association with these outcomes and RTS,S/AS01 vaccination. As a result, cerebral malaria, meningitis and differential impact on mortality by gender are not included as critical outcomes for a WHO recommendation. Further data should be collected on the safety of the vaccine (which includes the Matrix-M adjuvant) in the target age group, which can be monitored post-licensure.	malaria and, therefore, measurement of VE against these rare events is not required for a recommendation for use.
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	***Important uncertainty or variability*** ☐	***Possibly important uncertainty or variability*** ☐	***Probably no important uncertainty or variability*** ☐	***No important uncertainty or variability*** ☒	***No known undesirable outcomes*** ☐	The certainty of the importance of the desirable outcomes is very high. The demand for a malaria vaccine with at least moderate efficacy has been noted as “unprecedented” by Gavi. Undesirable outcomes are primarily limited to febrile convulsions without sequelae. These occur with other recommended childhood vaccines (including the RTS,S/AS01 vaccine).	

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	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ / *Probably No* ☐ / *Uncertain* ☐ / *Probably Yes* ☐ / *Yes* ☒ / *Varies* ☐	The high demand for the malaria vaccine among countries in Africa that have expressed interest and/or are planning vaccine introductions indicates the relative importance of the desirable outcomes of this intervention by the target population (children and their caregivers). As of July 2023, R21/Matrix-M has been approved by 3 national regulatory authorities for use in their country. To the extent R21/Matrix-M is expected to have similar delivery strategies, target population (children younger than 5 years), schedule, benefits and harms, to the RTS,S/AS01 vaccine—the following RTS,S/AS01 evidence can be considered applicable to R21/Matrix-M: RTS,S/AS01 MVIP Household surveys, administrative data, post-introduction evaluations, qualitative study (caregiver and health worker interviews) and statements from the MoH in the pilot countries indicate the high value of a malaria vaccine and high acceptability by the target population.	The SAGE/MPAG WG discussion notes that the undesirable effects are rare and desirable effects are large.
RESOURCE USE	Are the resources required small?	*No* ☒ / *Uncertain* ☐ / *Yes* ☐ / *Varies* ☒	Resources are required for commodity procurement and for the health system provision of the new vaccine. Existing platforms for childhood vaccination and health services could be leveraged. Support by immunization and malaria funding agencies may be available to certain countries. Cost-effectiveness modelling has assumed a vaccine price of US $3 per dose of R21/Matrix-M (range of $2—4). Currently available cost of delivery estimates on RTS,S/AS01 are assumed to be the most applicable. Resources required for malaria vaccine delivery are comparable to those needed for other new vaccine introductions. Malaria vaccine cost of delivery estimates	Resource requirement is largely dependent on the vaccine price and potential donor funding available to support vaccine purchase and introduction. There are implied costs of vaccine introduction, however, the size of resources required depends on perspective and cost-effectiveness. 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.

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				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. A retrospective cost of delivery study to evaluate the cost of phased subnational introduction and delivery of RTS,S/AS01 in each of the pilot countries using a four dose age-based delivery strategy estimated the non-vaccine financial cost per dose delivered ranges across US$ 1.04–2.46 (0.29—0.86 recurrent costs only) and non-vaccine economic cost per dose delivered ranges across US$ 1.52—4.62 (0.59—2.29 recurrent costs only). A prospective costing study to evaluate the cost of nationwide introduction and delivery of RTS,S/AS01 seaonally timed doses (with or without mass campaigns) in Mali or Burina Faso using a seven-dose regimen (based on the Phase 3b seasonal malaria vaccination trial) estimated 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, US$ 0.70 and US$ 1.37, and US$ 0.48 and US$ 0.82, respectively. 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.	

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	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Estimates of R21/Matrix-M cost-effectiveness per DALY averted are comparable with other malaria interventions and other childhood vaccines, noting 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. In 2023, a model by Imperial College predicts that R21/Matrix-M introduction 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 410 641 clinical malaria cases and between 216 and 733 malaria deaths for every 100 000 fully vaccinated children in settings with 3% and 65% $PfPR_{2–10}$, respectively (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 DALY averted in the same settings (3% and 65% $PfPR_{2–10}$). In settings representative of 20% $PfPR_{2–10}$, the model estimates median estimated incremental cost-effectiveness ratios at 20% of US$ 5—13 per clinical malaria case averted and US$ 23—69 per DALY averted. In lower transmission settings, 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% $PfPR_{2–10}$).	Estimated malaria cases, malaria deaths and DALYs averted are based on a modelled relationship between anti-CSP antibody titres and vaccine efficacy against *P. falciparum* malaria infection, using data measured during the R21/Matrix-M Phase 2b study in Nanoro, Burkina Faso evaluating seasonal administration in a highly seasonal transmission setting.

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						In settings representative of current levels of low P. falciparum transmission between 1 to 10% PfPR2-10, the model estimates that introduction of a 4-dose schedule of R21/Matrix-M could avert between 1870 to 48,413 cases for every 100,000 (age-based, seasonal and hybrid delivery) fully vaccinated children, over a 15-year time horizon. Assuming a vaccine price of US$ 3 per dose, the model estimates incremental cost effectiveness ratios between US$ 13—324 per case averted and US$ 52—697 per DALY averted in settings between 1 to 10% $PfPR_{2–10}$.	
EQUITY	What would be the impact on health inequities?	*Increased* ☐	*Uncertain* ☐	*Reduced* ☒	*Varies* ☐	The malaria vaccine provides protection against one of the leading causes of illness and death in African children younger than 5 years, contributing to the reduction of health inequities. Based on global evidence available on the currently recommended malaria vaccine, RTS,S/AS01, which has been introduced in pilot introductions in Ghana, Kenya, and Malawi, and to the extent that R21/Matrix-M has similar anticipated benefits and the same target population: • While in some settings, inequities in vaccine access by socio-economic status remain, overall malaria vaccine reduces inequities for access to at least one effective malaria prevention intervention. During the pilot introductions of RTS,S/AS01, similar vaccine coverage has been observed across socio-economic groups, between rural and urban areas, and between boys and girls. • Vaccine introduction did not negatively impact ITN use, uptake of other childhood vaccines, or health seeking behavior.	

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			• Introduction of the vaccine extended the reach of malaria prevention measures to vulnerable children—increasing the number of children with access to an ITN and/or malaria vaccine.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☒ *Comparison* ☐ ~~*Both*~~ *Neither* ☐ *Un-clear* ☐	R21/Matrix-M can be assumed to be acceptable to key stakeholders due to: • Balance of benefits and harms in favour of the intervention. • No important uncertainty or variability from the currently recommended malaria vaccine (for which strong evidence of acceptability is available from quantitative and qualitative studies, high uptake, etc.) • Very high demand for a malaria vaccine, with expressions of interest made to Gavi from more than 28 MoHs to introduce the vaccine. This translates to an estimated 40-60 million doses required by 2026, which is projected to exceed a need of 80-100 million doses by 2030. Initial supply of RTS,S/AS01 is insufficient 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. • Data from the Health Utilization Study, a qualitative longitudinal study within the MVIP, indicate positive perceptions from healthcare workers that malaria vaccines can help reduce hospital consultations and admissions due to malaria, while noting concerns over increased workload at vaccination clinics.	Judgment options defined as: - "Intervention:" Malaria vaccination plus other malaria control interventions is an acceptable option - "Comparison" other malaria control interventions is only acceptable option - "Neither" intervention nor the control are acceptable - "Unclear" if either intervention or control are acceptable - Note: "Both" removed due to lack of clarity in meaning

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	Which option is acceptable to target group?	*Inter-vention* ☒ *Comparison* ☐ *Neither* ☐ *Unclear* ☐	R21/Matrix-M assumed to be acceptable to the target group due to: • Malaria was seen by the population as a significant health risk and the malaria vaccine, together with other malaria prevention measures, were seen as acceptable interventions (based on interviews with caregivers and health workers in the qualitative Health Utilization Study in MVIP). • The MVIP showed high uptake and good coverage at or exceeding expectations for a new vaccine – even during a global pandemic. Of note, there was no impact on the use of ITNs or overall health seeking behavior for febrile illnesses following malaria vaccine introduction. Trust in the vaccine was also high. • Parents reported, as part of the Health Utilization Study in the MVIP, that their vaccinated children became sick with malaria less frequently and less severely than their children who were not vaccinated. • No serious safety concerns have been noted; associated febrile convulsions resolved without sequelae • No important uncertainty or variability from the currently recommended malaria vaccine with regards to target population, schedule, benefits, harms, delivery strategy, etc.	Judgment options defined as: - "Intervention:" Malaria vaccination plus other malaria control interventions is an acceptable option - "Comparison" other malaria control interventions is only acceptable option - "Neither" intervention nor the control are acceptable - "Unclear" if either intervention or control are acceptable - Note: "Both" removed due to lack of clarity in meaning
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	R21/Matrix-M has not been implemented by national immunization programmes, however, it is considered feasible due to: • No important uncertainty or variability from the currently recommended malaria vaccine	

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			with regards to target population, schedule, benefits, harms, delivery strategy, etc. • As of August 2023, over 5.4 million malaria vaccine doses have been administered, and more than 1.8 million children have received dose 1 (over 650 000 children have received dose 4) through the national immunization programmes of Ghana, Kenya, and Malawi as part of phased introductions. Feasibility data generated during the MVIP with RTS,S/AS01 introduction and scale-up are encouraging (reasonably high coverage of doses 1—3 in relatively short period with lower uptake of dose 4); findings would likely be similar with the introduction of R21/Matrix-M. • The MVIP found no impact on the use of ITNs or overall health seeking behavior for febrile illnesses following malaria vaccine introduction. Malaria was seen by the population as a significant health risk and the malaria vaccine, together with other malaria prevention measures, were seen as acceptable interventions (based on interviews with caregivers and health workers in a qualitative study). • Strong thermostability of R21/Matrix-M (2 weeks at 24°C and 48°C and shelf-life of 24 months at 2-8°C) and ongoing evaluation of single-dose vial formulation. There is currently limited evidence on co-administration of R21/Matrix-M with other childhood vaccines. However, studies are ongoing	

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				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 Hib), rotavirus, pneumococcal, and oral polio vaccines.		
Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐		The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation			We recommend the comparison ☐	We recommend against the intervention and the comparison ☐

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
		☐ Only in specific contexts or specific (sub)populations		
	Recommendation (text)	**WHO recommends the programmatic use of malaria vaccines for the prevention of *P. falciparum* malaria in children living in malaria endemic areas, prioritizing areas of moderate and high transmission.** • The malaria vaccine should be provided in a schedule of 4 doses in children from around 5 months of age[6] for the reduction of malaria disease and burden. • A 5th dose, given one 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. • Countries may consider providing the vaccine using an age-based, seasonal, or a 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. 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. **Role of the malaria vaccine among other preventive measures** 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, insecticide resistance patterns) and contextual factors (e.g. structure and functioning of the formal health system). **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.		

[6] 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.

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		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.		

	Implementation considerations	• In areas of perennial malaria transmission, the vaccine should be provided as a three-dose primary series, starting from around 5 months of age[6], with a minimal 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 second year of life vaccines 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 routine 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 periodic intensification of routine immunization (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 routine 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		

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		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 routine childhood vaccines.[7] • 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.		
	Monitoring and evaluation	**High priority M&E recommendations** • Post-licensure monitoring of R21/Matrix-M safety in infants and young children, including the occurrence of febrile seizures and mortality. Monitoring mortality may be most easily achieved in areas where there is a demographic surveillance system in place. • 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 A 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 M&E recommendations**		

[7] 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.

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

	Research priorities	**High priority research recommendations**
		• 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.		