

WHO preferred product characteristics and clinical development considerations for malaria vaccines

Draft for public consultation

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Introduction and background

The World Health Organization aims to promote the development of vaccines with high public health impact and suitability for use in low- and middle-income countries (LMICs). To support this, Preferred Product Characteristics (PPCs) are technical documents describing WHO preferred attributes of products for licensure, policy, and programmatic implementation in LMIC settings. They address several product characteristics including indication, target population, safety and efficacy, formulation and presentation, dose regimen, co-administration, route of administration, product stability and storage, and access and affordability. These preferences are shaped by the unmet public health needs in priority disease areas as well as the realities of the disease epidemiology and delivery systems in the target geographies. This document outlines the preferred product characteristics of vaccines intended for use in malaria control.

The primary target audience for this malaria vaccine PPC is any entity involved in malaria vaccine development, especially those intending to seek a WHO policy recommendation and prequalification for their product. PPC documents are reviewed and, where necessary, revised approximately every 5 years to reflect changes in the scientific or technical feasibility of product development and the needs of the field. PPCs are intended to encourage innovation and development of vaccines that perform in settings most relevant to the global unmet public health need. In contrast to target product profiles (TPPs), which are often developed by product developers with a specific candidate in mind, PPCs provide guidance with a public health perspective, specifying preferred characteristics as opposed to the minimally acceptable criteria often found in TPPs.

Malaria vaccine PPCs have been developed to be aligned and complementary to overall preferred vaccine characteristics addressed in more detail by other WHO departments and processes, such as the WHO Vaccine Presentation and Packaging Advisory Group (VPPAG) and WHO Prequalification (PQ). VPPAG interacts with manufacturers on questions related to presentation and packaging and has developed a preferred product profile to address these areas.¹ WHO PQ also details their process for assessing vaccines via the Programmatic Suitability for Prequalification (PSPQ) criteria.² WHO encourages developers to consult these documents, alongside malaria PPCs, particularly if they intend to seek a WHO recommendation for use or prequalification of their products.

WHO strategic priorities for malaria vaccines

The last two decades have seen major reductions in malaria morbidity and mortality. Building on these achievements, the Global Technical Strategy (GTS) for Malaria 2016-2030, adopted by the World Health Assembly in 2015, set goals to reduce global malaria incidence and mortality rates by at least 90% by 2030.³ Additionally, a number of countries are currently targeting malaria elimination, and since 2017, the WHO E-2020 Initiative has supported 21 countries to achieve zero indigenous cases.⁴ While insecticides for vector control and medicines for infection cure and prevention are the mainstay of malaria control strategies, both are susceptible to biological resistance. These risks, coupled with recent trends indicating that progress in malaria control has stagnated,⁵ mean that reaching the GTS goals will be a major challenge. Recently, the Strategic Advisory Group on Malaria Eradication (SAGEme), which advises the WHO on the potential strategies, feasibility, and cost of eradicating malaria, concluded that eradication will not be possible by 2050 even with full-scale-up of current interventions.⁶ A number of current efforts aim to improve on malaria control and elimination strategies. In 2018, a targeted response was launched to address the 3.5 million more cases in the 10 highest burden countries in Africa recorded in 2017 compared to 2016.⁷ Nevertheless, future strategies to combat malaria will require an expanded and improved set of tools, including vaccines against *Plasmodium falciparum* (*P. falciparum*) and *Plasmodium vivax* (*P. vivax*) to complement the existing pipeline of malaria drugs, diagnostics, and vector control tools. The COVID-19 pandemic has re-emphasised the importance of vaccines in epidemic preparedness and response to infectious

diseases, as well as overall disease control and prevention. Additionally, in response to global trends in antimicrobial resistance (AMR), the WHO has underscored the unique role of vaccines in the battle against AMR by preventing infections and reducing reliance on antimicrobial use.⁸ The COVID-19 experience has provided lessons for the rapid development of vaccines, which can be applied to accelerate the development of vaccines for other infectious diseases including malaria.

The malaria vaccine PPCs are aligned to the strategic priorities of the WHO and partners. More specifically, the Malaria Vaccine Technology Roadmap encourages efforts to address the following unmet priority public health goals:

- **Strategic goal 1:** Malaria vaccines against clinical malaria, suitable for administration to appropriate at-risk groups in malaria-endemic areas.
- **Strategic goal 2:** Malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection.

This document presents Preferred Product Characteristics and clinical development considerations that correspond to these goals. There are multiple R&D pathways to achieve these strategic goals. Vaccines may be designed as standalone products to either reduce clinical malaria or transmission. However, the development path for the latter may be particularly challenging and both strategic goals could be achieved by a highly efficacious pre-erythrocytic vaccine or a disease-reducing vaccine combined with antigens which induce transmission-blocking immunity.

In 2015, RTS,S/AS01 was the first malaria vaccine to receive a positive scientific opinion from the European Medicines Agency (EMA)⁹ and over the past 20 years, new malaria vaccine trials have been registered at a rate of approximately 10 trials per year.¹⁰ The current pipeline includes two vaccines approaching phase 3 evaluation (R21 and PfSPZ), 10 candidates in phase 2 evaluation, 12 candidates in phase 1 evaluation and over 20 in pre-clinical development. Regularly updated information on the development pipeline for malaria vaccines is available on the WHO Global Observatory on Health R&D (https://www.who.int/research-observatory/monitoring/processes/health_products/en/).¹¹

The current pipeline reflects the dynamic landscape of malaria vaccines. As with the continually evolving nature of malaria epidemiology, the strategic priorities for malaria vaccine R&D will need to adapt to reflect the needs of malaria control programmes.

Any malaria vaccine that becomes licensed and potentially available will undergo evidence-based assessment for policy recommendations by the Strategic Advisory Group of Experts (SAGE) on Immunisation and the Malaria Policy Advisory Group (MPAG).

PREFERRED PRODUCT CHARACTERISTICS

The Preferred Product Characteristics (PPCs) presented here correspond to two strategic goals for malaria vaccines: reduction of malaria morbidity and mortality and reduction of malaria transmission. The clinical development pathways to achieve these goals may involve R&D for vaccines designed specifically to either reduce morbidity and mortality or to reduce transmission, or as combination vaccines designed to target both disease reduction and transmission reduction in a single product. The latter could be in the form a multi-stage vaccine targeting antigens at different stages of the parasite life cycle (e.g., pre-erythrocytic or blood stage combined with sexual or mosquito stage antigens). Vaccines that are highly efficacious in the pre-erythrocytic stage also have the potential to reduce transmission and accelerate progress towards elimination. Although the PPCs are described separately for each use case, it is feasible that a single vaccine may be designed to address both.

PPCs for vaccines to reduce malaria morbidity and mortality

Parameters	Preferred Product Characteristics	Notes
Indication for use	Reduction of morbidity and mortality due to <i>P. falciparum</i> and/or <i>P. vivax</i> malaria. Prevention of clinical malaria, including manifestations of severe malaria, caused by either <i>P. falciparum</i> and/or <i>P. vivax</i>	The vaccine would be indicated initially for malaria disease control rather than transmission reduction or elimination. (Vaccines also seeking indication for transmission reduction can refer to PPCs for vaccines to reduce malaria transmission on page 12.) See report section <i>WHO strategic priorities for malaria vaccines</i> (page 2)
Target population	Population subgroups that contribute substantially to disease burden. In most settings, this will focus on infants and young children aged 5 years and under but may include people aged over 5 years where substantial disease burden exists in this age group. Ongoing changes in malaria epidemiology should be considered, accounting for potential shifts in	Vaccines that are highly efficacious at preventing clinical malaria can be considered for use in other high-risk groups (depending on available efficacy and safety data in this population) such as: • Women of child-bearing age and pregnant women living in areas of malaria transmission • Non-immune individuals moving to become resident in malaria-endemic areas. Non-immune individuals who settle in endemic areas where significant malaria transmission is expected to continue are a high-risk group whatever their age.

	high-risk populations by the time vaccines become available.	• Non-immune individuals who are visiting or temporarily employed in malaria-endemic areas. Non-immune individuals who visit malaria-endemic areas for leisure or are temporarily employed in these areas (including seasonal workers, deployed international organization or military personnel) are also at risk. • Patients with HIV, sickle cell disease or other underlying conditions Special consideration may be given to groups known to be at increased risk of severe malaria or malaria-associated death, including: • People living in malaria endemic places with disrupted health services or in emergency situations, internally displaced populations or refugees • Individuals with increased occupational risk of malaria exposure (e.g., forest workers) • Mobile and migrant populations • Ethnic minorities or marginalised populations See report section <i>Vaccination strategies for malaria control and elimination: Target groups and immunisation strategies</i> (pages 22-24)
Safety	The safety and reactogenicity of the vaccine is comparable to or better than WHO recommended vaccines in use in low and middle-income countries. Unless the delivery strategy excludes the possibility that vaccines will be given concomitantly with other vaccines, absence of clinically important interference with other	In addition to assessing quality of the product, WHO prequalification and guideline development processes also include a risk-benefit assessment. Safety will be assessed in the context of data from malaria endemic settings. It is critical that clinical studies include high quality data on safety in the relevant populations and age groups for which the vaccine is intended. Reporting should be according to international standards and accepted case definitions. Greater standardisation of data collection and reporting of safety and reactogenicity data in pre-

	childhood or EPI vaccines will have to be documented. Safety should also be demonstrated in high-risk or immunocompromised groups, such as HIV-infected children or adults. Studies should include plans for assessment of possible deferred increases in morbidity associated with rebound phenomenon (due to dynamics of waning vaccine-induced immunity and reduction in naturally acquired immunity).	licensure clinical trials is strongly encouraged (e.g., based on Brighton Collaboration benefit-risk assessment templates, Council for International Organizations of Medical Sciences (CIOMS) guides on vaccine safety surveillance). Vaccine developers and financing agencies are referred to the Global Vaccine Safety Initiative (GVSI). Pharmacovigilance systems strengthening is a high priority as outlined in the GVSI and consideration of safety data generation as part of phase 4 studies and pharmacovigilance systems is strongly encouraged. See report section <i>Clinical development pathways and evaluation tools: Safety considerations</i> (page 42)
Efficacy and duration	The vaccine should reduce the incidence of all clinical malaria episodes. A rational target level of efficacy should be justified in conjunction with targets for the duration of protection, variation of efficacy over time and other key drivers of public health impact in the primary target group. Thus, the initial efficacy and long-term dynamics of protection will be considered together.	Clinical data should allow assessment of the requirement for timing and effect of additional doses. The public health impact, in terms of cases averted or vaccine preventable disease incidence (VPDI), will be an important element in the public health assessment, estimated using a combination of baseline incidence of disease and vaccine efficacy dynamics.¹² Vaccine impact informed by estimates of VPDI or cases averted in a range of transmission intensities will help determine locally acceptable efficacy thresholds for efficacy and anticipated cost-effectiveness for malaria control programmes. Description of methods for ascertaining endpoints via active or passive case detection should be included, accounting for health systems factors that may affect detection between studies or sites (e.g., frequency of follow-up, variations in health seeking behaviour etc). While active detection is useful for measuring infection endpoints, passive case detection is preferred in phase 3 trials to determine public health impact on burden reduction in health facilities.

		Assessment of more severe endpoints, including severe malaria, malaria-related hospitalisations and mortality, and all-cause mortality that may be difficult to measure with precision in phase 3 trials and may be more suitable for evaluation in post-licensure or phase 4 studies. See report section <i>Clinical development pathways and evaluation tools</i> ▪ <i>Clinical development</i> (pages 36-37) ▪ <i>Endpoints, case definitions, and analytical strategies in late-stage clinical development</i> (pages 37-39) ▪ <i>Trial design considerations</i> (pages 39-42) ▪ <i>From vaccine efficacy to public health impact</i> (pages 42-44)
Dose regimen and schedule	Ideally, a single dose for primary immunisation, but additional doses (including annual doses) could be acceptable for strong and/or long-lasting immunity. Deviations from characteristics suggested by Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Working Group will result in referral to the PSPQ Standing Committee for review, discussion, and recommendation.	Multiple doses might be acceptable for primary immunisation. Research should determine the requirements for primary dosing regimens and the value of booster doses. If more than one dose is needed, aligning the dose schedule with existing delivery platforms is preferable. For vaccines presented for WHO Prequalification, the following schedules are deemed to meet the WHO Prequalification critical characteristic definition for dosing: ▪ Proposed vaccine is meant for use in children under five and is recommended to be given at one for more of the following immunisation visits: ○ Within 24 hours after birth ○ At not more than three visits, 4 to 8 weeks apart, with the first visit at or after 6 weeks of age and the third visit at or before 6 months of age ○ At not more than two visits between 9 and 12 months of age

		○ At not more than two visits between 12 and 24 months of age ○ At not more than one visit in the fifth year of life ▪ Proposed vaccine is designed to be given to adolescents aged 9 to 15 years, and requires no more than four contacts through health service or school-based immunisation programmes ▪ Proposed vaccine is given as a single dose and designed to be given exclusively in reactive campaigns (pandemics, disasters, humanitarian emergency action) ▪ Proposed vaccine is targeted at individuals over 5 years of age, and the dose intervals are two weeks or more apart If the vaccine does not fit into one of the above dosing criteria, it will be reviewed by the PSPQ Standing Committee. See report sections: ▪ <i>Clinical development pathways and evaluation tools: From vaccine efficacy to public health impact</i> (page 42-44) ▪ <i>WHO Prequalification</i> (page 44) ▪ <i>Programmatic suitability</i> (pages 44-45)
Co-administration	Immunogenicity data are required if vaccination against malaria is to be combined with vaccination against other pathogens. Such data should provide confidence that immunogenicity and safety of both the malaria and non-malaria vaccines are maintained in co-administration and there is absence of clinically relevant interference.	It may not be feasible to study every vaccine combination that could be co-administered. Choice of vaccines for co-administration studies should be driven by the vaccines in use at the intended target age group in the target populations. If drug prophylaxis is routinely administered in any target population (including seasonal malaria chemoprevention or mass drug administration), clinically relevant interference between the vaccine and drug(s) should be evaluated. If necessary, further co-administration studies could be performed in parallel or following completion of phase 3 efficacy studies. The

		principles of the design of these studies are discussed in WHO Guidelines on clinical evaluation of vaccines: regulatory expectations. Manufacturers may be requested to design, collect and analyse data on co-administration of vaccines commonly used in routine immunisation schedules, catch up schedules, or to protect against outbreak-prone vaccine-preventable diseases (e.g., influenza, measles). Manufacturers are encouraged to provide post-marketing data on co-administration. See report section <i>Clinical development pathways and evaluation tools: Safety considerations</i> (page 42)
Formulation/presentation	Vaccines seeking WHO Prequalification should meet WHO defined criteria for programmatic suitability regarding formulation, presentation, packaging, and disposal.² Deviations from characteristics suggested by Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Working Group will result in referral to the PSPQ Standing Committee for review, discussion, and recommendation.	As suggested by the Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Working Group, vaccines presented for prequalification that are injectable and indicated for infants and/or young children (<5 years old) should not be more than 1 ml per dose.² Vaccines presented for prequalification that are injectable, in ready to use (no reconstitution) presentation and are in multi-dose containers of more than two doses per vial, should be adequately preserved, defined as having either a standard thiomersal concentration or the preservative has demonstrated its anti-microbial efficacy to control for contamination for 28 days using a multi-challenge test as described in the European Pharmacopoeia. See report sections <i>WHO Prequalification</i> (page 44) and <i>Programmatic Suitability</i> (pages 44-45)
Route of administration	Vaccines seeking WHO Prequalification should not require an intravenous route of administration,² as suggested by the	Depending on the data and efficacy evidence for the vaccine, benefits will be weighed against risks. Deviations from characteristics suggested by Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Working Group will result in referral to the PSPQ Standing

	Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Working Group	Committee for review and discussion, including whether issues can be mitigated (e.g., appropriate health worker training for intravenous administration).
Product stability and storage	Vaccines or any component presented for WHO Prequalification should not require storage at less than -20°C, ² as suggested by the Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Working Group	Depending on the data and efficacy evidence for the vaccine, benefits will be weighed against risks. Deviations from characteristics suggested by Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Working Group will result in referral to the PSPQ Standing Committee for review and discussion, including whether issues can be mitigated (e.g., appropriate management of ultra-cold chain).
Programmatic suitability	The WHO defined criteria for programmatic suitability of vaccines¹³ should be met, following guidance on vaccine presentation, packaging, thermostability, formulation, and disposal.¹ The vaccine should be prequalified to support purchasing by United Nations agencies.¹⁴ Vaccines presented for WHO prequalification will be assessed for programmatic suitability according to mandatory, critical, unique or innovative, and preferred characteristics.² The vaccine should be prequalified according to the process outlined in <i>Procedures for assessing the acceptability, in principle, or vaccines for purchase by the United Nations agencies</i> (WHO/BS/10.2155). Depending on the data and efficacy evidence for the vaccine, benefits will be weighed against risks. Deviations from characteristics suggested by Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ)	As outlined in <i>Assessing the programmatic suitability of vaccine candidates for WHO prequalification (2015)</i>:² Mandatory characteristics include anti-microbial preservatives for injectable vaccines, thermostability/storage, dose volume, and route of administration. Critical characteristics include vaccination visits, process of preparation for administration, thermostability/storage, use of vaccine vial monitors, materials, primary and secondary packaging, injection material, pre-filled injection devices, dose volume, and anti-microbial preservatives. Additionally, WHO Prequalification indicates a list of preferred characteristics for programmatic suitability. These do not directly influence the prequalification process, but national immunisation programmes and procuring agencies are likely to select vaccines with these characteristics, all other aspects being equal. These include: • Antigenic stability after reconstitution • Adequate use of antimicrobial preservatives

	Working Group will result in referral to the PSPQ Standing Committee for review, discussion, and recommendation.	• Smaller packed volumes (see Guidelines on the international packaging and shipping of vaccines¹⁵) • Smaller and standardised dose volumes for oral vaccines • Doses per primary container for non-campaign settings: ○ Vials with <10 doses per vial (WHO EPI, VPPAG gPPP: optimal number of doses per primary container, work programme) ○ Minimal number of doses per vial that cannot be reused in subsequent sessions once container is open • Doses per primary container for campaign settings: ○ Vials with >10 doses per vial are preferred • Doses per secondary container should reflect logistics schedule and needs in order to minimise stock accumulation at the peripheral level See report sections: ▪ <i>Clinical development pathways and evaluation tools: From vaccine efficacy to public health impact</i> (pages 42-44) ▪ <i>WHO Prequalification</i> (page 44) ▪ <i>Programmatic suitability</i> (pages 44-45)
Access and affordability	Dosage, regimen, and cost of goods should enable affordable supply. Favourable cost-effectiveness should be established and price should not be a barrier to access, including in low- and middle-income countries.	The vaccine impact on health systems (such as reduction in malaria-related medical attendance and hospitalisation) and other aspects of implementation science should be evaluated in both modelling and real vaccine use studies. See report section <i>Access and affordability</i> (pages 45-47)

PPCs for vaccines to reduce malaria transmission

Parameters	Preferred Product Characteristics	Notes
Indication for use	Prevention of malaria transmission through a mosquito vector at the community level. The vaccine may be indicated for malaria control, elimination and/or prevention of re-introduction post-elimination, depending on the clinical data submitted, and may have application in low, moderate, and high transmission settings.	Vaccines interrupting transmission may be suitable for administration in mass campaigns to all ages or targeted age groups and populations. The frequency of periodic mass preventive campaigns will depend on the duration of protection and population birth and in-migration rates. For vaccines with long-lasting efficacy, introduction of routine vaccination in infants, young children, or other relevant age groups may also be appropriate. Immunisation strategies may be influenced by factors such as malaria transmission intensity, seasonality patterns, species composition, other malaria interventions in use, and duration of protection. See report section <i>WHO strategic priorities for malaria vaccines</i> (page 2)
Target population	Children and adults, including women of child-bearing age Ongoing changes in malaria epidemiology should be considered, accounting for potential shifts in high-risk populations by the time vaccines become available.	The infectious reservoir for transmission of malaria to <i>Anopheline</i> mosquitoes in malaria endemic areas extends from infancy through childhood to adults. While the per person infectivity is highest in young children, older children and adults remain infectious to mosquitoes, and, given the number of people in these age groups, represent a major contributor to transmission from humans to mosquitoes. The optimal ages for inclusion in mass campaigns may differ between geographical locations and can be adjusted to reflect local epidemiology. See report section <i>Vaccination strategies for malaria control and elimination: Target groups and immunisation strategies</i> (pages 22-24)

Safety	The safety and reactogenicity of the vaccine are comparable to or better than WHO recommended vaccines in use in low and middle-income countries. The individual-level risk/benefit assessment for transmission-reducing vaccines may differ from that of disease-reducing vaccines if there is no direct effect on either infection or disease for the individual recipient. Studies should include plans for assessment of possible deferred increases in morbidity associated with rebound phenomenon (due to the dynamics of waning vaccine-induced immunity and reductions in naturally acquired immunity).	Same as vaccines to reduce morbidity and mortality See report section <i>Clinical development pathways and evaluation tools: Safety considerations</i> (page 42)
Efficacy and duration	The vaccine should reduce malaria transmission, resulting in the reduction of incident human malaria infections at the community level.	Transmission reduction effect will be influenced by the efficacy of the product, vaccination coverage achieved in the infectious reservoir, and duration of protection. The efficacy against infection or clinical malaria measured in clinical trials may be dependent on the baseline transmission intensity because of the non-linear relationship between malaria transmission and the incidence of clinical malaria. The duration of efficacy is as important as the level of efficacy. Thus, the initial efficacy and duration of protection will be considered together. Minimum acceptable thresholds for efficacy, duration, and coverage can be informed by malaria vaccine impact modelling. Clinical data should allow assessment of the requirement for and timing of booster doses. The public health impact, particularly the potential for elimination, will be an important element in the WHO assessment. It is advisable to consult with WHO prior to finalisation of key clinical proof-of-concept and pivotal studies in this area.

		See report section <i>Clinical development pathways and evaluation tools</i> ▪ <i>Clinical development</i> (pages 36-37) ▪ <i>Endpoints, case definitions, and analytical strategies in late-stage clinical development</i> (pages 37-39) ▪ <i>Trial design considerations</i> (pages 39-42) ▪ <i>From vaccine efficacy to public health impact</i> (pages 42-44)
Dose regimen and schedule	Minimum number of doses to enable high coverage	Given the particular importance of achieving very high coverage, single dose regimens are preferred. See report section <i>Clinical development pathways and evaluation tools: From vaccine efficacy to public health impact</i> (pages 42-44)
Co-administration	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Formulation/presentation	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Route of administration	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Product stability and storage	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Programmatic suitability	Same as vaccines to reduce morbidity and mortality	For vaccines used in mass campaigns or outside routine immunisation schedules, the ability to administer and store a large number of vaccines without access to powered cold chain will be important. The acceptability of multi-dose vials for administration outside of vaccination clinics, which can reduce transport and cold chain costs, may be an important consideration. Cost of administration for transmission blocking vaccines may potentially be much higher than vaccines for clinical malaria if targeting a wider population. See report sections:

		▪ <i>Clinical development pathways and evaluation tools: From vaccine efficacy to public health impact</i> (page 42-44) ▪ <i>WHO Prequalification</i> (page 44) ▪ <i>Programmatic suitability</i> (pages 44-45)
Access and affordability	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality

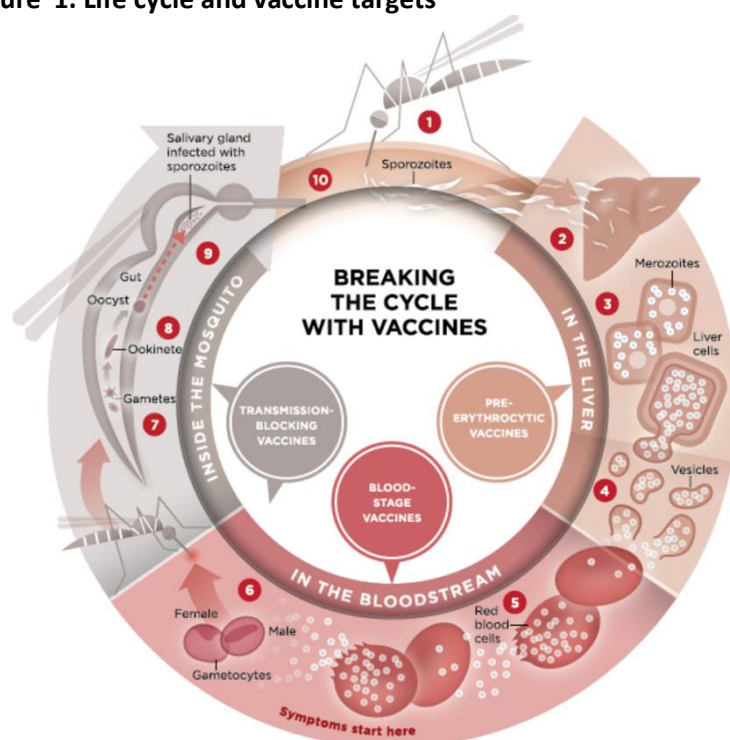
CLINICAL DEVELOPMENT CONSIDERATIONS

Vaccine development strategies and tools

The malaria parasite life cycle and vaccine design

The developmental complexity of the malaria parasite has strong implications for vaccine design and the evaluation of vaccine efficacy. Pre-erythrocytic vaccines target sporozoite or liver stage antigens with the aim to inhibit early parasite development, replication, and survival. Functionally, pre-erythrocytic vaccines elicit antibody responses to either clear sporozoites from the skin or bloodstream (Figure 1, 1-2), block sporozoite invasion of hepatocytes (Figure 1, 3), or generate T-cell responses against the liver stage to kill infected hepatocytes (Figure 1, 4). Blood stage vaccines have multiple strategies (Figure 1, 5), including the prevention of merozoite entry into erythrocytes, prevention of adhesion of parasitised erythrocytes, and the inhibition of parasite replication or survival. This ultimately reduces the blood stage parasite load and inhibits pathogenesis i.e., reduced fever and severe malaria complications. Vaccines interrupting malaria transmission (VIMTs) can include highly efficacious pre-erythrocytic vaccines that have an indirect effect on transmission or more “classical” transmission blocking vaccines, which prevent human-to-mosquito transmission by specifically targeting the sexual, sporogonic, or mosquito stage (SSM-VIMTs). SSM-VIMTs aim to directly eliminate sexual stage gametocytes in humans (Figure 1, 6) or block subsequent parasite development in the mosquito (Figure 1, 7-9). This functionality is measured by quantifying the presence of parasites in the mosquito midgut or salivary glands. SSM-VIMTs would not directly prevent malaria infection in the immunised individual. However, by reducing the number of mosquitoes carrying the parasite, SSM-VIMTs would indirectly reduce the number of infected individuals in the community (Figure 1, 10). Finally, while vaccines that protect the general population may also benefit pregnant women, vaccines have also been developed that target chondroitin sulfate A (CSA) binding parasites that lead to sequestration of parasitised erythrocytes in the placenta. Natural antibodies to CSA-binding parasites, often acquired over successive pregnancies amongst women in endemic areas, have been associated with protection against placenta malaria.

Figure 1. Life cycle and vaccine targets



A number of different vaccine types have been designed and tested for malaria. Subunit and viral vector vaccines contain or encode for selected fragments of the pathogen as antigens instead of the whole pathogen. Antigenic proteins can be purified from preparations of the whole pathogen or produced by recombinant genetic engineering. RTS,S is a prime example, where a recombinant protein based on the fusion of the *P. falciparum* surface protein gene and the hepatitis B surface antigen (HBsAg) is expressed in yeast and forms virus like particles (VLPs) that induce an immune response. Live-attenuated vaccines are based on whole pathogens, which are weakened, altered or selected to be less pathogenic than the wild-type pathogen. Inactivated vaccines based on whole pathogens use heat, radiation or chemical methods to destroy a pathogen's ability to cause disease but still maintain its immunogenicity. More recently, genetically attenuated malaria parasites have also been developed as vaccines using whole sporozoites. Notably, the ability to isolate purified, aseptic and cryopreserved radiation attenuated sporozoites has allowed for field studies of this vaccine candidate. Generating strong T-cell responses with subunit vaccines can require different immunisation platforms, and viral vectors have been used to address this for malaria. DNA or RNA vaccines, which inject DNA or RNA encoding antigenic components of target pathogen proteins into host cells, aim to provide a stable and long-lived source of the protein that can induce antibody and cell-mediated immune responses to a variety of antigens. DNA vaccines with genes encoding different malaria antigen components have been developed, with a number of candidates evaluated in field trials, while RNA vaccines are in early-stage R&D.

Multi-component vaccines. One challenge in developing single target malaria vaccines is the wide array of antigens across the parasite life cycle (all eliciting varying degrees of immunogenicity) and the high levels of parasite genetic diversity that may lead to variant-specific immunity. Antigenic diversity is one reason immunity against malaria is acquired slowly and almost never complete. In the case of SSM-VIMTs, achieving a sustained high-level of antibodies over time and adequate coverage to reach herd immunity are particular challenges. The promise of poly-valent vaccines directed at several stages of the parasite life cycle or multiple *Plasmodium* species has been discussed, with the potential for additive or synergistic improvements in protective efficacy compared to single target vaccines. For instance, mosquito/sexual stage targets could be combined with pre-erythrocytic vaccines to prevent infection in humans and transmission to mosquitoes, or with blood-stage vaccines to reduce disease and transmission. Alternatively, multiple single-target vaccines could be implemented in combination. Multi-component vaccines will need to consider the most appropriate clinical development pathway, informed by regulatory requirements on which R&D stages are appropriate for evaluation of components independently or in combination.

Preclinical development, proof-of-concept, and evaluation technologies

Since 2010, more than 100 phase 1-3 malaria vaccine trials have been conducted, of which over 90% have targeted *P. falciparum*.¹⁰ The dynamics of malaria infection throughout the parasite life cycle presents challenges for evaluating vaccine efficacy. Protective immunity has been found to be associated with a wide range of variables, including human host characteristics (genetics, age, gender, co-infections), parasite and mosquito factors (strain multiplicity, transmission intensity), selection of target antigens, vaccine platforms (recombinant proteins, whole organisms, viral vectors), vaccine regimen (prime boost, delayed or fractional dose), as well as experimental conditions. However, there are still no agreed correlates of protective immunity against malaria. Due to the distinct localisation of life cycle stages, immune responses may be organ specific. For example, measuring immune responses in the peripheral blood may correlate poorly with critical cellular responses in the liver. Additionally, there is still limited understanding of how the pre-vaccination immune status of naturally exposed individuals in endemic settings affects vaccine efficacy. A variety of baseline immune functions have been associated with either increased or decreased efficacy in both RTS,S and PfSPZ trials, but results are not yet consistent.

An array of functional assays is currently used at multiple R&D stages to confirm the mechanism and level of protection conferred by vaccine candidates (Table 1). This ranges from measures of sporozoite

mobility and hepatocyte invasion in the pre-erythrocytic stages, to growth inhibition assays (GIA) or measures of complement fixation of phagocytosis for blood stage vaccines, and binding inhibition assays for placenta malaria vaccines. Despite differences in the pathogenic mechanisms leading to death from malaria between mice or non-human primates and humans, *in vivo* assays in animal models of malaria infection to measure protective efficacy against death, or decreases in peak or total parasitaemia, have been used and will continue to be useful.

For SSM-VIMTs, efforts have been made to standardise membrane feeding assays to compare results between studies and sites. These assays measure gametocyte infectivity in mosquitoes feeding on human blood meals containing gametocytes. Standard Membrane Feeding Assays (SMFAs), using cultured gametocytes, are considered the gold standard. By contrast, Direct Membrane Feeding Assays (DMFAs) use whole blood from naturally infected individuals, while Direct Skin Feeding Assays (DSFAs) place laboratory-reared mosquitoes directly on the skin. When gametocytes are combined with whole plasma/serum or purified IgG from test and control samples, these assays can assess the ability of antibodies to inhibit oocyst development in the mosquito. However, there is still a large gap to bridge results to field studies as these assays may not accurately replicate natural mosquito biting and transmission conditions. Studies are also underway to better quantify the association between antibody levels and reductions in human-to-mosquito gametocyte transmission.

For all life cycle stages, the diversity of assays and efficacy endpoints across trials has been a major obstacle in identifying robust correlates of protection; the harmonisation of their use can help improve quantitative vaccine assessment.

Table 1. Functional assays by malaria life cycle stage

Life cycle stage	Assays
Animal models	▪ Murine models, infection with <i>P. berghei</i>, <i>P. chabaudi</i>, <i>P. yoelii</i>, <i>P. vinckei</i> ▪ Humanised mouse models containing human hepatocytes, infection with <i>P. falciparum</i> and <i>P. vivax</i> ▪ Non-human primate models, (<i>Aotus</i>, <i>Saimiri</i>, and <i>Macaca mulatta</i> species for infection with <i>P. falciparum</i>, <i>P. vivax</i> and <i>P. malariae</i>, rhesus monkeys for infection with <i>P. knowlesi</i>, <i>P. simiovale</i>, <i>P. cynomolgi</i>)
Pre-erythrocytic	▪ Inhibition of sporozoite (spz) gliding ▪ Inhibition of hepatocyte traversal by spz ▪ Inhibition of hepatocyte invasion by spz (ISI) ▪ Inhibition of liver-stage development (ILSDA) ▪ Complement fixation on spz (with or without lysis), or with recombinant spz antigens ▪ Opsonic phagocytosis of spz, or spz antigen-coated beads
Blood stage	▪ Asexual growth inhibition assay (GIA) ▪ Complement fixation on merozoites or parasitised red blood cells (pRBCs) (with or without lysis) ▪ Opsonic phagocytosis of merozoites or pRBCs ▪ Antibody-dependent cellular inhibition (ADCI) ▪ Antibody-dependent respiratory burst (ADRB) ▪ Prevention of schizont egress ▪ Inhibition of tissue receptor binding (e.g., chondroitin sulfate A (CSA))
Sexual stage	▪ Direct skin feeding (DSFA) ▪ Direct membrane feeding (DMFA) ▪ Standard membrane feeding (SMFA)

*Adapted from Staniscic and McCall (2021)¹⁶

Controlled human malaria infection

Controlled human malaria infection (CHMI) studies have been used to understand the mechanisms of protective immunity and to search for immune correlates of protection.¹⁷ Through controlled timing and dosing, CHMI studies can more precisely investigate associations between exposure, immune response, and protection. For logistical reasons, CHMIs have historically been performed in malaria-naïve populations, but studies are increasingly being done in malaria-endemic countries. Investigating mechanisms of protection in individuals with naturally-acquired immunity in field conditions will be particularly important to understand the effect of prior and frequent malaria exposure on the dynamics of immune response.¹⁸

CHMI studies have been used to inform vaccine formulation, dose, route, schedule, and other aspects of clinical development. The most established CHMI models involve exposing study participants to the bites of *Plasmodium*-infected mosquitoes raised in insectaries. A number of other CHMI models are in development. Direct venous infection (DVI) of *P. falciparum* sporozoites has been used with a view to improve standardisation of the assay and allow more precise dosing of infectious load. However, bypassing the skin may circumvent an important component in the development of immunity. Intradermal and intramuscular injection of sporozoites is also feasible but may be complicated by variation in the number of sporozoites required, infection rates, and time to patent infection.

Blood stage CHMI, which does not require entomology facilities and is more specific than sporozoite challenge in assessing parasite multiplication rate for proof-of-concept, has been used for phase 2 evaluation of *P. falciparum* blood stage vaccine candidates.^{19–21} A number of *P. vivax* blood stage CHMI studies have also been conducted²² as proof-of-concept²³ and to assess human-to-mosquito transmission in direct and membrane feeding assays.²⁴ *P. vivax* CHMI using mosquito bite inoculation faces limitations due to the lack of continuous *in vitro* culture systems for *P. vivax*, requiring fresh gametocytes from naturally infected donors to produce sporozoite-infected mosquitoes. Adapted CHMI transmission models for evaluation of sexual stage candidates have been developed,^{25,26} with the aim to induce gametocytaemia and assess gametocyte transmission to mosquitoes via feeding assays. These CHMI models can help bridge between standard membrane feeding assays and field studies to support the assessment of vaccine efficacy, with potentially more efficient evaluation of sexual stage vaccine candidates in particular.

The availability of CHMI models for malaria research is hugely advantageous, allowing controlled exposure in efficacy trials of candidate vaccines using smaller sample sizes and shorter timeframes than feasible under conditions of natural exposure. However, studies so far have failed to show consistent immunological correlates of vaccine-induced protection in CHMI and against naturally acquired infections as identified in field trials.

Parasite strains for homologous and heterologous CHMI challenge. A major challenge for malaria vaccine candidates in both CHMI and field studies will be the ability to induce strain-transcending protective efficacy. In RTS,S phase 3 trials, protective efficacy was found to be greater against *P. falciparum* infections with a circumsporozoite protein genotype matching the vaccine strain, arising from the allele-specific nature of vaccine-induced immune response.²⁷ Therefore, the use of well defined, genetically distinct parasite strains for heterologous malaria challenge in CHMI studies will be valuable in evaluating vaccine candidates against a diverse range of parasite strains and optimising vaccine formulation prior to field trials.

There are currently only a limited number of defined *P. falciparum* strains available for use in CHMI (NF54, West African; 3D7, clonal line derived from NF54; 7G8, clonal line of Brazilian IMTM22 isolate; NF135.C1, clone derived from Cambodian isolate; HMP02, Ghana, blood stage challenge only),¹⁷ with even fewer available for *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. However, it is unclear how representative these strains are of the antigenic diversity in malaria endemic areas. Future CHMI studies would benefit from improved characterisation and development of additional parasite strains which can consistently produce gametocytes and sporozoites, be cloned to produce a genetically

homogenous parasite population, are sensitive to commonly used antimalarials, and are genetically and geographically distinct from NF54. However, not all *P. falciparum* isolates are easily culture adapted, and for some non-*falciparum* species, it is challenging to develop the large-scale culture required to manufacture blood-stage parasite banks.

Given currently available options, interpretation of data from CHMI and generalisability of efficacy to field conditions will need to take into account not only whether homologous or heterologous challenge is used, but whether strains used in heterologous challenge are representative of the parasite diversity expected in settings where vaccines are intended for use. Furthermore, caution should be taken when comparing results between studies when target populations and follow-up times differ. Standardisation of follow-up times used in CHMI vaccine studies can improve comparability between study results.

Systems vaccinology. While a number of malaria studies have identified antibody, cell-mediated and functional correlates of protection, these appear to differ by vaccine type. Novel data science approaches in systems biology and vaccinology are now being used to better understand the immune response to vaccination for pathogens such as influenza²⁸ and may have application in malaria. By collating and analysing large-scale cohort data, these computational methods study associations between molecular or gene expression signatures in the population and antibody responses (or other mechanisms of immune protection), which can help inform future vaccine design. Several studies have recently used these approaches to investigate immunological correlates of malaria infection and vaccination.^{29,30}

Monoclonal antibodies. Other tools being used to assist in the preclinical characterisation of the human antibody response to vaccines and parasite infection are monoclonal antibodies (mAbs). By identifying key mAbs and their binding targets, the most potent epitopes can be displayed on the surface of a vaccine construct and used to induce a human antibody response. mAbs are also being used in clinical trials to help define efficacious antibody thresholds for vaccine development.

In addition to their application in vaccine design, mAbs with suitable pharmacokinetics and pharmacodynamics may have the potential for use as a preventive intervention.³¹ Improvements in production and manufacturing have reduced some cost barriers for the prophylactic use of mAbs. Additionally, compared to small molecule development, antibodies may be less prone to off-target safety and toxicity issues and thus, may offer advantages when deployed in vulnerable populations such as pregnant women or immunocompromised individuals. As with vaccines, deployment of mAbs as an intervention will need to demonstrate safety and durable protection, and consider factors related to manufacturing capacity, formulation, cost of goods, route of administration and programmatic suitability. A standalone PPC for mAbs will be available in a separate document.

Adjuvants and vaccine delivery platforms. To date, most malaria vaccines in development based on malaria protein subunits have elicited limited immunogenicity. Suitable adjuvants and delivery platforms are needed to achieve sufficient immune responses for protection from infection and disease. Facilitating access to adjuvants currently in development and ensuring downstream availability and affordability will be a critical component in the advancement of new vaccines.

Recent years have seen increased investment in adjuvant development. The US National Institute of Allergy and Infectious Diseases (NIAID) 2018 Strategic Plan for Vaccine Adjuvant Research encompasses a range of R&D areas, from fundamental immunology and adjuvant discovery to preclinical and clinical adjuvant development and evaluation.³² This has led to a number of funding opportunities, including research on adjuvant comparison and characterisation³³, molecular mechanisms of combination adjuvants (MMCA),³⁴ production of adjuvant mimics,³⁵ and adjuvant development for vaccines.³⁶ The Vaccine Adjuvant Compendium (VAC) was also established by NIAID in 2020 to foster collaborations between NIAID-supported adjuvant researchers and the broader scientific community. VAC displays adjuvant characteristics and meta data to help vaccine developers identify suitable adjuvants for various vaccine indications (<https://vac.niaid.nih.gov/>).³⁷ Similarly, the Vaccine Formulation Institute (VFI) also provides a range of adjuvants, technology, and expertise to

support the optimisation of vaccines in pre-clinical and clinical settings (<https://www.vaccineformulationinstitute.org/>).

In the area of vaccine delivery platforms, virus like particles and vesicle-based technologies have been tested, as well as mixed-modality prime-boost immunisation regimens using vectored and protein-based components to maximise cellular and humoral immune responses.³⁸

Mathematical modelling. From the experience of RTS,S, mathematical models can support the development of impact projections and cost-effectiveness estimates, supporting decisions and investment planning for product developers, WHO, Gavi, and other partners. For example, an ensemble of models provided economic impact estimates using assumptions informed by phase 3 trial data, concluding that RTS,S/AS01 could achieve significant public health impact and is highly cost-effective across a range of epidemiological settings. In the future, modelling can inform preferred product characteristics for vaccines with regard to minimum thresholds for vaccine efficacy, duration of protection, timing of immunisation and target populations to achieve public health impact. These can be used to support decision making when appropriately formulated and informed by reasonable parameter estimates, and country estimates of health and budget impact.

Malaria vaccine pipeline: status as of April 2021

RTS,S/AS01 pilot implementation and additional studies

In July 2015, RTS,S/AS01 was the first malaria vaccine to receive a positive scientific opinion from the European Medicines Agency (EMA).⁹ Subsequently, in order to inform policy on the wider use of RTS,S/AS01, and on the advice of the WHO Strategic Advisory Group of Experts (SAGE) on Immunisation and the Malaria Policy Advisory Committee (MPAC), WHO recommended pilot implementation in moderate-to-high malaria transmission settings in sub-Saharan Africa.³⁹ A 4-dose schedule of RTS,S/AS01 vaccine was recommended in children from 5 months of age, with the first 3 doses given a minimum of 4 weeks apart and the 4th dose provided approximately 15-18 months after dose 3.^{40,41} This recommendation was based, in large part, on results from a large phase 3 clinical trial conducted at 11 sites in 7 African countries, which included a follow-up period of approximately 3-4 years, depending on age-category.⁴² Extended follow-up in three of the phase 3 trial sites later confirmed significant vaccine efficacy against clinical malaria during the full 7 years of follow-up in children receiving both 3 or 4 vaccine doses.⁴³

The Malaria Vaccine Implementation Programme (MVIP) was developed to respond to the SAGE/MPAC recommendation through a phased introduction of RTS,S/AS01 through the Expanded Programme on Immunisation (EPI)⁴⁴. Vaccinations began in 2019 in Malawi, Ghana, and Kenya.^{44,45} In parallel, phase 4 studies were implemented by GlaxoSmithKline as part of their risk management plan and post-authorisation evaluation programme.⁴⁶ Administration as a fractional dose has been evaluated in children in endemic settings (NCT03276962),⁴⁷ and a comparative field trial of seasonal vaccination of RTS,S/AS01 with or without seasonal malaria chemoprevention (SMC) has been conducted in Burkina Faso and Mali (NCT03143218).⁴⁸

Clinical development

Over the past 20 years, new malaria vaccine trials have been registered at a rate of approximately 10 trials per year.¹⁰ As of early 2021, several pre-erythrocytic candidates in development are approaching phase 3 evaluation.¹ These include PfSPZ Vaccine, a pre-erythrocytic radiation attenuated vaccine platform using aseptic, purified, vialled, cryopreserved *P. falciparum* sporozoites (NCT03521973, NCT03503058)^{49,50}, and the R21 anti-sporozoite subunit candidate vaccine (NCT04704830, NCT03580824)⁵¹⁻⁵³ targeting the same circumsporozoite protein antigen (CS) as RTS,S, but with

ⁱ Regularly updated information on the development pipeline for malaria vaccines is available on the WHO Global Observatory on Health R&D (https://www.who.int/research-observatory/monitoring/processes/health_products/en/).¹¹

enhanced efficacy related to different immunogenic properties⁵⁴ and combined with Matrix-M adjuvant technology.⁵⁵ Blood-stage vaccine candidates in earlier stage development target infected red blood cells (RBCs) or merozoites and include *P. falciparum* reticulocyte-binding protein homologue 5 (Rh5) (NCT04318002)^{56,57} and SE36, a single recombinant protein based vaccine candidate targeting the *P. falciparum* serine repeat antigen 5 (SERA5).⁵⁸ SSM-VIMT candidates include pre-fertilisation antigens, Pfs230 (NCT03917654⁵⁹) and Pfs48/45⁶⁰, and post-fertilisation antigens, Pfs25 (NCT04271306)⁶¹ and Pfs28.^{62,63}

Malaria in pregnancy is associated with sequestration of *P. falciparum* infected erythrocytes that bind to chondroitin sulfate A (CSA) in the placenta via the VAR2CSA protein. There are currently two VAR2CSA antigen-based candidate vaccines in phase 1 trials, PRIMVAC (NCT02658253)⁶⁴ and PAMVAC (NCT02647489)⁶⁵. Additionally, any vaccines that can prevent *P. falciparum* infection that can be delivered safely to women of childbearing age or early in pregnancy have the potential to reduce the burden of malaria in pregnancy.

In regions where both *P. falciparum* and *P. vivax* are prevalent, vaccines targeting both species are highly desirable. In 2019, the global burden of *P. vivax* stood at 6.9 million cases⁵ and standard malaria control measures are less effective against *P. vivax* due to the difficulty of targeting the dormant hypnozoite stage in the liver. Modelling suggested that pre-erythrocytic vaccines preventing dormancy, blood-stage vaccines, SSM-VIMTs, or multi-stage vaccines targeting liver-, blood- and sexual stages, all have the potential to achieve elimination. A number of *P. vivax* vaccines have reached clinical trials. This includes the subunit vaccine VMP001/AS01 and VMP002 targeting CSP (NCT01157897)⁶⁶, a radiation attenuated *P. vivax* sporozoite candidate⁶⁷, blood stage candidate vaccines targeting the *P. vivax* Duffy-binding protein (PvDBP),^{68,69} and a sexual-stage candidate Pvs25H/Alhydrogel protein vaccine.⁷⁰

Vaccination strategies for malaria control and elimination

Target groups and immunisation strategies

The development of any malaria vaccine will have to take into account potential epidemiological changes across a range of settings. Several factors should be considered when determining the target age range or population for vaccination. As transmission intensity declines, changing patterns of immunity associated with persistent malaria exposure will shift the burden of uncomplicated malaria to older age groups. However, changes in the age pattern of complicated and fatal malaria will be less pronounced while there is stable malaria transmission. Reductions in transmission also produce changes in the relative contribution of different malaria species, with *P. vivax* rapidly becoming the dominant species in many areas outside sub-Saharan Africa. In the Asia Pacific and the Americas, persistent *P. vivax* is a major hurdle for malaria elimination efforts, where the biology and associated disease dynamics of this species may pose unique challenges for the design and evaluation of vaccines.⁷¹

A number of factors are commonly considered in malaria risk stratification, some of which can be used as a basis to determine potential target groups for vaccination.⁷² These include overall epidemiological metrics such as parasite prevalence, clinical case counts and incidence, malaria-specific and all-cause mortality that can be used to determine the primary age groups experiencing a substantial proportion of malaria disease or infection, or to identify communities or populations in areas where malaria is highly localised. Other factors include human behavioural patterns, such as seasonal migration or other behaviours associated with increased exposure or risk, such as occupation. The risk of resurgence or reintroduction in post-elimination settings may be dependent on both ecological and entomological factors, including altitude, temperature, rainfall, agriculture, housing infrastructure, and mosquito species and behaviour. Finally, contextual factors such as socio-political conflicts, location of refugees and internally displaced persons or other humanitarian emergencies may be associated with increased malaria risk.

Overall, ongoing changes in malaria epidemiology should be considered, accounting for potential shifts in high-risk populations by the time vaccines become available.

Target age group. In high transmission areas, infants and children under 5 years old are typically at greatest risk, with the age groups at highest risk for severe disease and death being inversely related to the intensity of transmission. Morbidity from uncomplicated disease may nevertheless be significant in older children and adults, as may non-health impacts of malaria disease (e.g., educational outcomes, economic productivity), and they may represent an additional target group for malaria vaccination. In settings with *P. vivax*, adults in addition to infants and small children are often at risk in moderate to low transmission settings.⁷¹

Malaria in pregnancy. Pregnant women are highly susceptible to *P. falciparum* malaria, resulting in substantial maternal, perinatal, and infant morbidity and mortality.⁷³ Primigravid women are at particular risk due to the immunological and physiological changes during pregnancy. In stable transmission areas, WHO recommends chemoprevention through intermittent preventive treatment (IPTp) with sulfadoxine pyrimethamine (SP). Given that women may develop malaria before receiving their first IPTp dose, IPTp only provides partial protection and, as a result, rates of malaria in pregnancy still remain high. This, coupled with ongoing challenges with IPTp compliance and coverage (in 2019, 62% of women in 33 African countries receive their first IPTp dose, and only 49% and 34% receive their second and third dose⁵) suggest that vaccines could provide substantial additional health benefits to women and their babies. Vaccines used in children and adults can potentially be used in pregnant women and women of child-bearing age. These vaccines, as well as vaccines targeting pregnancy-specific antigens to prevent placental malaria would either need to induce long-lasting protection in women of childbearing age or overcome the major operational challenge of targeting women early in pregnancy.

Testing of malaria vaccines in pregnant women will be critical to not only demonstrate the safety and efficacy of vaccines to specifically protect against malaria in pregnancy, but also to allow the inclusion of pregnant women, who may represent an important infectious reservoir, as part of mass vaccination campaigns. Inclusion of pregnant women in clinical trials can help establish effective dosing during pregnancy and minimise risk to both the mother and infant in all trimesters. Such trials would need to consider definitions for pregnancy-specific endpoints (e.g., placental and peripheral parasitaemia) and maternal and infant outcomes (e.g., low birthweight, delivery complications, still birth or neonatal death, and maternal anaemia).

Other potential target populations. The epidemiology of malaria in areas such as the Greater Mekong Region is shifting towards adult migrant men who are typically exposed to vectors when engaging in high-risk work in forest or construction sites, particularly when sleeping outdoors or working at night. Population mobility is strongly associated with shifting land use, where rural infrastructure projects or agricultural industries attracting migrant labour can increase human-vector contact. Border communities, ethnic minorities, and forest-fringe communities are also impacted by mobility. In the Americas, mobile populations such as miners, domestic and cross-border migrants, and labourers have also been found to be at increased risk of malaria in Venezuela, Peru, Ecuador, Colombia and Brazil. These hard-to-reach mobile and migrant populations often have variable access to health services and poor uptake of mosquito nets or other vector control interventions, which presents major challenges for malaria control and elimination programmes.⁷⁴

Immunisation strategies

Priority immunisation strategies will depend on the indication and use case of the vaccine, as well as the target population and feasibility of achieving adequate coverage in the settings where it will be deployed. For vaccines targeting clinical disease, administration through routine immunisation programmes using schedules compatible with existing immunisation visits is envisaged where infants and young children are the primary risk group. In settings where older children and adults may also be at risk, initial vaccine introduction may be through mass immunisation campaigns to cover the

susceptible population rapidly, followed by the addition of the vaccine to routine immunisation programmes in young children, depending on the duration of protection induced by the vaccine.

Transmission reducing vaccines are expected to be administered primarily through periodic mass preventive campaigns to a broad age range, where the frequency of campaigns will depend on the duration of protection and population birth and in-migration rates. Transmission reducing vaccines with long-lasting efficacy may also be considered in routine vaccination of infants and young children after, or in addition to, initial mass campaigns.

For both indications, the use of periodic mass immunisation campaigns can be used to reduce the risk of clinical malaria in populations living in malaria-endemic areas where significant transmission is expected to continue, as well as to control malaria epidemics and re-importation outbreaks in post-elimination settings.

Ultimately, the aim is to deliver malaria vaccines using strategies which achieve the highest impact. This may involve variations in malaria vaccine implementation including, for example, the delivery of additional doses before peak transmission seasons or the targeting of areas with stubbornly poor access to case management or preventive malaria interventions. Many countries are now tailoring strategies at the subnational level to account for heterogeneities in epidemiology and health systems capacity.

Seasonal or emergency situations. While highly efficacious vaccines with a long duration of protection are preferred, vaccines with moderate efficacy and/or limited duration of protection that can be delivered easily at an affordable cost may have important public health impact. If next generation and future vaccines provide a relatively short period of high-level protection, they could be considered in seasonal or emergency settings where the required period of protection is shorter. This includes a substantial proportion of the most highly burdened countries in Africa, 80% of which have areas in intensely seasonal transmission settings.^{75–77} Approximately 39 million children under the age of 5 live in areas of sub-Saharan Africa in which seasonal malaria chemoprevention is deemed appropriate, where 33.7 million episodes of malaria and 152,000 deaths amongst children due to malaria are reported each year.⁷⁶ Additionally, nearly all settings with perennial transmission also experience some seasonal increases in transmission and disease. Therefore, the use of seasonal vaccination combined with routine vaccination through the childhood Expanded Programme on Immunization (EPI) or other year-round malaria control interventions are potential strategies. In emergency situations caused by environmental or socio-political disasters, vaccines may be needed to prevent or contain epidemics.

Whether administered seasonally or in emergency settings, the duration of protection provided by the vaccine will ideally match the maximum period of malaria risk. Reducing to a minimum the number of doses required to provide adequate protection is particularly important in seasonal and emergency settings, where access to the target population may be difficult. If efficacy wanes, the use of additional doses will need to be considered in the context of the duration of the malaria transmission season. An example of seasonal vaccination is provided by a study evaluating the efficacy of a primary course (3 doses) of the vaccine before the rainy season, followed by an additional dose annually, prior to each subsequent rainy season.^{78,79} Recently, the Coalition for Epidemic Preparedness Innovations (CEPI) was established to accelerate vaccine development for emerging infectious diseases, but also to enable access to vaccines during outbreaks. During major infectious disease outbreaks such as Ebola, substantial increases in untreated malaria cases can occur due to declines in health facility attendance and disruptions in community-based malaria control programmes^{80,81}, highlighting the potential application of malaria vaccination in such settings.

Special PPC considerations for seasonal vaccination

Parameters	Preferred Product Characteristics	Notes
Indication for use	Seasonal vaccination to reduce morbidity and mortality due to <i>P. falciparum</i> and/or <i>P. vivax</i> malaria. Prevention of clinical malaria, including manifestations of severe malaria, caused by either <i>P. falciparum</i> and/or <i>P. vivax</i>	This is a variation of the burden reduction PPC. Only differences or important additional considerations are highlighted in this PPC table. See report section <i>Seasonal or emergency situations</i> (page 24)
Target population	Populations which contribute substantially to disease burden in geographical regions where malaria risk is highly seasonal or transmission is limited to a short period (e.g., several months per year) Ongoing changes in malaria epidemiology should be considered, accounting for potential shifts in high-risk populations by the time vaccines become available.	In most settings, this will focus on infants and young children aged 5 years and under but may include people aged over 5 years where substantial disease burden exists in this age group. See report section <i>Vaccination strategies for malaria control and elimination: Target groups and immunisation strategies</i> (pages 22-24)
Safety	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Efficacy and duration	High efficacy matching the period of malaria risk	Same as vaccines to reduce morbidity and mortality
Dose regimen and schedule	Single or minimal number of doses to protect during period of malaria risk	A primary immunisation course should be administered before an individual's first transmission season (e.g., to children who will enter the malaria season at an age at high risk of severe malaria or malaria death). See report section <i>Clinical development pathways and evaluation tools: From vaccine efficacy to public health impact</i> (page 42-44)

Co-administration	Same as vaccines to reduce morbidity and mortality	Vaccine doses may be more likely to be given in conjunction with seasonal malaria chemoprevention (SMC). See report sections <i>Vaccination strategies for malaria control and elimination: Use of vaccines with other malaria interventions</i> (page 36) and <i>Clinical development pathways and evaluation tools: Safety considerations</i> (page 42)
Formulation/presentation	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Route of administration	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Product stability and storage	Ease of operation outside powered cold chain particularly important	Same as vaccines to reduce morbidity and mortality
Programmatic suitability	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Access and affordability	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality

Special PPC considerations for vaccination in emergency situations

Parameters	Preferred Product Characteristics	Notes
Indication for use	Human populations affected by complex emergencies / disasters associated with natural hazards occurring in geographical areas at risk of malaria	This is a variation of the burden reduction PPC. Only differences or important additional considerations are highlighted in this PPC table. Additional considerations can be referenced in the following WHO reports: ▪ <i>Vaccination In Acute Humanitarian Emergencies</i>⁸² ▪ <i>Vaccination in Humanitarian Emergencies: Implementation Guide</i>⁸³ See report section <i>Seasonal or emergency situations</i> (page 24)
Target population	Target population experiencing the high risk of malaria in complex emergencies, which may include expanded target age groups or demographics compared to routine vaccination. This may also include populations not directly affected by the emergency, but living in close proximity to those that are, whether hosting displaced populations or experiencing increased risk due to changing local circumstances to health service delivery. A guiding principle should be equitable access to vaccination for those at equal risk.	Special considerations include: ▪ The target population may be highly unstable, e.g. with new arrivals and departures from a camp setting ▪ There may be special high-risk population groups in some areas (e.g., high HIV/AIDS burden, high prevalence of malnutrition, young population and/or high birth rate) ▪ Affected areas may be particularly hard-to-reach ▪ Specific conditions may impact on vaccine implementation (e.g., overcrowding; insufficient access to water, sanitation, and hygiene; reduced access to health services)
Safety	Same as vaccines to reduce morbidity and mortality	Due to the difficulties associated with the collection of epidemiological data in complex humanitarian emergency settings, safety and efficacy data does not necessarily need to be generated in emergency situations and data from evaluations in more stable settings can be considered.

Efficacy and duration	High efficacy with duration matching period of malaria risk.	Due to the difficulties associated with the collection of epidemiological data in complex humanitarian emergency settings, safety and efficacy data does not necessarily need to be generated in emergency situations and data from evaluations in more stable settings can be considered. The use of study designs suitable for emergency settings is encouraged. If the intervention is designed for use as part of a combination with other tools, technologies or approaches, evidence of a statistically significant additive impact can be beneficial. This evidence needs to be generated using similar assessments and epidemiological endpoints as for already established interventions. Vaccines should be suitable for use in humanitarian emergency settings and consider the optimal level of protection achievable in relation to the envisaged delivery strategy (e.g., determine the vaccine efficacy and effectiveness at full, less than full course, and fractional dose use. See report section <i>Fractional dosing and dose sparing</i> (page 31)
Dose regimen and schedule	Single or minimal number doses or schedule matching period of malaria risk and to avoid operational challenges of follow-up during complex emergencies.	▪ Vaccination should be feasible to deliver before the population begins to disperse/move on or back to their homes ▪ Routine immunization services will need to be maintained or established quickly ▪ Schedule should be feasible and/or adjustable (e.g. vaccine given at an earlier age in an outbreak setting) for a humanitarian emergency-affected population ▪ In case of vaccine supply constraints for certain vaccines, fractional dose can be considered if adequate efficacy is maintained

		For refugee populations, feasibility of administering immunization schedule of country of origin may need to be considered See report section <i>Clinical development pathways and evaluation tools: From vaccine efficacy to public health impact</i> (page 42-44)
Co-administration	Data on malaria and non-malaria vaccines as well as drugs that may be co-administered in emergency situations (e.g., cholera, meningococcal meningitis, malaria chemoprophylaxis used in seasonal malaria chemoprevention or mass drug administration) to ensure immunogenicity and safety are maintained and there is absence of clinically relevant interference.	In many cases, the vaccination intervention may also be used as a vehicle to add other distributions, be it other vaccines, or drugs and commodities such as vitamin A, soap, jerry cans, shovels, insecticide treated nets, blankets, etc. The demand for certain products and interventions for the target population needs to be assessed and given due consideration. In instances where for example nutrition is the utmost priority for a population, this needs to be addressed in conjunction with the delivery of immunisation services. Nevertheless, depending on the context, the addition of each additional item to vaccination delivery should be approached cautiously to minimise the risk of overwhelming limited human and logistic resources.
Formulation/presentation	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Route of administration	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Product stability and storage	Enhanced stability would be an asset in many emergency situations, where capacity and functionality of cold chain may be limited or not available.	Same as vaccines to reduce morbidity and mortality
Programmatic suitability	Same as vaccines to reduce morbidity and mortality	Distribution primarily through top-down delivery channels managed by agencies providing humanitarian assistance. Should be suitable for procurement through global donor mechanisms and distribution through delivery channels used for other emergency commodities.

		In emergencies, it is essential to consider different, non-traditional places for vaccination. A combination of fixed and mobile vaccination posts may be used. This may mean that sites are open during non-traditional hours and dispersed across the geographic area so that individuals can access a site. A classical programme-based strategy may not be the most appropriate. Opportunities such as vaccination at registration if the emergency entails refugees, or integration with other interventions, such as food distribution, should be considered.
Access and affordability	Should be suitable for procurement through global donor mechanisms and distribution through delivery channels used for emergency situations.	Vaccines can be directly purchased from the manufacturer, UNICEF response mechanisms, CSOs or stockpiles. International donor stockpiles are managed through an International Coordinating Group on Vaccine Provision (ICG), which reviews country requests for vaccines as a response to outbreak. Approvals are based on epidemiological evidence of outbreak, availability of an action plan for mass vaccination, and adequate storage conditions.

Elimination and prevention of outbreaks. Vaccines that protect against infection and clinical malaria could be a component in the intervention package used during the final stages of an elimination programme. In areas where prevalence of infection is very low or highly localised, vaccination may have the potential to interrupt transmission through all-age vaccination campaigns in targeted, high-risk communities. In post elimination settings, vaccines could be used to prevent resurgence or reintroduction in areas where other malaria control interventions, such as vector control, are no longer in routine use. Modelling suggests that when combined with mass drug administration, which can clear a large number of infections from a population, vaccines that protect against infection with durations as short as one year could have a substantial impact on delaying resurgence.⁸⁴

Fractional dosing and dose sparing. Vaccine efficacy is dependent on the number of doses in a recommended schedule or course of a vaccine administered. There has been increasing interest in the delayed administration of smaller doses (i.e., fractional dosing or dose sparing), which may help to increase vaccine efficacy when a fractional dose is administered later in the primary immunisation schedule. Fractional dosing may also help to mitigate vaccine shortages or extend vaccine coverage to a larger number of individuals. Fractional dosing strategies have been used for meningococcal vaccine⁸⁵, yellow fever vaccine⁸⁶, and inactivated poliovirus vaccine⁸⁷. Study results for the administration of RTS,S as a fractional dose in children in endemic settings are expected in 2021 (NCT03276962).⁴⁷ Delayed fractional dosing of the vaccine candidate Rh5.1/AS01_B has also been tested as part of a phase 1a dose escalation study in healthy adult volunteers in the United Kingdom.⁵⁷

In some settings or situations, population movements or erratic access to populations due to security of logistical constraints may impair the ability to deliver the full recommended vaccine course. This is particularly true in emergency situations following environmental or humanitarian disasters. In these settings, decision-making on vaccine use in these scenarios need to balance the best available information on vaccine efficacy at less than full course with the potential benefit of vaccination for the target population.⁸² It may also be important to determine if different possible schedules other than those used in routine immunisation would be better suited to accommodate the emergency situations. For vaccines currently in development, evaluating the efficacy of fractional dosing prior to phase 3 trials could be considered to provide valuable data for decision-making in the use case scenarios described above.

*Special considerations for *P. vivax* vaccine development.* There has been renewed interest in the control of *P. vivax* due to research documenting the global burden of the *Plasmodium* species, particularly in the Asia Pacific and Latin America where persistent *P. vivax* presents ongoing challenges.^{88,89} The unique biology of *P. vivax* may require special approaches for the development and testing of *P. vivax* vaccines. Relapses from persistent liver-stage hypnozoite forms of the parasite may lead to multiple waves of blood stage infections that arise from a single infective bite. While the general principles of trial design for *P. vivax* vaccines should be similar to *P. falciparum*, the dormant phase impacts the design of vaccine trials, particularly the long-term follow-up of trial populations and the ability to distinguish new liver stage infections from relapses. The duration of protection will also need to be sufficiently long to cover both initial infections and relapses.

Clinical immunity to *P. vivax* is acquired more rapidly than *P. falciparum*, under conditions of both natural exposure^{90,91} and experimental infection^{92,93}, meaning that *P. vivax* is a predominantly paediatric illness in moderate to high transmission settings. However, in low transmission settings, non-immune children and adults have been found to be equally susceptible even after onset of age-dependent clinical immunity to *P. falciparum*.⁹⁴ These potential differences in immune status with age and transmission will need to be considered in the design of vaccine trials. Therefore, there is potential for *P. vivax* vaccine to be administered through routine childhood immunisation programmes, as well as through mass vaccination in areas where adults are also at risk of clinical disease. Given that the incidence of severe disease and mortality from *P. vivax* is substantially lower than *P. falciparum*, trials may need to be conducted in highly endemic areas where incidence of disease is sufficiently high to maintain feasible sample sizes⁷¹.

To evaluate the efficacy of pre-erythrocytic *P. vivax* vaccines, measuring the incidence of infection may require treatment-reinfection designs to clear liver stage infections upon vaccination. However, 8-aminoquinoline drugs used to eliminate hypnozoites can cause severe haemolytic anaemia in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency⁹⁵, a phenotype that is particularly common in *P. vivax* endemic areas. Therefore, the use of radical cure to improve detection of incidence of *P. vivax* infection would require careful screening and exclusion of G6PD-deficient volunteers.

In areas endemic to both *P. vivax* and *P. falciparum*, the effect of co-infection or shifting dynamics of species distribution due to vaccination may need to be monitored in phase 3 vaccine trials or post-licensure studies. Some studies have found increased disease severity in mixed *P. vivax*/*P. falciparum* infections.^{96–98} Due to the co-endemicity of *P. vivax* with *P. falciparum* in most areas, the development of a multi-species vaccine is likely to be preferred to a single species vaccine. Studies in dual endemic zones may help to determine if there is a need to include *P. falciparum* vaccine components to prevent *Plasmodium* species replacement and/or interaction.⁷¹

Special PPC considerations for malaria vaccines for *P. vivax*

Parameters	Preferred Product Characteristics	Notes
Indication for use	Reduction of morbidity and mortality due to <i>P. vivax</i> malaria infection.	Envisaged as vaccines that target pre-erythrocytic or blood-stage <i>P. vivax</i> antigens. Vaccines to block transmission of <i>P. vivax</i> is considered to be methodologically similar to those for <i>P. falciparum</i>, though longer follow-up may be required due to potential for relapse infections. See report section <i>Special considerations for P. vivax vaccine development (pages 31-32)</i>
Target population	Differences in local epidemiology and the impact of immune status on age patterns of disease that may differ from <i>P. falciparum</i> need to be taken into account in trials and the target population.	Due to more rapidly acquired clinical immunity to <i>P. vivax</i>, in areas of moderate to highly endemic transmission, <i>P. vivax</i> is a predominantly paediatric illness. However, in low transmission areas, individuals of all ages may be affected. The target population may also depend on the deployment strategy, and whether long-duration routine vaccination or short-duration seasonal vaccination is used.
Safety	Monitoring potential increases in incidence and severity of <i>P. falciparum</i> episodes following <i>P. vivax</i> vaccination may be needed in areas where both parasites are present. If treatment-reinfection study designs are to be used, safe treatment of 8-aminoquinolines should require testing for G6PD-deficiency.	Co-infection with <i>P. vivax</i> may modulate the incidence and severity of <i>P. falciparum</i> illness. Evidence on cross-protection is conflicting and some studies have found exacerbation of the risk of severe disease in mixed infections. Measuring a potential increase in <i>P. falciparum</i> risk in the <i>P. vivax</i> vaccine group is a major safety issue to be addressed. This could be conducted through health facility-based case detection and/or repeated cross-sectional surveys. To overcome problems of subpatent parasitaemia, parasitological assessments by microscopy can be conducted. Relapse has implications for design of trials and long-term follow-up of study populations in particular if use of drugs to eliminate

		hypnozoites cannot be safely administered in areas with high prevalence of G6PD deficiency.
Efficacy and duration	For vaccines deployed seasonally or for short-term management of epidemics, vaccine would need to provide sufficiently long protection to cover both initial infection and relapses from long lasting liver-stages. If incidence of infection is to be used as a trial endpoint for pre-erythrocytic vaccines, trial duration will need to account for the hypnozoite stage and the effect of latent/recurrent disease and consideration of G6PD testing if treatment-reinfection study designs are to be used.	The incidence of mortality and severe disease are estimated to be substantially lower than those associated with <i>P. falciparum</i>, which may impact sample sizes needed in phase 3 trials, though <i>P. vivax</i> infections might be a significant co-factor to mortality from other causes. Interactions between <i>P. vivax</i> and <i>P. falciparum</i> infections will need to be monitored to assess the overall impact of the intervention on malaria infection and morbidity. Monitoring the risk of <i>P. falciparum</i> infections and disease may influence the choice of the clinical case detection system. Until it has been determined that a reduction in <i>P. vivax</i> incidence through vaccination does not lead to increased risk of <i>P. falciparum</i> disease, monitoring the risk of severe disease associated with <i>P. falciparum</i> infection may require rapid access to early diagnosis and treatment for symptomatic children in trials sites. Choice of case definition may thus differ between proof-of-principle phase 2b trials and later stage field efficacy studies (large phase 2b and 3). In proof-of-principle studies, higher incidence of clinical episodes detected using active case detection may allow determination of efficacy and allow close monitoring of <i>P. falciparum</i> disease. Once a sufficient body of clinical safety data indicates no significantly increased risk of <i>P. falciparum</i> morbidity, passive case detection may be preferable in phase 3 trials to more accurately measure clinical efficacy as experienced by the health system. For pre-erythrocytic vaccines, unless it is predicted that the vaccine may be therapeutic by acting on established hypnozoites, a treatment-reinfection design where the last vaccine dose is followed by radical treatment of liver and blood stages may be most suitable if the primary endpoint is incidence of infection. For blood-stage vaccines, a traditional cohort design without radical cure can be

		suitable. The balance between the scientific benefit of radical cure to improve detection of efficacy against incidence of infection with pre-erythrocytic vaccines and concerns of serious side-effects associated with amino-quinolines in individuals with G6PD deficiency will need to be carefully addressed. At minimum, careful screening and exclusion of G6PD-deficient volunteers may be required. Currently there are no pyrogenic thresholds for mixed infections or standard approaches to attribute risk of illness to individual infections. For <i>P. vivax</i> vaccine trials, a conservative option is to use the same pyrogenic thresholds as in single infections, and to consider that all mixed infections exceeding the thresholds are individual assigned as <i>P. vivax</i> and/or <i>P. falciparum</i> episodes.
Dose regimen and schedule	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Co-administration	An efficacy trial in dual endemic zones would allow early assessment of whether there is the need for co-administration or inclusion of a <i>P. falciparum</i> vaccine component to prevent potential <i>Plasmodium</i> species replacement and interaction.	A reduction in the incidence of <i>P. vivax</i> may lead to an increase in the incidence of other <i>Plasmodium</i> species. Assessment of multiple species during the surveillance period may be needed.
Formulation/presentation	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Route of administration	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Product stability and storage	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Programmatic suitability	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality
Access and affordability	Same as vaccines to reduce morbidity and mortality	Same as vaccines to reduce morbidity and mortality

Use of vaccines with other malaria interventions

Malaria vaccines will likely be tested and deployed in conjunction with other WHO recommended malaria control measures, including vector control with long-lasting insecticide-treated mosquito nets and/or indoor residual spraying with insecticide, malaria chemoprevention, the use of quality-assured rapid diagnostic tests and effective anti-malarial chemotherapy. Routine immunisation programmes often achieve higher coverage than other malaria control strategies. The use of multiple interventions and delivery strategies can help maximise the number of children receiving at least one preventive malaria intervention, thus reducing inequities.

For example, malaria vaccination may be an option in seasonal transmission settings, alongside or instead of seasonal malaria chemoprevention (SMC) if, for example areas are facing difficulties achieving or sustaining coverage and compliance, or where drug resistance is undermining the effectiveness of SMC. Administration of a single vaccine through annual vaccination prior to the peak transmission season may be logistically easier than multiple rounds of drug treatment. Studies in Burkina Faso and Mali have evaluated the priming of young children with RTS,S/AS01 followed by a single additional dose before subsequent transmission seasons compared to and in combination with SMC with sulfadoxine pyrimethamine (SP) and amodiaquine (AQ).⁷⁸ In addition to safety and efficacy, data on the relative costs of vaccination compared to other malaria interventions can help to inform WHO policy processes and guideline development.

Other key complementary measures that may form part of malaria control and elimination programmes with malaria vaccines include routine surveillance for targeting of preventive and treatment interventions and high-quality, affordable and high-throughput diagnostics to facilitate identification of transmission foci.

Clinical development pathways and evaluation tools

Clinical development

Clinical development of a potential malaria vaccine requires a series of clinical trials. Preliminary trials (phase 1 and 2) assess safety, immunogenicity, dose regimen and schedule, and formulation. Evidence of efficacy against endpoints of interest, including those related to biomarkers of efficacy (e.g., mosquito feeding data for transmission blocking vaccines and bridging studies) can also be obtained at this stage. These trials are typically designed to provide sufficient safety and immunogenicity data to support the selection of one or more candidate formulations for evaluation in a pivotal trial. Pivotal trials (phase 2b and 3) are intended to provide robust evidence to support licensure, usually based on demonstration of safety and efficacy in randomised controlled trials with clinical endpoints as there is currently no accepted single correlate of vaccine-induced protection. Whereas phase 1 and 2a trials tend to be conducted in non-immune populations, pivotal studies generate data in the target population.

Approaches to achieve desired efficacy and duration of protection through vaccines which combine targets from different stages of the parasite life cycle require special consideration. These include determining at which stage in clinical development to test the different components of a multi-stage vaccine independently and at what point to test the combination.

Regulatory agencies should be consulted when planning all pivotal trials to ensure that the trial design meets regulatory expectations for licensure. Interactions with WHO are also strongly recommended prior to the finalisation of pivotal trial protocols so that global guideline considerations can be taken into account. Readers are encouraged to refer to the WHO Guidance on clinical evaluation of vaccines for details on regulatory expectations.¹³

Trials to demonstrate impact on transmission. Demonstrating an impact on transmission will require trial designs that differ from efficacy trials to establish reduction in clinical disease. Cluster randomised

trials, where the unit of randomisation is the community or cluster of individuals, may be used, where the primary measure of efficacy will likely be the incidence or risk of human malaria infections. The feasibility of measuring efficacy with clinical endpoints may be dependent on the baseline transmission intensity. In low transmission settings, low incidence of clinical disease is likely to result in prohibitively large sample sizes to achieve adequate statistical power to determine efficacy against clinical endpoints. Highly efficacious vaccines for transmission reduction may be valuable in moderate and high transmission settings, particularly if co-administered or formulated as part of vaccines targeting disease reduction. Trials conducted in high transmission settings will have more statistical power to measure impact on clinical endpoints, and potentially community level transmission, than trials in lower transmission settings. However, the generalisability of trial results to other transmission intensities may need careful consideration. The minimum threshold of vaccine efficacy required to maintain an effect on transmission in the community may also differ from vaccines to reduce morbidity and mortality. These parameters can potentially be informed by modelling and confirmed in pre- or post-licensure studies.

Developers are encouraged to explore alternative trial designs for proof-of-concept studies, particularly those that validate the use of surrogate biomarkers in the clinical development pathway. It will be important to fully assess possible surrogate biomarkers for vaccines that target human-to-mosquito transmission. Vaccine developers and regulatory agencies are encouraged to engage in early dialogue regarding possible regulatory pathways for such vaccines.

Post-licensure and phase 4 studies. In addition to monitoring vaccine safety in routine use, post-licensure phase 4 studies may provide critical additional data depending on the vaccine indication. For instance, post-licensure studies may be used to demonstrate the generalisability of efficacy or effectiveness results in transmission settings that differ from those in which the vaccine was trialled, and to confirm transmission reducing effects. Conditional licensure granted on the basis of surrogate endpoints may also require demonstration of effectiveness in routine use.

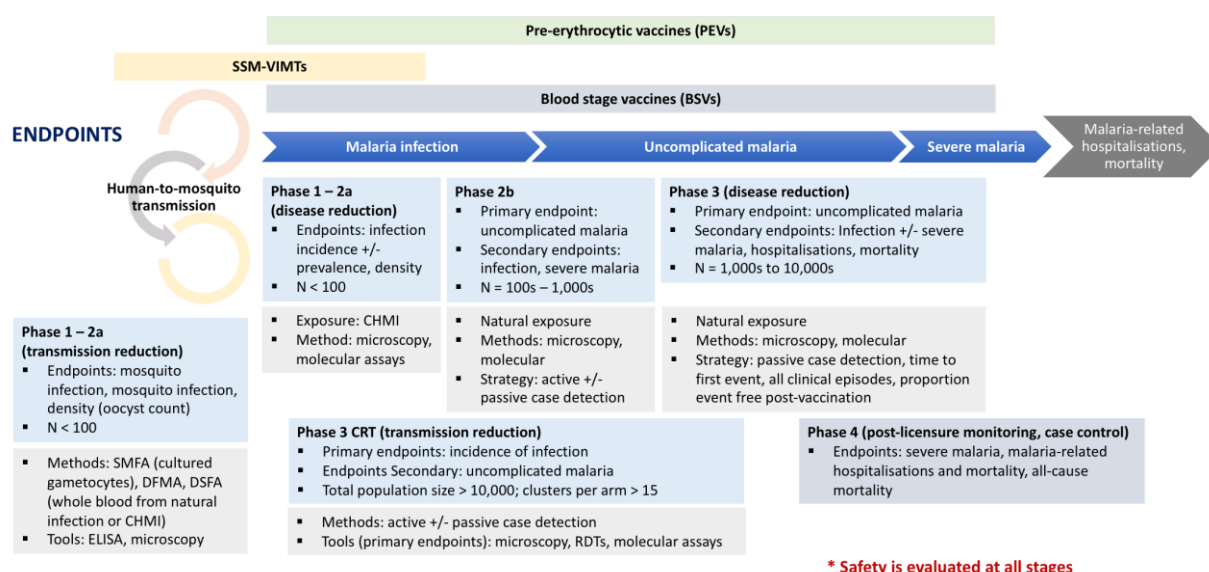
A number of endpoints, including severe malaria, malaria-related hospitalisations and mortality, and all-cause mortality, while relevant to determining broader public health impact of vaccines, may not be feasible to measure with precision in phase 3 trials and could be evaluated in post-licensure or phase 4 studies.

Endpoints, case definitions, and analytical strategies in late stage clinical development

The optimal approach to measuring vaccine efficacy and public health impact will vary according to evaluation phase, intended use case, and the transmission intensity of the study setting. For detailed guidance on choice of immunogenicity and efficacy endpoints, case definitions and analysis methods, readers are encouraged to refer to the background and clinical section of “Guidelines on the quality, safety, and efficacy of recombinant malaria vaccines targeting the pre-erythrocytic and blood stages of *Plasmodium falciparum*.”⁹⁹

When considering the selection of endpoints, it may be helpful to consider a simple model of how the vaccine is expected to work (Figure 2). Endpoints closer to the point of biological action tend to be used in early stage vaccine evaluation, whereas endpoints further downstream are used in later development. For example, while evidence of clinical efficacy in phase 2 prior to large scale field studies is ideal, demonstration of a reduction in parasite density can be useful in early clinical evaluation of prospective blood stage vaccines. This has the advantage of requiring a smaller sample size than demonstration of downstream outcomes, such as uncomplicated malaria or mortality, and is less likely to be influenced by factors unrelated to the vaccine. Such ‘proof of concept’ studies in early clinical development can provide supporting evidence for larger, longer studies of distal endpoints in naturally exposed populations.

Figure 2. Malaria vaccine evaluation endpoints and analytical strategies



SSM-VIMT: sexual, sporogonic, or mosquito stage vaccine interrupting malaria transmission, SMFA: standardised membrane feeding assay; DFMA: direct feeding membrane assay; DSFA: direct skin feeding assay; CHMI: controlled human malaria infection; ELISA: enzyme-linked immunosorbent assay; CRT: cluster randomised trial; RDT: rapid diagnostic test.

Potential primary and secondary endpoints for disease-reducing vaccines may include, but are not limited to:

- **Infection**, through controlled human malaria infection (CHMI) challenge trials. These have increasingly been used in early screening of disease-reducing vaccines (see Annex 3, Appendix 1, page 195-6, WHO Technical Report Series 980, 63rd report of Expert Committee of Biological Standardization “Controlled human malaria infection trials”). Efficacy against infection, rather than disease, may also be used in phase 2 field trials.

In some phase 2 studies, drug treatment to clear parasites prior to vaccination or before the final dose may be used to i) reduce the immunosuppressive effects of existing malaria infections and enhance the immunogenicity of the vaccine and/or ii) ensure any parasitaemia detected in the follow-up period is due to new infections. Safety concerns associated with any drug treatment will need to be considered (e.g., use of aminoquinolines to treat *P. vivax* in G6PD-deficient individuals). Use of pre-vaccination parasite clearance in phase 3 studies will have strong implications for the product labelling for licensure and indication for use. Therefore, treating study subjects prior to vaccination is not encouraged since this would not reflect the expected mode of deployment.⁹⁹

- **Incidence of all episodes of clinical malaria**, in phase 2b and phase 3 trials. The definition of a clinical malaria episode should include history of fever in the previous 48 hours or measured fever (e.g. axillary temperature of >37.5 degrees centigrade) at presentation and a parasite density threshold which delivers an acceptable level of sensitivity and specificity.¹⁰⁰ This threshold may vary according to the endemicity of malaria in different settings and include, for example, any detectable parasites in low transmission settings and a minimum parasite density of 5,000/μl in moderate or high transmission settings. Assuring a specific case definition will reduce the bias towards the null of vaccine efficacy estimates. The vaccine effect on the incidence of first episodes of malaria may also be evaluated, although this is less relevant than impact on all episodes of malaria to understand the potential public health benefit of disease-reducing vaccines.

The case detection system also has an important bearing on the interpretation of vaccine efficacy. Either active case detection (ACD) or passive case detection (PCD) may be used. In phase 2b efficacy studies with a relatively modest number of study subjects, the use of ACD that includes

regular home visits by study staff may be appropriate. PCD will generally be preferred for phase 3 trials to measure the public health impact on reducing the burden on health facilities, even if ACD may identify higher numbers of malaria cases and more accurately estimate the burden of malaria in the community as a whole.⁹⁹ The results of study endpoints detected through PCD systems will be impacted by a number of factors, such as distance from the health facility, treatment seeking behaviour, differences in clinical characteristics of cases or clinical diagnosis. Therefore, clear descriptions of PCD systems, including potential limitations or variations, at study sites should be well documented. Significant differences in PCD systems between studies or sites can present major confounding factors, making the comparison of results between locations difficult to interpret. Potential confounding factors in ACD system used, such as frequency of follow-up, should also be clearly described.

- **Severe malaria, malaria-related hospitalisations and mortality, and all-cause mortality.** Although these endpoints are of greatest relevance to public health, they are less common than uncomplicated disease and require considerably larger sample sizes. These endpoints may be more amenable to evaluation in post-licensure and phase 4 studies.

Primary and secondary endpoints will differ for transmission-reducing vaccines.

- **Incidence of human infection at the community level** is likely the earliest measurable endpoint reflecting reduction in transmission. In contrast to disease-reducing vaccines, the use of ACD will be more useful for measuring infection as a primary endpoint, as opposed to clinical endpoints.
- **Clinical malaria and other clinical endpoints** such as malaria-related hospitalisations could be considered as secondary endpoints.
- **Human-to-mosquito transmission** endpoints (e.g., prevalence of mosquito infection, direct membrane feeding assays or direct skin feeding assays) are playing an increasing role for the evaluation of sexual stage and mosquito antigen vaccines. Any candidate measure will require sufficient analytical and biological validation if such data are to be used as surrogate endpoints for efficacy. If such measures were developed and accepted for licensure, effectiveness studies may be required to confirm transmission reduction.

Analytical strategies may also vary according to the stage of clinical evaluation. Proof-of-concept can be demonstrated by an increase in the time to infection in CHMI or field studies or quantifying the proportion of participants who do not experience an infection. Subsequent studies may evaluate the effect of a candidate on the incidence of infection or clinical disease. Analysis of the rates of all malaria episodes is preferred because it has greater public health relevance but will need to account for lack of independence of multiple clinical episodes within individuals. Studies may also choose to evaluate the effect on rates of first episodes per participant.

Ultimately, improved standardisation and documentation of endpoints and key study parameters is needed for better comparisons between study results or extrapolation to non-study populations, or to determine if comparison or extrapolation is feasible. Factors that have the potential to affect estimates of efficacy are the study population (location, prior exposure status, age), case-ascertainment methods, follow-up timepoints, case definitions (clinical criteria, laboratory criteria), and follow-up approaches to analyses. Annex 1 illustrates example data standardisation templates that could be used for CHMI studies or field studies under conditions of natural exposure.

Trial design considerations

Comparator arms for second generation vaccines. Following recommendation for broad use of a first-generation malaria vaccine, trial designs may need to consider licensure of the first-generation vaccine in the country where the trial is planned. Readers are referred to the report of the 2013 WHO Consultation on the Use of Placebos in Vaccine Trials.¹⁰¹ Whether superiority or non-inferiority trials are appropriate will depend on the type of vaccine being compared as well as the needs of the

regulatory and public health stakeholders. A superiority trial design compares the incidence of the primary efficacy endpoint between those receiving either the new vaccine or a comparator (which can be either placebo, control non-malaria vaccine or the current malaria vaccine recommended, licensed or in use). A non-inferiority trial is designed to determine that the new vaccine is not “unacceptably worse” than the comparator vaccine within an agreed maximum margin of acceptable difference. Annex 2 Table 5 shows some of these field design options.

One potential approach to achieve the desired target of malaria vaccines with superior efficacy and durability could be the combination of vaccines that target different stages of the parasite. Table 5 shows two situations that could result from this approach in the two right hand columns. One situation could be also be a new vaccine which includes the biological activity of both the 1st generation vaccine and the 2nd generation vaccine as a combined presentation, which is then compared to the 1st generation vaccine. The second approach could be the comparison of a combined co-administration of the 1st and 2nd generation vaccine against the 1st generation vaccine and placebo. Non-inferiority trials are often used to evaluate new products that may bring advantages such as reduced cost, fewer doses, a simpler schedule, ease of administration, delivery and storage or an improved safety and tolerability profile. The acceptable non-inferiority margin will be determined based on scientific, clinical and public health opinion and needs. Annex 2 Table 6 shows indicative sample size calculations for superiority or non-inferiority designs based on efficacy margins of 5% and 10% that have previously been used for vaccines for other diseases. Larger samples sizes will be required for superiority trials to compare against existing vaccines, as well as trials to demonstrate small margins of non-inferiority. Consultations with WHO and regulatory agencies are strongly recommended when planning and prior to finalisation of designs for pivotal trials. This may advance timelines by avoiding the need to perform repeated phase 3 trials if global policy considerations were not adequately addressed in phase 3 trials.

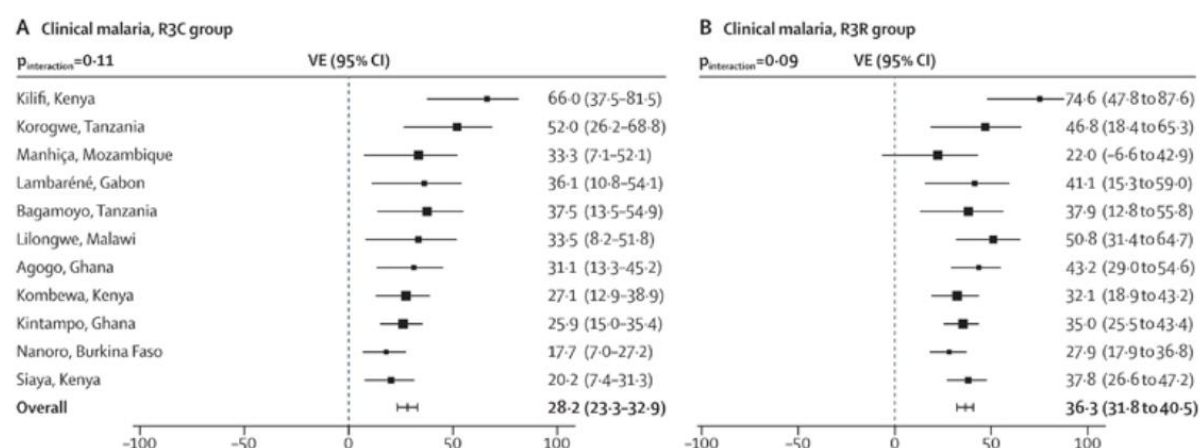
Standard of care. The experience of the RTS,S phase 3 trials has highlighted that improved quality of care can reduce the ability to measure more severe clinical endpoints, such as severe malaria or malaria-related hospitalisations and mortality. Sufficient funding for RTS,S trials allowed the study to provide increased access to both outpatient and inpatient care, additional clinical and laboratory equipment, ensure reliable supplies of essential medications, oxygen, and blood, and increase clinical staffing. In Siaya, Kenya, a case control study based on data from the Health and Demographic Surveillance Survey (HDSS) estimated a 70% reduction in all-cause mortality associated with enrolment in the RTS,S trial, regardless of study arm (personal communication, Mary Hamel). 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 mortality and other severe outcomes.⁴² While these endpoints may provide important information on public health impact, their evaluation may be more feasible in post-licensure or phase 4 studies.

Non-vaccine malaria control interventions. Study designs will need to document carefully any control measures, such as the use of ITNs, indoor residual spraying or chemoprevention programmes, so that the context in which the vaccine’s efficacy was measured can be established; phase 3 studies will also need to document the comparability of the trial arms with respect to these factors. Well-designed clinical trials can aim to control for confounding effects from vector control efforts and programmes aimed at promoting prompt diagnosis and treatment, while longer-term public health consequences of the simultaneous use of malaria vaccine and other control measures would be well suited for post-licensure studies.⁹⁹

Vaccine efficacy and transmission intensity. Vaccine efficacy and cases averted have been shown to differ according to transmission intensity, as observed in the results from the RTS,S/AS01 phase 3 trial, where during 12 months of follow up vaccine efficacy was highest (reaching 75%) in the site with lowest malaria transmission and was lower in areas of moderate to high transmission. Nonetheless, the highest impact was seen in areas of moderate to high transmission, reaching thousands of cases averted per 1000 children vaccinated during 4 years of follow-up in the areas of moderate to high transmission (Figures 3 and 4). Overall, study designs will need to consider the potential for the

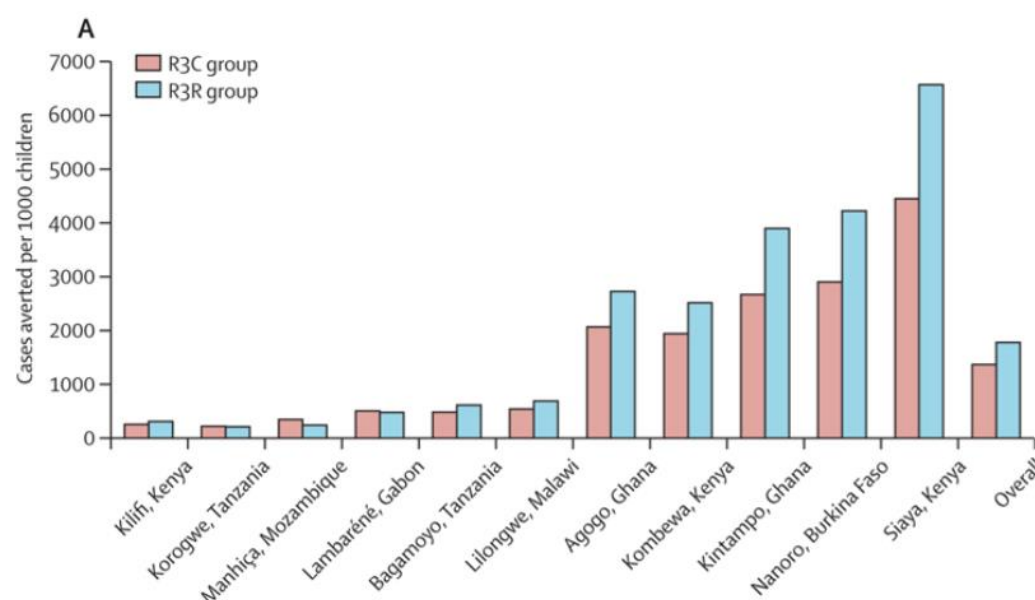
apparent vaccine efficacy to vary not only by transmission intensity, but also by the degree of seasonal variation in transmission and the vaccination strategy (e.g., seasonal administration).

Figure 3. RTS,S/AS01 vaccine efficacy against clinical malaria by study site in children aged 5-17 months, by study site.* Study sites are ordered from lowest (Kilifi) to highest (Siaya) incidence of clinical malaria measured in control infants 6-12 weeks of age at enrolment during 12 months of follow-up. R3C: RTS,S/AS01 primary schedule, R3R: RTS,S/AS01 primary schedule with fourth dose 18 months after dose 3.



*Adapted from RTS,S Clinical Trials Partnership. doi: 10.1016/S0140-6736(15)60721-8.⁴²

Figure 4. Cases of clinical malaria averted in children aged 5-17 months during 48 months of follow-up, by RTS,S phase 3 study site.* Data are ordered by increasing malaria incidence at each study site. R3C: RTS,S/AS01 primary schedule without booster, R3R: RTS,S/AS01 primary schedule with booster.



*Adapted from RTS,S Clinical Trials Partnership. doi: 10.1016/S0140-6736(15)60721-8.⁴²

Studies should be conducted in settings with a range of transmission intensities and seasonal variation. Data on efficacy should be obtained from a representative selection of areas in which the vaccine may ultimately be deployed. The sponsor may choose to perform separate studies in different geographical areas, or to conduct one large study that includes sites representative of intended future

use. If the latter approach is adopted, a pre-defined stratification of enrolment by area could be used to support secondary analyses of efficacy by area or by transmission pattern.⁹⁹

Safety considerations

Acceptable levels of safety will vary depending on the indication for use. Ideally, the safety and reactogenicity of the vaccine should be comparable to or better than WHO recommended vaccines in malaria endemic countries, but the levels of adverse events tolerated will need to be balanced against the expected cases averted or disease incidence prevented in a given setting. In the case of transmission blocking vaccines, the individual-level risk/benefit assessment may differ for vaccines with no direct effect on either infection or disease for the individual, compared to vaccines that confer direct protection to the vaccinated individual in addition to indirect/transmission effects in the community.

The absence of clinically relevant interference (e.g., immunogenicity and safety) between the malaria vaccine and other vaccines that may be administered concomitantly should be confirmed in co-administration studies. While it may not be feasible to study the interactions between all potential combinations of vaccines that may be co-administered, the choice of vaccines for these studies should be driven by the vaccines in use in the intended target age group and populations. For example, for RTS,S/AS01, non-inferiority criteria were met for the serological responses to all EPI vaccines given with RTS,S/AS01. This included vaccines against hepatitis B, diphtheria, tetanus, pertussis, polio, measles, yellow fever. The potential of co-administered vaccines to influence the immunological effects of the candidate malaria vaccine should also be considered.

Another consideration, if malaria or other chemoprevention strategies are routinely used in a target population, is the potential for clinically relevant interference between the vaccine and co-administered drugs, such as those used for malaria chemoprevention or treatment for non-malaria pathogens, such as helminths.

Finally, vaccine developers should be cognisant of the potential of vaccines – or any other efficacious malaria prevention tool – to interfere with the development of naturally acquired immunity. As such, if vaccine-induced protection wanes over time, individuals may experience a period during which they are at increased risk of malaria compared to similarly aged individuals who did not receive the vaccine and acquired immunity naturally. The resulting ‘rebound effect’ may warrant extended follow-up of study participants to quantify the extent of the effect and manage any potential deferred increases in morbidity. Key issues related to the potential for malaria rebound will be considered by a WHO technical consultation in late 2021.

From vaccine efficacy to public health impact

Vaccine efficacy is usually defined as $100 \times (1 - (\text{rate in vaccine recipients} / \text{rate in control group}))$. In addition to demonstrating vaccine efficacy in these terms, which is required for most vaccine licensure, complementary measures can be used to assess the overall public health utility of a vaccine. Vaccine preventable disease incidence (VPDI), or the vaccine attributable rate reduction, measures the absolute difference in disease incidence between vaccinated and unvaccinated groups.¹² By accounting for both baseline disease incidence and vaccine efficacy, high VPDI may occur despite low vaccine efficacy in settings with high disease incidence. In addition to the assessment of VPDI in individually randomised clinical trials, VPDI can be calculated in cluster randomised trials to capture differences in disease incidence between residents of control and intervention clusters regardless of individual-level vaccine status.

Broader definitions of public health impact are useful to account for the indirect effects of malaria vaccines on health and malaria transmission. Any intervention which reduces infections in individuals who receive the intervention will reduce transmission and potentially benefit people who do not receive the intervention. In addition to the severe disease caused directly by malaria infection, *Plasmodia* may increase the risk and severity of disease of co-infections.^{102,103} Whereas a malaria

infection may not necessarily cause death by itself, the presence of co-morbidities may increase the risk of a severe outcomes. Interventions may therefore confer substantial indirect effects that are comparable to or exceed the level of direct protection. Outcomes such as all-cause hospital admission and all-cause mortality better assess the total potential impact of a vaccine and are substantially easier to measure than severe malaria or malaria-specific mortality.

In addition to selection of suitable trial endpoints to evaluate vaccine efficacy, vaccine performance should be evaluated in the context of local dynamics of malaria, including seasonal patterns of transmission. Given that levels of vaccine efficacy measured in trials may vary by setting as a result of variable transmission dynamics or heterogeneities in population immunity due to genetic or nutritional differences, interpretation of the results of a vaccine trial may require a comprehensive set of baseline data for a given trial location. This can also be ascertained through contemporaneous control arms in standard RCTs and cluster randomised control trials (CRTs), where children randomised to the control arms would receive a comparator or placebo vaccines and any other malaria control interventions already in place.

Ultimately, the acceptability of a vaccine will need to be determined by local authorities considering not only vaccine efficacy, but overall value for money.^{104,105} This includes cost-effectiveness, which will be highly dependent on transmission intensity and baseline disease burden, as well as local costs. Opportunity costs to other malaria interventions or other vaccination and health services should also be considered. Given the heterogeneity of malaria risk, the optimal combination of interventions in different subnational strata will need to be assessed, as well as the value added by a malaria vaccine to overall malaria control programmes. Equity is another important component of value for money. Routine immunisation programmes have been shown to reach higher coverage than is achieved by existing approaches to malaria control, which could reduce inequities in access to malaria control interventions. A recent 2020 analysis of Demographic Health Survey (DHS) and Malaria Indicator Survey (MIS) data from 20 African countries showed that amongst the 33 million children who do not use insecticide treated nets, 23 million (70%) are reached by routine immunisation 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 if vaccinating children already using an ITN.¹⁰⁶

While the development of highly efficacious long-lasting vaccines (e.g., targeting 75% vaccine efficacy or above) remains a strong public health priority, it is increasingly recognised that vaccines with more modest efficacy can deliver substantial public health impact. For example, implementation of RTS,S is estimated to avert approximately 400-500 deaths per 100,000 fully vaccinated children,¹⁰⁷ on par with *Haemophilus influenzae* type B and pneumococcus vaccination (400 and 500 childhood deaths averted per 100,000 vaccinated) and higher than measles and meningitis A vaccination (238 and 144 childhood deaths averted per 100,000 vaccinated, respectively).¹⁰⁸ New vaccines with similar efficacy to RTS,S would provide added value in meeting the expected demand and assuring a healthy market.

For future vaccines, efficacy levels should be considered together with improvements in duration of protection, dosing regimens, product stability and storage, and other characteristics that may increase programmatic suitability or access and affordability. The relative importance of these factors will vary by use case scenario (Table 2). In the case of routine immunisation to reduce disease in children, key priorities will include duration of protection and safe co-administration with other childhood vaccines if they are to be delivered through the Expanded Programme on Immunization (EPI). By contrast, the use of vaccines in short-duration targeted or seasonal immunisation campaigns will need to prioritise high efficacy with a duration matched to the period of risk, minimise the number of doses (single dose ideally) and ensure ease of programmatic delivery outside clinical settings. Seasonal administration will also require a dose schedule that is deliverable within the transmission season, while vaccines to prevent malaria in pregnancy should ideally be administered before pregnancy and last throughout pregnancy or include a booster vaccination during pregnancy. Similarly, single dose regimens will be particularly important for vaccines used in emergency situations, where follow-up of displaced or mobile populations will be acutely challenging. For vaccines to interrupt transmission, the potential

need to vaccinate a wider age range and population will require robust manufacturing and production capacity to ensure adequate supply to reach coverage targets. Mass vaccination campaigns may also need to consider safety and efficacy in the context of co-administration with other non-vaccine malaria interventions, such as mass drug administration or seasonal chemoprevention.

Table 2. Relative importance of different vaccine characteristics by use case scenario

Use-case scenario	Preferred Product Characteristics							Level of importance
	Efficacy	Duration	No. doses	Schedule	Supply	Delivery	Co-admin	
Disease-reduction, routine immunisation								
Disease-reduction, mass immunisation								
Transmission-reduction, routine immunisation								
Transmission-reduction, mass immunisation								
Seasonal administration								
Emergency situations								
Malaria in pregnancy								
* safety is classified as very high priority for all use case scenarios								
PPC descriptions								
Efficacy	High efficacy							
Duration	Long duration							
Safety	Comparable to or better than other WHO approved vaccine in malaria endemic areas							
Number of doses	Minimal number of doses							
Schedule	Short dosing schedule							
Supply	Reliable production and manufacturing infrastructure to ensure sufficient vaccine supply for mass immunisation							
Delivery	Minimal need for cold chain for storage and distribution							
Co-administration	Need for co-administration studies with other vaccines and drugs (malaria and non-malaria)							

WHO Prequalification

Vaccines that are procured by United Nations agencies and for financing by other agencies, including Gavi, require WHO Prequalification. The WHO PQ process provides an international assurance of quality, safety, efficacy and suitability for LMIC immunisation programmes. WHO encourages vaccine developers and manufacturers to be aware of the WHO PQ process, even at the early stages of development and to discuss product and regulatory requirements with WHO PQ staff early in the process, as regulatory pathways can impact eligibility for prequalification. Registration by a national regulatory authority (NRA), or the European Medicines Agency (EMA) for centralised marketing authorisation in Europe, will be required prior to any consideration of prequalification. Additionally, the PQ process requires regulatory oversight by the NRA of Record, which is usually the NRA of the country where the vaccine is manufactured or the NRA of the country of finishing and distribution, and such an NRA should have been assessed as functional by WHO. The prequalification procedure is described in detail in the document *Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies* (WHO/BS/10.2155).¹⁰⁹

Programmatic Suitability

In addition to meeting quality, safety and efficacy requirements, it is also important that developers and manufacturers understand WHO's preferences for parameters that have a direct operational impact on immunisation programmes. Low programmatic suitability of new vaccines may impair the overall public health impact, for example if they present challenges for vaccine introduction and achieving adequate uptake and coverage. Additionally, introduction of new vaccines that have higher volumes, cold chain capacity or disposal demands may have a negative impact on the existing operation of immunisation programmes. Therefore, early-stage consideration of presentation and packaging parameters is encouraged. Deferring these considerations may lead to additional costs and delays required for reformulation later in the development pathway.

To achieve standardisation of the programmatic suitability requirement for prequalification, a Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Working Group was formed in 2010. Subsequently, the document “Assessing the programmatic suitability of vaccine candidates for WHO prequalification” was developed in 2012¹¹⁰, and revised in 2014,² to define characteristics that determine programmatic suitability for developing country public-sector immunisation programmes. The document describes key vaccine characteristics for PSPQ and the process for assessing compliance with these characteristics.

Vaccine characteristics are organised into several groups: mandatory, critical, unique and innovative, and preferred characteristics.

- “Mandatory” characteristics are those for which compliance is compulsory at the time of application for WHO prequalification and which should be unconditionally met prior to evaluation. Deviations may lead to rejection of an application for prequalification evaluation.
- “Critical” characteristics are also compulsory, but deviations will result in referral to the PSPQ Standing Committee for review, discussion and recommendation. After consideration, the vaccine may be accepted or rejected for PQ evaluation.
- “Unique and innovation” characteristics are those for which there is no specific guidance and not otherwise specified as “mandatory” or “critical” and will be referred to the PSPQ SC for review, discussion and recommendation. After consideration, the vaccine may be accepted or rejected for PQ evaluation.
- “Preferred” characteristics are intended to reflect what WHO, procuring agencies, and national immunisation programmes would like to see as characteristics in vaccines intended for use in LMICs. Compliance with preferred characteristics is not compulsory, but they may become “critical” characteristics in the future. For vaccines still under development, these characteristics should serve as guidance to manufacturers on the minimum desirable standards.

Access and affordability

Production and manufacturing

In addition to meeting safety and efficacy requirements, development of vaccines must consider the feasibility of large-scale manufacturing and production to meet global demand. Ensuring a path to adequate production should ideally begin early in development planning, including negotiations with potential manufacturers for the volume and timescale required and at a cost that can be affordable to deliver the vaccine to the countries most in need. The process to design, validate and begin commercial manufacturing can take up to 7 years for some vaccines. In the future, the use of new vaccine designs, such as mRNA vaccines, may have the advantage of reducing manufacturing timelines, but developments in this area is still at an early stage.

The running of production facilities with the skilled workforce needed to ensure smooth operations is a major challenge. Innovations in manufacturing techniques have reduced space requirements, enhanced automation and reduced processing complexity. These improvements have made manufacturing more feasible in countries traditionally lacking the skilled workforce required to run plants, shorten processing times and lower overall operational costs.¹¹¹ As a result, vaccine production is increasingly undertaken in LMICs, which can provide affordable vaccines at scale, thus facilitating global access.

Manufacturing process development often runs in parallel to clinical development programmes, but the degree of parallelism depends on the investment available and the risk tolerance. The primary risk will be the need to repeat clinical trials, which can arise from significant changes in the manufacturing process (raw materials, process steps, release steps, equipment, facilities etc) that may affect the

purity, safety, or effectiveness of the vaccine compared to the product evaluated in the original clinical studies.

Estimated industry investments in manufacturing during phase 1 of vaccine development can range from \$2 to \$60 million USD.¹¹² In phase 1, it is ideal to finalise formulation choices, define and qualify all manufacturing process steps prior to phase 2, begin process optimisation, and determine primary packaging. Packaging decisions such as a choice of containers or vials can significantly affect production and facility requirements. During phase 2, it is typical to initiate construction of commercial manufacturing facilities, develop initial cost of goods projections, begin producing phase 3 supplies and initiate stability studies. By phase 3, release specifications are usually established, final commercial facilities and consistency studies completed, and final cost of goods confirmed. The estimated capital required for these activities across phase 2 and 3 range from \$200 to \$600 million USD.¹¹² Given that a number of decisions as early as phase 1 can critically impact the production and manufacturing process and costs, vaccine developers are encouraged to explore options early in development, and consult with relevant WHO departments for guidance.

Health systems and delivery

Vaccine delivery requires management and coordination of diverse stakeholders across a range of complex activities. The context of a country's overall strategy for health promotion and disease prevention and control is crucial when planning vaccine procurement and budgeting, prioritisation and targeting of populations for vaccination, training and supervision, monitoring and evaluation, cold chain logistics and infrastructure, safety surveillance, and vaccine advocacy and communications.

Alignment with existing delivery mechanisms and potential trade-offs with other vaccine distribution or malaria control intervention programmes needs to be considered so that new vaccine introduction can be sustained without adversely affecting other services. As the number of vaccines increase, national vaccine supply chains can become strained and will need to adapt. Robust supply chain management is needed for effective storage and distribution, monitoring of vaccine stock and waste rates, and other logistics management. Investment and funding for vaccine introduction may need to account for specific areas such as education about the new vaccine for health workers and the community, increase in personnel such as EPI staff; expansion of cold chain, dry storage and vaccine transport systems; costs of new delivery strategies such as school-based vaccination or to special target groups; establishment or strengthening of disease surveillance, including expansion of laboratory capacity; support for vaccine coverage surveys and post-introduction evaluations, and strengthening of pharmacovigilance and Adverse Event Following Immunisation (AEFI) surveillance, reporting, and management.

The dual market challenge

While early stage development has been historically conducted by industry and biotechnology companies, strong public-private partnerships in the last decade have encouraged vaccine discovery and enabled candidates to advance beyond proof-of-concept to late stage clinical development. However, the lack of a dual market (targeting both high-income and low- and middle-income countries) for malaria vaccines makes investment in phase 3 efficacy trials financially unsustainable for industry, shifting the burden to donor agencies and the public sector. Experience from other infectious diseases lacking a dual market such as the meningococcus A conjugate vaccine (MenAfriVac) and Ebola vaccines highlight that early consideration of late stage development challenges are important, including long-duration funding commitments to cover R&D, engaging with public health officials in endemic countries to determine acceptable vaccine costs, negotiating cost-effective vaccine production agreements and the use of advanced market commitments to guarantee vaccine demand.^{113,114} However, bridging the gap to late stage development still faces significant funding hurdles and will require innovative financing mechanisms or early stage R&D collaboration and technology transfer agreements with industry partners. Ultimately, any malaria vaccine will be almost

exclusively used in low- and middle-income markets, where the assessment of programmatic suitability and sustainable access in endemic countries will be critical.

Full public health value of malaria vaccines

While funding for R&D remains a challenge, it is important to consider the full public health value of future malaria vaccine implementation.¹¹⁵ RTS,S phase 3 trials have shown that, even with moderate vaccine efficacy, RTS,S has the potential for considerable impact. Over a period of 4 years during phase 3 trials, RTS,S, was able to avert more than 4,000 clinical malaria cases per 1000 vaccinees (receiving 4 doses) in high transmission settings such as Nanaro, Burkina Faso and Siaya, Kenya. With an estimated incremental cost effectiveness ratio (ICER) of \$25 (range \$16 – 222) per clinical case averted,¹⁰⁷ the value of RTS,S is comparable to several other vaccines and in the range of other malaria interventions. While perhaps not as cost-effective as insecticide treated nets (ITNs) due to the very low unit cost of bed nets, pilot implementations have shown that malaria vaccines can achieve rapid scale-up and higher coverage through the established and functioning routine EPI services compared to other malaria prevention tools. As noted earlier, a 2020 analysis of Demographic Health Survey (DHS) and Malaria Indicator Survey (MIS) data from 20 African countries showed that 70% of children not using ITNs successfully received DTP3 vaccines.¹⁰⁶ This highlights the incredible reach vaccines can achieve through routine immunisation programmes, providing the opportunity to reduce inequities in access to life-saving malaria control interventions. Malaria vaccine visits also present an opportunity to use a well-developed platform to deliver further malaria control and other health interventions and messages. For example, the training for new vaccine introduction for the RTS,S vaccine emphasises the need to remind parents at each visit that children should sleep under ITNs and should be brought promptly for testing and treatment of fever. Thus, the overall public health impact of any malaria vaccine may be greater than what can be measured in clinical trials. Regional expertise, engagement, and advocacy are needed to convey this public health value to the population at risk, and vaccination and malaria experts should be regularly consulted to understand the range of perspectives on the usefulness of a malaria vaccine.

Since the establishment of the Millennium Development Goals (MDGs), reducing malaria morbidity and mortality has been considered a major global development issue, in light of substantial research documenting the impact of the disease on the economic development of endemic countries.¹¹⁶ Historically, malaria and poverty have been directly and indirectly linked. In multi-country analysis of data from 1965 to 1990, the long-term effect of malaria was estimated to reduce the level of gross national product (GNP) per capita in malarious countries by more than half in comparison with non-malarious countries.^{117,118} More recent analysis of data from 180 countries between 2000 and 2015 indicate that a 10% decrease in malaria incidence is associated with a 1% increase in per capita gross domestic product (GDP), while malaria eradication is associated with a 5% increase in per capita GDP.¹¹⁹ In addition to health systems costs and decreased household income due to missed work, malaria has also been associated with reduced education through absenteeism, impaired cognitive development for infants and children, increased vulnerability to other infections, and risk of reducing already low household income levels into extreme poverty.^{117,120,121} Analysis of data from the United States, Mexico, Brazil, and Colombia, have estimated that persistent childhood malaria infection reduces adult income by 50%.¹²² The range of socio-economic impacts of malaria prevention should be considered as part of the full public health value of malaria vaccines and can help to inform policy, prioritisation, and decision-making.

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Annex 1. Clinical development data standardisation templates

Table 3. Example data template for controlled human malaria infection (CHMI) studies

Vaccine candidate	Challenge strain	Study population			Infection endpoint			Vaccinated		Controls		Vaccine efficacy
		Location	Exposure	Age range	Measurement	Assay	Follow-up	# infected	# non-infected	# infected	# non-infected	
	Pf7G8	USA	Malaria naive	Adults (18-65 years)			28 days					

Table 4. Example data template for field trials under conditions of natural exposure

Vaccine candidate	Study population		Endpoint				Vaccinated			Controls			Vaccine efficacy
	Location	Age range	Exposure	Endpoint	Method	Follow-up	Sample size / PYAR	# episodes	Infection rate	Sample size / PYAR	# episodes	Infection rate	
			Natural exposure	Infection	ACD	6 months							
						12 months							
			Natural exposure	Uncomplicated malaria	ACD	6 months							
				Uncomplicated malaria	PCD	6 months							
						12 months							

PYAR: Person years at risk

Annex 2. Potential comparator arms and sample sizes for superiority and non-inferiority trials

Table 5. Considerations of different trial design options for second generation malaria vaccines*

Field efficacy trial options	2 nd generation vs placebo	2 nd generation vs. 1 st generation	1 st and 2 nd generation vs. 1 st generation	1 st and 2 nd generation vs. 1 st generation vs. placebo
Estimate of efficacy	Absolute efficacy	Relative efficacy	Relative efficacy	Absolute and relative efficacy
Type of assessment	Superiority to no treatment	Non-inferiority to 1 st generation or superiority to 1 st generation	Superiority to 1 st generation	Superiority to 1 st generation and to no treatment.
Limitations and considerations	May be considered unethical to randomise to placebo if 1 st generation is available and recommended in country.	Large sample sizes may be needed. Non-inferiority design would not clearly show progress towards absolute efficacy goal but could make alternative vaccines available.	Large sample sizes may be needed. 1 st and 2 nd generation vaccines could be given together or as prime-boost strategy.	Large sample sizes may be needed (may not be feasible). May be considered unethical to randomise to placebo, if 1 st generation vaccine is available and recommended.
	Efficacy relative to 1 st generation vaccine would not be estimated with confidence.	Efficacy relative to no treatment would not be estimated with confidence.	This design would not demonstrate efficacy of the 2 nd generation vaccine independent of the 1 st generation vaccine. Efficacy relative to no treatment would not be estimated with confidence.	This design would not demonstrate efficacy of the 2 nd generation vaccine independent of the 1 st generation vaccine.

* modified from Vannice et al. Malaria Journal 2012 11:372 doi:10.1186/1475-2875-11-372.¹²³

Table 6. Estimated sample sizes required for field studies of a second-generation vaccine to demonstrate non-inferiority or superiority (assuming intention-to-treat and calculated using Z-test with continuity correction*)

Power ($1-\beta$)		80%	
Two-sided significance level (α)		5%	
Control vaccine efficacy		50%	
Follow-up time for sample size calculation		2 years	
Incidence rate of clinical malaria in those not vaccinated		0.1 per person per year	
New vaccine efficacy (%)	Superiority	Non-inferiority margin	
		5%	10%
50	--	28,700	7,300
55	27,400	7,000	3,200
60	6,6000	3,000	1,700
65	2,900	1,600	1,100

* modified from Vannice et al. Malaria Journal 2012 11:372 doi:10.1186/1475-2875-11-372.¹²³