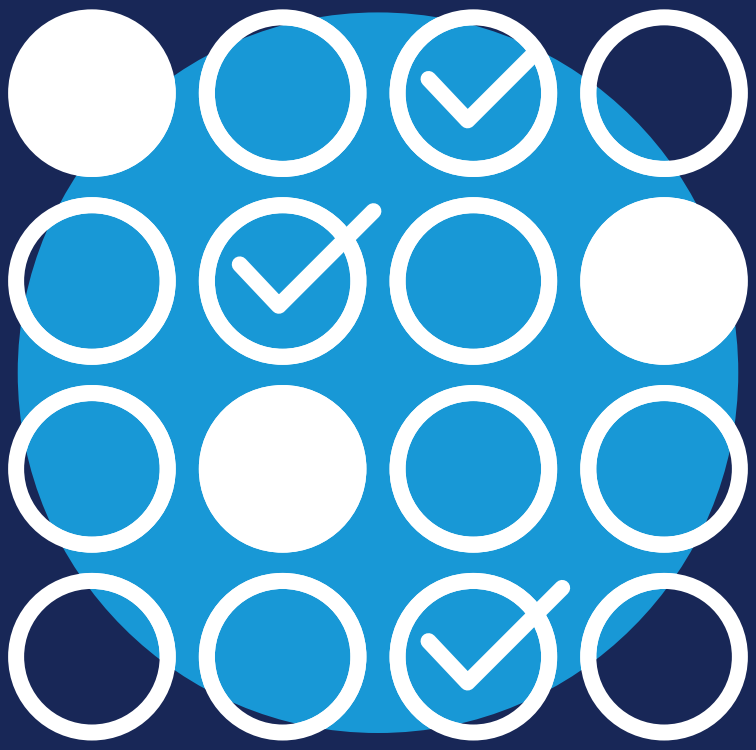
Malaria vaccines

Preferred product characteristics and clinical development considerations



World Health Organization

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The Global Malaria Programme (GMP) and Department of Immunization, Vaccines and Biologicals (IVB) of the World Health Organization (WHO) would like to thank the many individuals who contributed to the development of this document.

WHO preferred product characteristics (PPCs), as a class of research-oriented normative guidance documents, were initially conceived by Vasee Moorthy (WHO Science Division) working with WHO colleagues, WHO management and WHO advisors in 2012-2013. The first-in-class of these documents was the first edition of the WHO PPCs for malaria vaccines (WHO/IVB/14.09), developed in 2013-2014 following the update of the Malaria Vaccine Technology Roadmap. This process was led by Vasee Moorthy in liaison with Andrea Bosman (GMP) and supervised by Robert Newman (former Director GMP, 2009-2014) and Jean-Marie Okwo-Bele (former Director IVB, 2004-2017).

The document published here is an update to the 2014 malaria vaccine PPCs and was prepared by David Schellenberg (GMP), Lindsey Wu (GMP) and Mary Hamel (IVB) under the leadership of Pedro Alonso (former Director GMP) and Kate O'Brien (Director IVB), with review by and contributions from the Malaria Vaccine Advisory Committee (MALVAC) and the expert working group on late-stage development of malaria vaccines to reduce disease burden.

MALVAC members included: Edwin Asturias (University of Colorado, United States of America); Philip Bejon (KEMRI-Wellcome Trust Research Programme, Kenya); Chetan Chitnis (Institut Pasteur, France); Katharine Collins (Radboud University, Netherlands); Brendan Crabb (Burnet Institute, Australia); Socrates Herrera (Institute of Immunology, Colombia); Miriam Laufer (University of Maryland, United States of America); Regina Rabinovich (ISGlobal, Spain); Meta Roestenberg (Leiden University, Netherlands); the late Adelaide Shirley (John Snow Institute, Zimbabwe); Halidou Tinto (Institut de Recherche en Sciences de la Santé, Burkina Faso); and Marian Wentworth (Management Sciences for Health, United States of America).

The working group on late-stage development included: Willis Akhwale (Ministry of Health, Kenya); Kwaku Poku Asante (Kintampo Health Research Centre, Ghana); Fred Binka (University of Health and Allied Sciences, Ghana); Alejandro Cravioto (Universidad Nacional Autonoma de Mexico, Mexico); Umberto D'Alessandro (Medical Research Council Unit, The Gambia at the London School of Hygiene & Tropical Medicine); Brian Greenwood (London School of Hygiene & Tropical Medicine, United Kingdom of Great Britain and Northern Ireland); David Kaslow (PATH, United States of America); Rebecca Kiptui (Ministry of Health, Kenya); Miriam Laufer (University of Maryland, United States of America); Kamini Mendis (Independent Consultant, Sri Lanka); Kathy Neuzil (University of Maryland, United States of America); Terry Nolan (Murdoch Children's Research Institute, Australia); Folake Olayinka (United States Agency for International Development, United States of America); Regina Rabinovich (ISGlobal, Spain); Larry Slutsker (PATH, United States of America); Peter Smith (London School of Hygiene & Tropical Medicine, United Kingdom of Great Britain and Northern Ireland); Marian Wentworth (Management Sciences for Health, United States of America); Dyann Wirth (Harvard T.H. Chan School of Public Health, United States of America).

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The PPCs for malaria vaccines were developed in accordance with the WHO Standard Procedure for Target Product Profiles, Preferred Product Characteristics, and Target Regimen Profiles (V1.02, 3 August 2020). Declarations of any competing interests were received from all experts. WHO processes were used to assess declared interests and to manage any conflicts of interest. Five MALVAC members declared potential competing interests, including grants for non-malaria or non-vaccine related research, non-financial collaborations with malaria vaccine developers, and holding patent or inventor status for malaria vaccine candidates. After review and due diligence by the WHO Secretariat, it was concluded that these interests were not significant for the specific topics discussed in the development of this report.

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ABBREVIATIONS

ACD	active case detection
AMR	antimicrobial resistance
AQ	amodiaquine
CHMI	controlled human malaria infection
CSA	chondroitin sulfate A
CSP	circumsporozoite protein
DALY	disability-adjusted life year
DCVMN	Developing Countries Vaccine Manufacturers Network
DMFA	direct membrane feeding assay
DSFA	direct skin feeding assay
DVI	direct venous infection
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
G6PD	glucose-6-phosphate dehydrogenase
GDP	gross domestic product
GIA	growth inhibition assay
GTS	Global technical strategy for malaria 2016–2030
HBHI	High burden to high impact
IPTp	intermittent preventive treatment of malaria in pregnancy
ITN	insecticide-treated net
LMIC	low- or middle-income country
mAb	monoclonal antibody
MDA	mass drug administration
MPAG	Malaria Policy Advisory Group
MVIP	Malaria Vaccine Implementation Programme
NRA	national regulatory authority
NIAID	National Institute of Allergy and Infectious Diseases
PCD	passive case detection
PPC	preferred product characteristic
PQ	Prequalification
pRBC	parasitized red blood cell
PSPQ	Programmatic Suitability for Prequalification
R&D	research and development
RDT	rapid diagnostic test
SAGE	Strategic Advisory Group of Experts on Immunization
SAGme	Strategic Advisory Group on Malaria Eradication
SMC	seasonal malaria chemoprevention
SMFA	standard membrane feeding assay
SP	sulfadoxine-pyrimethamine
SSM-VIMT	vaccine interrupting malaria transmission targeting sexual, sporogonic or mosquito stages
TPP	target product profile
UN	United Nations
VAC	Vaccine Adjuvant Compendium
VLP	virus-like particle
VPDI	vaccine preventable disease incidence
WHO	World Health Organization

OVERVIEW

The *Global technical strategy for malaria 2016–2030* (GTS) *(1)* aims to harness and expand research to accelerate progress towards the elimination of malaria and to counteract the emerging threat of drug and insecticide resistance. It encourages innovation and the development of new tools, including vaccines, and strategies to maintain progress in malaria control and advance towards elimination. To accelerate implementation of the GTS, in 2018, the World Health Organization's (WHO) Global Malaria Programme reviewed its policy-making process to ensure that it is transparent, consistent, efficient and predictable. One of the outcomes of the review was the adoption of "preferred product characteristics" (PPCs) as a key tool to incentivize and guide the development of urgently needed health products. The use of PPCs is aligned with an organization-wide effort to improve communication about public health needs and to facilitate innovation to meet those needs.

WHO PPCs aim to:

- communicate unmet public health needs;
- stimulate the development of relevant new products to meet those needs; and
- facilitate the timely, effective assessment of new products, and the formulation of policy recommendations and prequalification listings.

To promote the development of vaccines with high public health impact and suitability for use in low- and middle-income countries (LMICs), the Global Malaria Programme and the Department of Immunization, Vaccines and Biologicals have jointly developed these malaria vaccine PPCs. Vaccine PPCs describe 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 by the realities of the disease epidemiology and delivery systems in the target geographies.

WHO PPCs were initially conceived in 2012-2013 as a class of research-oriented normative guidance documents. The first edition of the WHO PPCs for malaria vaccines (WHO/IVB/14.09), published in 2014 *(2)*, was the first-in-class of these documents. The document published here is an update to the 2014 edition.

Malaria vaccine PPCs have been developed to align with and complement the overall preferred vaccine characteristics addressed in more detail by other WHO departments and processes, such as the WHO Product Development for Vaccines Advisory Group (PDVAC) and WHO Prequalification (PQ). PDVAC is a WHO committee of experts providing external advice to WHO related to priority infectious disease pathogens, associated vaccine product development approaches and related manufacturing and delivery technologies *(3)*. WHO PQ also details its process for assessing vaccines via the Programmatic Suitability for Prequalification (PSPQ) criteria *(4)*. WHO encourages developers to consult these documents, alongside the malaria vaccine PPCs, particularly if they intend to seek a WHO recommendation for use or prequalification of their products.

TERMINOLOGY

Preferred product characteristics (PPCs) are designed to communicate unmet public health needs identified by WHO, stimulate innovation and investment in the identified areas, and communicate the desired performance and operational characteristics of health products to address those needs. The target audience consists of product developers including researchers, regulatory agencies, procurement agencies, and funders of research and development (R&D). PPCs are usually developed before a mature pipeline of products is available and should reflect the ideal characteristics of interventions required to rapidly and effectively achieve global health impact.

Target product profiles (TPPs) in the context of public health are planning tools used to set R&D targets for manufacturers and researchers to guide the development of specific products. TPPs provide more detailed information than PPCs and include both minimally acceptable and preferred performance characteristics. The minimum performance characteristics should be considered a "go/no-go" decision point in the product development process.

1. BACKGROUND AND PURPOSE

The last two decades have seen major reductions in malaria morbidity and mortality. Building on these achievements, the *Global technical strategy for malaria 2016–2030* (GTS) set goals to reduce global malaria incidence and mortality rates by at least 90% by 2030 *(1)*. Under the WHO E-2025 initiative, 25 countries are aiming to reduce malaria cases to zero by 2025 *(5)*. However, recent data indicate that progress in malaria control has stagnated. While insecticides for vector control and medicines for treatment and prevention are the mainstay of malaria control strategies, both are susceptible to biological resistance. Global malaria incidence and mortality in 2020 was estimated to be 59 cases per 1000 people at risk and 15 deaths per 100 000 people at risk, signalling inadequate progress against the GTS targets of 35 cases per 1000 and 7.2 deaths per 100 000 *(6)*. In 2019, the WHO Strategic Advisory Group on Malaria Eradication (SAGme) concluded that eradication will not be possible by 2050, even with full scale-up of current interventions *(7)*. While a number of efforts have aimed at improving malaria control and elimination strategies, including the "High burden to high impact" (HBHI) targeted response launched in 2018 *(8)*, SAGme has highlighted the pivotal role that malaria vaccines could play in achieving eradication.

Future strategies to combat malaria will likely require vaccines to complement the existing pipeline of malaria drugs, diagnostics and vector control tools. The COVID-19 pandemic has re-emphasized the importance of vaccines in epidemic preparedness for infectious diseases, as well as overall disease control and prevention. In response to global trends in antimicrobial resistance (AMR), WHO has also underscored the unique role of vaccines in the battle against AMR by preventing infections and reducing reliance on antimicrobials *(9)*.

Since the first malaria vaccine PPCs were published in 2014 *(2)*, major milestones in malaria vaccine R&D have been achieved. In 2015, RTS,S/AS01 became the first malaria vaccine to receive a positive scientific opinion from the European Medicines Agency (EMA) *(10)* and, in October 2021, it was recommended by WHO for use in moderate- to high-transmission settings in sub-Saharan Africa. RTS,S/AS01 and other vaccines with moderate efficacy against clinical malaria have the potential to achieve substantial public health impact through widescale use.

WHO strategic priorities for malaria vaccines

An intensified focus is now needed on developing higher efficacy long-duration vaccines that can serve as truly transformative tools in efforts not only to reduce malaria burden, but also to achieve elimination and eradication. This will require sustained R&D in areas such as parasite biology, vaccinology and immunization strategies. The malaria vaccine PPCs set forth strategic priorities focused on the following unmet priority public health goals:

- **Strategic goal 1:** Malaria vaccines that prevent human blood-stage infection at the individual level
- **Strategic goal 2:** Malaria vaccines that reduce morbidity and mortality in individuals at risk in malaria-endemic areas
- **Strategic goal 3:** Malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human infection in the community

These goals aim to address various aspects of malaria control and elimination.

The development of highly efficacious long-duration vaccines against blood-stage infection (strategic goal 1) has proven elusive to date, but is a top priority given their potential to achieve multiple strategic goals. Such vaccines would not only prevent individual-level infection, thereby reducing disease and death (strategic goal 2), but could also reduce community-level transmission (strategic goal 3) if given to a substantial proportion of the population that infect mosquitoes with malaria. These vaccines are a highly desirable tool to reduce malaria burden and achieve malaria elimination. The large majority of vaccines in the current R&D pipeline are pre-erythrocytic vaccines that partially prevent blood-stage infection, and blood-stage vaccines that decrease parasite density. These vaccines could achieve substantial public health impact by reducing the burden of malaria disease and death (strategic goal 2); however, they would have less of an effect on transmission (strategic goal 3). Finally, vaccines with no direct activity in reducing blood-stage parasitaemia could prevent malaria parasite transmission to mosquitoes and, if deployed widely, indirectly avoid subsequent infections and disease at the community level.

Over the past 20 years, new malaria vaccine trials have been registered at a rate of approximately 10 trials per year *(11)*. As of August 2022, the pipeline includes two vaccines in or approaching Phase 3 evaluation (R21 and PfSPZ), and additional candidates in Phase 2 and Phase 1 evaluation. 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/observatories/global-observatory-on-health-research-and-development/monitoring/health-products-in-the-pipeline-from-discovery-to-market-launch-for-all-diseases) *(12)*. As the epidemiology of malaria continues to evolve, the strategic priorities for malaria vaccine R&D will need to adapt to reflect the needs of malaria control programmes and remain cognizant of the long development timelines. For any malaria vaccine to become widely available, it will have to undergo evidence-based assessment by WHO.

This document presents PPCs and clinical development considerations that correspond to the strategic goals.

2. PREFERRED PRODUCT CHARACTERISTICS

The preferred product characteristics (PPCs) presented here correspond to three strategic goals for malaria vaccines: i) prevention of blood-stage infection, ii) reduction of malaria morbidity and mortality, and iii) reduction of malaria transmission. Vaccines that are highly efficacious in the pre-erythrocytic stage have the potential to prevent blood-stage infection, reduce disease at the individual level, and reduce transmission at the community level if delivered to a sufficient proportion of the infectious population. Highly efficacious blood-stage vaccines that suppress parasitaemia such that vaccinees have no detectable infection could also be within the scope of strategic goal 1. Pre-erythrocytic vaccines that only partially prevent blood-stage infection and/or blood-stage vaccines that reduce parasite densities have the potential to reduce disease incidence. Pre-erythrocytic vaccines, blood-stage vaccines, and vaccines targeting sexual, sporogonic or mosquito stages (SSM-VIMTs) could all potentially reduce human-to-mosquito transmission and incidence of infection and disease at the community level. Multi-stage vaccines targeting antigens at different stages of the parasite life cycle (e.g. pre-erythrocytic or blood stage combined with sexual or mosquito stage antigens) may achieve multiple strategic goals.

2.1 PPCs for malaria vaccines to prevent infection

Parameters	Preferred Product Characteristics	Notes
Indication for use	Prevention of blood-stage infection due to *P. falciparum* and/or *P. vivax* malaria at the individual level The vaccine may be indicated for malaria control, elimination and/or prevention of reintroduction post-elimination, and may have application in low-, moderate- and high-transmission settings.	Vaccines that prevent infection may be suitable for administration in routine immunization programmes or mass campaigns to targeted age groups. The frequency of periodic mass 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 be appropriate. Immunization strategies may be influenced by factors such as malaria transmission intensity and seasonality, species composition, other malaria interventions in use, and duration of protection. If given to a sufficient proportion of the population, vaccines that prevent blood-stage infection could also reduce community-level transmission. This could be demonstrated in Phase 4 studies after licensure on the basis of individual-level infection and/or disease prevention (see PPCs for vaccines to reduce transmission on p. 12). See report section WHO strategic priorities for malaria vaccines (pp. 1–2).

Parameters	Preferred Product Characteristics	Notes
Target population	To maximize the public health impact of an infection-prevention vaccine, the immediate need will be to target populations or age groups who experience high incidence of infection. However, community-wide effects on transmission could be achieved by vaccinating a substantial proportion of the population that infects mosquitoes. Potential changes in malaria epidemiology should be considered, anticipating shifts in ages with the highest infection incidence at the time vaccines become available.	The target ages for infection reduction may differ between geographical locations and over time as epidemiological conditions evolve. Evaluation in a wide range of ages and risk groups (e.g. occupational exposure among miners, forest workers, etc.) may enhance the number of use cases for the vaccine. In some settings, a very large proportion of the population may need to be vaccinated to reduce community transmission (see PPCs for vaccines to reduce transmission on p. 12). See report section Vaccination strategies for malaria control and elimination: Target populations and Immunization strategies (pp. 24–26).
Safety	The safety and reactogenicity of the vaccine should be comparable to or better than WHO-recommended vaccines in use in LMICs. Safety should also be demonstrated in high-risk or immunocompromised groups, such as HIV-infected children or adults. Developers should be aware of possible deferred increases in morbidity due to the dynamics of waning vaccine-induced immunity and reductions in naturally acquired immunity. Plans for assessment of such effects may be required either in Phase 3 or Phase 4 evaluation.	Methods for documenting and reporting safety data during vaccine clinical trials are described in the *WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (13)*. 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 standardization of data collection and reporting of safety and reactogenicity data in pre-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 Blueprint *(14)*. This document outlines pharmacovigilance systems strengthening as a high priority. Consideration of safety data generation as part of Phase 4 studies and pharmacovigilance systems is strongly encouraged. In addition to assessing quality of products, WHO prequalification and guideline development processes also include a risk–benefit assessment, whereby safety will be assessed in the context of efficacy data from malaria-endemic settings. See report section Clinical development pathways and evaluation tools: safety considerations (pp. 43–44).

Parameters	Preferred Product Characteristics	Notes
Efficacy and duration	The vaccine should dramatically reduce incidence of blood-stage infection (e.g. 90% over 12 months of follow-up post-immunization) at the individual level. 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.	Efficacy data should enable assessment of the requirement for, timing, and effect of additional doses. Description of methods for ascertaining end-points via active case detection (ACD) or passive case detection (PCD) 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 ACD is useful for measuring infection end-points, PCD is preferred in Phase 3 trials to determine public health impact on burden reduction in health facilities. Potential secondary endpoints include impact on severe malaria, malaria-related hospitalizations and mortality, and all-cause mortality. However, these endpoints can be difficult to measure in Phase 3 trials and may be more suitably evaluated in post-licensure studies. If the intervention is designed for use in combination with other tools, technologies or approaches, evidence of a statistically significant beneficial impact may be needed to justify use of the vaccine. This evidence needs to be generated using similar assessments and epidemiological end-points, and in similar contexts as for the established interventions. Vaccines with moderate efficacy against infection may still have considerable value for disease reduction (refer to the PPCs for vaccines to reduce malaria morbidity and mortality, p. 9). Use of infection-prevention vaccines to reduce transmission can potentially be evaluated in post-licensure studies, measured, for example, as reduction in incident human infections at the community level (see PPCs for vaccines to reduce transmission on p. 12). See report section Clinical development pathways and evaluation tools: • Clinical development (pp. 36–37) • End-points, case definitions and analytical strategies in late-stage clinical development (pp. 37–41) • Trial design considerations (pp. 41–43) • From vaccine efficacy to public health impact (pp. 44–46).

Parameters	Preferred Product Characteristics	Notes
Dose regimen and schedule	Single dose for primary immunization is preferred, but additional doses (including annual doses) are likely to be needed for strong and/or long-lasting immunity (e.g. efficacy > 90% and/or duration > 1 year).	More than one dose is acceptable for primary immunization. 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 preferred. Vaccines that can easily be incorporated into existing national immunization programmes in LMICs will harness existing systems and resources and expedite vaccine deployment in the target population. WHO prequalification requires vaccine schedules that meet critical characteristic definitions for dosing *(4)*. Deviations from characteristics suggested by the PSPQ Working Group will result in referral to the PSPQ Standing Committee for review, discussion and recommendation. See report sections: • Clinical development pathways and evaluation tools: from vaccine efficacy to public health impact (pp. 44–46) • WHO prequalification (p. 47) • Programmatic suitability (p. 47).
Co-administration	Immunogenicity data are required if the malaria vaccine may be co-administered with vaccines against other pathogens. Data should provide confidence that immunogenicity and safety of both the malaria and non-malaria vaccines are maintained and there is no clinically relevant interference.	Manufacturers may be requested to design, collect and analyse data on co-administration of vaccines commonly used in routine immunization schedules and catch-up schedules or to protect against outbreak-prone vaccine-preventable diseases (e.g. influenza, measles). Choice of vaccines for co-administration studies should be driven by the vaccines in use for the target population, such as vaccines used in the Expanded Programme on Immunization (EPI). If malaria chemoprevention is used in the target population, immunogenicity data should be generated when the vaccine is co-administered with the drug(s). Relevant co-administration studies are typically included in pre-licensure clinical development plans. If necessary, further co-administration studies could be performed in parallel with or following completion of Phase 3 efficacy studies. The principles of the design of these studies are discussed in the *WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (13)*. See report section Clinical development pathways and evaluation tools: safety considerations (pp. 43–44).

Parameters	Preferred Product Characteristics	Notes
Formulation/ presentation	Vaccines seeking WHO prequalification should meet WHO-defined criteria for programmatic suitability regarding formulation, presentation, packaging, thermostability and disposal *(4)*.	For vaccines that are injectable and indicated for infants and/or young children (< 5 years old), the PSPQ Working Group requires vaccines to be no more than 1 mL per dose, which is mandatory at the time of application for WHO prequalification *(4)*. WHO prequalification mandatory requirements also indicate that vaccines that are injectable, in ready-to-use presentation (no reconstitution) and in multi-dose containers of more than two doses per vial should be adequately preserved, defined as having either a standard thiomersal concentration or a preservative that has demonstrated its antimicrobial efficacy to control for contamination for 28 days using a multi-challenge test, as described in the European Pharmacopoeia *(15)*. Deviations from characteristics suggested by the PSPQ Working Group will result in referral to the PSPQ Standing Committee for review, discussion and recommendation. See report sections WHO prequalification (p. 47) and Programmatic suitability (p. 47–48).
Route of administration	Vaccines seeking WHO prequalification should not require an intravenous route of administration *(4)*, a mandatory requirement by the PSPQ Working Group whereby compliance is compulsory at time of application to WHO prequalification.	However, deviations from characteristics suggested by the 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 health worker training for intravenous administration).

Parameters	Preferred Product Characteristics	Notes
Product stability and storage	Vaccines stable under refrigerated conditions (2–8°C) for 24 months are preferred. Vaccines or any component presented for WHO prequalification should not require storage at less than -20°C *(4)*, a mandatory requirement by the PSPQ Working Group whereby compliance is compulsory at time of application to WHO prequalification.	However, deviations from characteristics suggested by the PSPQ Working Group can be referred 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	Vaccines presented for WHO prequalification will be assessed for programmatic suitability according to mandatory, critical, unique or innovative, and preferred characteristics *(4)*. The vaccine should be prequalified in order to support purchasing by United Nations (UN) agencies *(16)*, according to the process outlined in *Procedure for assessing the acceptability, in principle, or vaccines for purchase by the United Nations agencies* (WHO/BS/10.2155) *(17)*.	For use in mass campaigns or outside routine immunization schedules, the ability to administer and store a large number of vaccines without access to a 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. See report sections: • Clinical development pathways and evaluation tools: from vaccine efficacy to public health impact (pp. 44–46) • WHO prequalification (p. 47) • Programmatic suitability (p. 47–48).
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 LMICs.	The resource implications of vaccine introduction will be considered in the WHO guideline development process *(18)*. The vaccine impact on health systems (such as reduction in malaria-related medical attendance and hospitalization) and other aspects of implementation science should be evaluated in modelling and/or real vaccine use studies. See report section Access and affordability (pp. 48–50).

2.2 PPCs for vaccines to reduce malaria morbidity and mortality

Parameters	Preferred Product Characteristics	Notes
Indication for use	Reduction of clinical malaria, including severe malaria and death due to *P. falciparum* and/or *P. vivax*	Envisaged as vaccines that target pre-erythrocytic or blood-stage antigens The vaccine would be indicated for malaria disease control. See report section WHO strategic priorities for malaria vaccines (pp. 1–2).
Target population	Population subgroups at highest risk of malaria morbidity and mortality. In most settings, this will focus on infants and young children aged 5 years and under, but may include people aged over 5 years (e.g. school-aged children or older) where substantial disease risk exists in this age group. Ongoing changes in malaria epidemiology should be considered, accounting for potential shifts in the ages at highest risk of disease at the time a vaccine becomes available.	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 childbearing age and pregnant women living in areas of malaria transmission (see report sections on Malaria in pregnancy [p. 25]); • 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); • 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 organizations or military personnel] are also at risk; • people 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 marginalized populations. See report section Vaccination strategies for malaria control and elimination: Target populations and Immunization strategies (pp. 24–26).

Parameters	Preferred Product Characteristics	Notes
Safety	Same as for vaccines to prevent infection, listed above	Same as for vaccines to prevent infection, listed above
Efficacy and duration	The vaccine should reduce the incidence of all clinical malaria episodes. Vaccine efficacy to reduce clinical malaria of 90% over 12 months of follow-up post-immunization is highly preferred, but vaccines with lower efficacy, e.g. 45% over 32 months of follow-up, also have the potential for significant public health impact. 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.	Efficacy data should enable 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 *(19)*. Vaccine impact informed by estimates of VPDI or cases averted in a range of transmission intensities will help to determine locally acceptable thresholds for efficacy and anticipated cost-effectiveness for malaria control programmes. Description of methods for ascertaining end-points via ACD or PCD should be included, accounting for health systems factors that may affect detection in different studies or sites (e.g. frequency of follow-up, variations in health-seeking behaviour, etc.). While ACD is useful for measuring infection end-points, PCD is preferred in Phase 3 trials to determine public health impact on burden reduction in health facilities. Potential secondary endpoints include impact on severe malaria, malaria-related hospitalizations and mortality, and all-cause mortality. However, these endpoints can be difficult to measure in Phase 3 trials and may be more suitably evaluated in post-licensure studies. If the intervention is designed for use in combination with other tools, technologies or approaches, evidence of a statistically significant beneficial impact may be needed to justify use of the vaccine. This evidence needs to be generated using similar assessments and epidemiological end-points, and in similar contexts as for the established interventions. See report section Clinical development pathways and evaluation tools: • Clinical development (pp. 36–37) • End-points, case definitions and analytical strategies in late-stage clinical development (pp. 37–41) • Trial design considerations (pp. 41–43) • From vaccine efficacy to public health impact (pp. 44–46).

Parameters	Preferred Product Characteristics	Notes
Dose regimen and schedule	Same as for vaccines to prevent infection, listed above	Same as for vaccines to prevent infection, listed above
Co-administration		
Formulation/ presentation		
Route of administration		
Product stability and storage		
Programmatic suitability		
Access and affordability		

2.3 PPCs for vaccines to reduce malaria transmission

Parameters	Preferred Product Characteristics	Notes
Indication for use	Prevention of malaria transmission at the community level The vaccine may be indicated for malaria control, elimination and/or prevention of reintroduction post-elimination, and may have application in low-, moderate- and high-transmission settings.	Vaccines to reduce transmission may include SSM-VIMTs, as well as highly efficacious pre-erythrocytic and blood-stage vaccines or combination vaccines targeting antigens from multiple stages. 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 prevention 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 children or other relevant age groups may also be appropriate. Immunization strategies may be influenced by factors such as malaria transmission intensity and seasonality, species composition, other malaria interventions in use, and duration of protection. See report section WHO strategic priorities for malaria vaccines (pp. 1–2).
Target population	Children and adults, including women of childbearing age, represent the infectious reservoir and will need to be targeted to maximize the vaccine's impact on transmission. Ongoing changes in malaria epidemiology should be considered, accounting for potential shifts in high-risk populations at the time a vaccine becomes available.	The infectious reservoir for transmission of malaria to *Anopheles* mosquitoes in malaria-endemic areas extends from infancy through to adulthood. While per person infectivity tends to be highest in school-aged children, both adolescents and adults remain infectious to mosquitoes. Given the number of people in these age groups, adolescents and adults 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. The vaccine coverage needed to reduce transmission at the population level in a given region can be informed by modelling designed to reflect the expected level and duration of vaccine efficacy, and the intended use cases and settings. See report section Mathematical modelling (pp. 21–22). See report section Vaccination strategies for malaria control and elimination: Target populations and Immunization strategies (pp. 24–26).

Parameters	Preferred Product Characteristics	Notes
Safety	The safety and reactogenicity of the vaccine should be comparable to or better than WHO-recommended vaccines in use in LMICs.	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. See report section Clinical development pathways and evaluation tools: safety considerations (pp. 43–44).
Efficacy and duration	The vaccine should reduce malaria transmission, resulting in the reduction of incident human infections at the community level.	Given that the efficacy required to reduce transmission is dependent on a number of factors that are not yet well specified, this PPC does not include a specific efficacy target. Minimum acceptable thresholds for efficacy, duration and coverage can be informed by modelling designed to reflect the intended use cases and settings for a given vaccine candidate. See report section Mathematical modelling (pp. 21–22). The 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 nonlinear 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. Clinical trial data should enable 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 finalization of key clinical proof-of-concept and pivotal studies in this area. See report section Clinical development pathways and evaluation tools: • Clinical development (pp. 36–37) • End-points, case definitions and analytical strategies in late-stage clinical development (pp. 37–41) • Trial design considerations (pp. 41–43) • From vaccine efficacy to public health impact (pp. 44–46).

Parameters	Preferred Product Characteristics	Notes
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, unless given with pre-erythrocytic or blood-stage vaccines. See report section Clinical development pathways and evaluation tools: from vaccine efficacy to public health impact (pp. 44–46).
Co-administration	As listed in previous PPC tables above	As listed in previous PPC tables above
Formulation/ presentation		
Route of administration		
Product stability and storage		
Programmatic suitability		
Access and affordability		

3. CLINICAL DEVELOPMENT CONSIDERATIONS

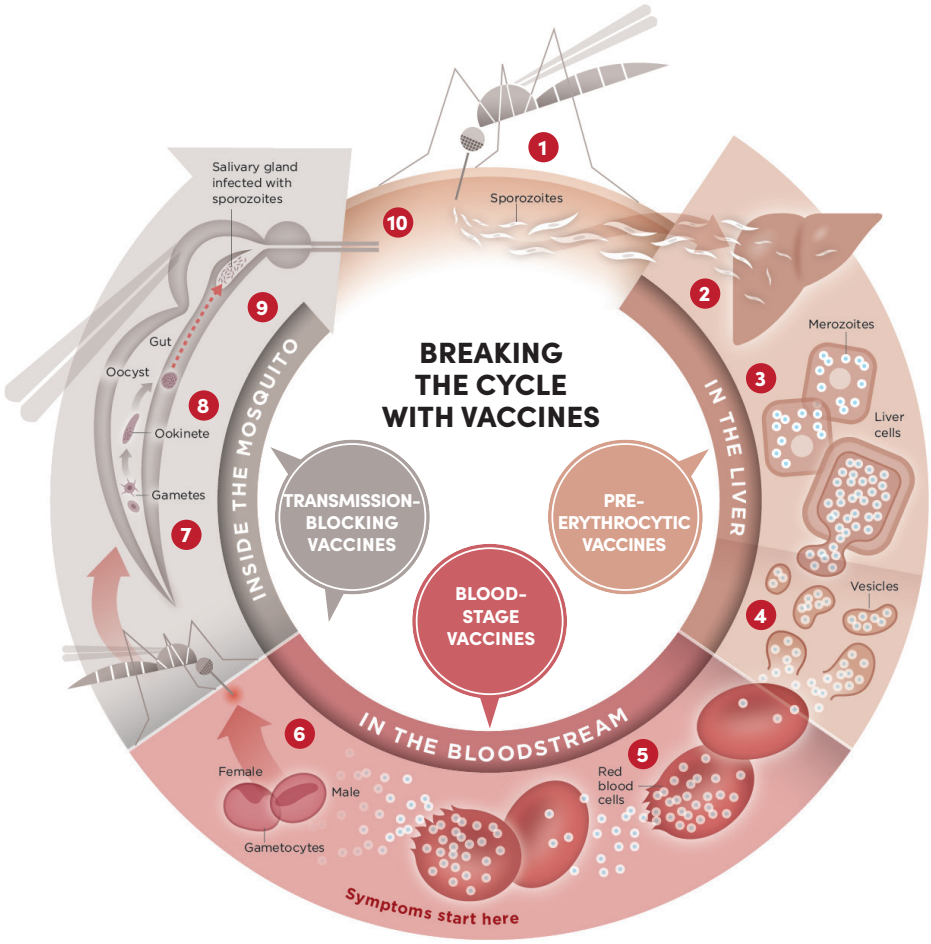
3.1 Vaccine development strategies and tools

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 of inhibiting early parasite development, replication and survival. Functionally, pre-erythrocytic vaccines elicit antibody responses to clear sporozoites from the skin or bloodstream (Fig. 1, stages 1–2), block sporozoite invasion of hepatocytes (Fig. 1, stage 3), or generate T-cell responses against the liver stage to kill infected hepatocytes (Fig. 1, stage 4). Blood-stage vaccines have multiple strategies (Fig. 1, stage 5), including the prevention of merozoite entry into erythrocytes, prevention of adhesion of parasitized erythrocytes, and inhibition of parasite replication or survival. Vaccines that protect the general population may also benefit pregnant women, but vaccines are also being developed to inhibit sequestration of parasitized erythrocytes in the placenta by targeting chondroitin sulfate A (CSA)-binding parasites. Natural antibodies to CSA-binding parasites, often acquired over successive pregnancies by women in endemic areas, have been associated with protection against placental malaria. While pre-erythrocytic and blood-stage vaccines have direct effects at the level of the individual vaccinee, transmission-blocking SSM-VIMTs could be used at the community level to prevent infection, with consequent reductions in morbidity and mortality. SSM-VIMTs aim to directly eliminate sexual stage gametocytes in humans (Fig. 1, stage 6) or block subsequent parasite development in the mosquito (Fig. 1, stages 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 infection in the immunized individual. However, by reducing the number of mosquitoes carrying the parasite, SSM-VIMTs would indirectly reduce the number of infected individuals in the community (Fig. 1, stage 10).

A number of different types of candidate malaria vaccines have been designed and tested. Subunit and viral vector vaccine candidates contain or encode 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* circumsporozoite 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 vaccine candidates are based on whole pathogens that 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 potential 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 immunization 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 antigenic components have been developed, with a number of candidates evaluated in Phase 1 trials *(20–23)*; RNA vaccines are in early-stage R&D.

Fig. 1. Life cycle and vaccine targets *(24).* Malaria parasite infection begins when an infected female *Anopheles* mosquito bites and injects *Plasmodium* parasites in the form of sporozoites into the bloodstream (1). Subsequently, sporozoites pass into the human liver (2) and multiply asexually in the liver cells (3). Merozoites are released from liver cells in vesicles, which eventually disintegrate, freeing merozoites to enter the blood stage of development (4). Merozoites invade erythrocytes in the bloodstream and multiply until cells burst, causing fever, before invading erythrocytes to repeat the cycle (5). Some merozoites leave the asexual multiplication cycle and develop into sexual-stage gametocytes (6). Gametocytes are ingested by mosquitoes when biting an infected human. Gametocytes then develop into gametes (7). Fertilized female gametes develop into ookinetes, burrow through the mosquito midgut wall and form oocysts on the exterior surface (8). Inside the oocyst, thousands of active sporozoites develop, and the oocyst eventually bursts, releasing sporozoites that travel to mosquito salivary glands (9). The cycle of human infection begins again when the mosquito bites a human again (10).



Multi-component vaccines. One challenge in developing single-target malaria vaccines is the wide array of antigens (with varying degrees of immunogenicity) across the parasite life cycle and the high levels of parasite genetic diversity that may lead to variant-specific immunity. Antigenic diversity is one reason that immunity against malaria is acquired slowly and is almost never complete. In the case of SSM-VIMTs, it is particularly challenging to achieve a sustained high level of antibodies over time and adequate coverage to reach herd immunity. The promise of polyvalent 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. The clinical development of multi-component vaccines needs to carefully consider which R&D stages should be completed independently before components are combined.

Preclinical development, proof-of-concept and evaluation technologies

Protective immunity has been associated with a wide range of variables, including human host characteristics (genetics, age, gender, coinfections), 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), and experimental conditions. There are still no agreed correlates of protective immunity against malaria. Due to the distinct localization 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 a reliable correlate of protection has not been identified from controlled human malaria infection (CHMI) or field studies.

An array of functional assays are currently used to evaluate the extent to which a vaccine candidate influences different steps in the parasite life cycle (Table 1). These range from measures of sporozoite mobility and hepatocyte invasion in the pre-erythrocytic stages, to growth inhibition assays (GIAs) or measures of complement fixation and phagocytosis for blood-stage vaccines, and binding inhibition assays for placental malaria vaccines. Despite differences in the pathogenic mechanisms leading to death from malaria between mice or non-human primates and humans, in vivo assays using *P. berghei* or *P. yoelii* orthologs of *P. falciparum* antigens or transgenic parasites and humanized mice have been used for functional screening of vaccine efficacy in mice *(25)*.

For SSM-VIMTs, efforts have been made to standardize 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 and/or sporozoite development in the mosquito. However, there is still a need to bridge results between laboratory and field transmission measures, given that they use different end-points (i.e. reduction in oocyst density versus infection prevalence). This includes studies to evaluate the suitability of SMFAs as a pre- and early clinical measure that reliably predicts natural transmission. Studies are underway to quantify the association between antibody levels and reductions in human-to-mosquito transmission, as determined using different assays and end-points.

For all life cycle stages, the diversity of assays and efficacy end-points across trials has complicated the identification of robust correlates of protection; the harmonization of their use could help improve quantitative vaccine assessment.

Table 1. Functional assays by malaria life cycle stage

Life cycle stage	Assays
Animal models	• Murine models, infection with *P. berghei, P. chabaudi, P. yoelii, P. vinckei* • Humanized mouse models containing human hepatocytes, infection with *P. falciparum* and *P. vivax* • Murine models for expressing chimeric and transgenic parasite strains • Non-human primate models (*Aotus, Saimiri*, and *Macaca mulatta* species for infection with *P. falciparum, P. vivax* and *P. malariae*; *Macaca mulatta* for infection with *P. knowlesi, P. simiovale, P. cynomolgi*)
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 parasitized red blood cells (pRBCs) (with or without lysis) • Opsonic phagocytosis of merozoites or pRBCs • Antibody-dependent cellular inhibition (ADCI) • Antibody-dependent respiratory burst (ADRB) • Antibody-dependent cellular cytotoxicity (ADCC) • Prevention of schizont egress • Inhibition of tissue receptor binding (e.g. chondroitin sulfate A [CSA])
Sexual stage	• Direct skin feeding assay (DSFA) • Direct membrane feeding assay (DMFA) • Standard membrane feeding assay (SMFA)

*Adapted from Stanisic and McCall (2021) *(26)*

Controlled human malaria infection

CHMI studies have been used to understand the mechanisms of protective immunity, to search for immune correlates of protection and to evaluate candidate malaria vaccines *(27)*. 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 under field conditions will be particularly important to understand the effect of prior and frequent malaria exposure on the dynamics of immune response *(28)*.

CHMI studies have been used to inform vaccine formulation, dose, route of administration, 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 have been developed. Direct venous infection (DVI) of *P. falciparum* sporozoites has been used to enable 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 does not require entomology facilities and is more specific than sporozoite challenge in assessing parasite multiplication rate for proof-of-concept. As a well established method for the evaluation of drugs *(29)*, it has also been used for Phase 2 evaluation of *P. falciparum* blood-stage vaccine candidates *(30–32)*. *P. vivax* blood-stage CHMI studies have also been conducted *(33,34)* as proof-of-concept *(35)* to assess human-to-mosquito transmission in direct and membrane feeding assays *(36)*, and to evaluate the efficacy of *P. vivax* vaccines *(37)*. *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 *(38,39)*, with the aim of inducing gametocytaemia and assessing gametocyte transmission to mosquitoes via feeding assays. These CHMI models can help bridge between SMFAs 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, enabling controlled exposure in efficacy trials of vaccine candidates using smaller sample sizes and shorter timeframes than is feasible under conditions of natural exposure. However, studies so far have failed to show consistent immunological correlates of vaccine-induced protection in CHMI models and against naturally acquired infections in field trials.

Parasite strains for homologous and heterologous CHMI challenge. An important consideration in the development of malaria vaccines is their ability to induce strain-transcending protective immunity. In RTS,S Phase 3 trials, the protective efficacy was greater against *P. falciparum* infections with a circumsporozoite protein (CSP) allele matching the vaccine strain compared to infections with malaria parasites with mismatched CSP alleles, arising from the allele-specific nature of vaccine-induced immunity *(40)*. 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 optimizing vaccine formulation prior to field trials.

A number of *P. falciparum* strains are currently available for use in CHMI studies (NF54, West African; 3D7, clonal line derived from NF54; 7G8, clonal line of a Brazilian IMTM22 isolate; NF135.C1, clone derived from a Cambodian isolate; NF166.C8, clone derived from a clinical isolate of a child who travelled to Guinea [West Africa] *(41)*; HMP02, Ghana, blood-stage challenge only; Cam3.II^{R539T}, artemisinin-resistant strain for blood-stage challenge *(42)*), with fewer strains available for *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi (27)*. It is unclear how representative these strains are of the parasite diversity in malaria-endemic areas. Future CHMI studies would benefit from improved characterization and development of additional parasite strains that can consistently produce gametocytes and sporozoites, be cloned to produce a genetically homogeneous 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.

Interpretation of data from CHMI and generalizability 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 strains expected in settings where vaccines are intended to be used. Furthermore, caution should be exercised when comparing results between studies with different target populations and follow-up times. Standardization of follow-up times used in CHMI vaccine studies should improve comparability of results between different studies and different vaccines at this stage of testing (see Annex 1, Table A1.1).

Systems vaccinology. Numerous malaria studies have attempted to define vaccine-induced protective immunity, identifying a variety of host immune responses associated with post-vaccination clinical outcomes. However, there are still no clear or consistent mechanistic explanations to predict vaccine efficacy. Vaccine performance under field conditions will be affected by many factors including parasite diversity, transmission intensity and seasonality, coinfections, host nutritional and metabolic status, as well as vaccine composition, vaccine dosing and schedule, study follow-up durations and end-points. Novel data science approaches in systems biology and vaccinology are being used to better understand the immune response to vaccination for pathogens such as influenza *(43)* and may have application in malaria *(44)*. 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 used these approaches to investigate immunological correlates of *Plasmodium* infection and vaccination *(45,46)*. This type of large-scale data integration and analysis will require collaboration across institutions and sectors. Data-sharing agreements developed according to FAIR (Findable, Accessible, Interoperable, Reusable) Guiding Principles for scientific data management and stewardship *(47)* can help large research networks with the infrastructure to comprehensively analyse data from immunology, vaccine and field studies. Several U.S. National Institute of Allergy and Infectious Diseases (NIAID)-supported research programmes provide open science research environments such as the Systems Biology Consortium for Infectious Diseases *(48)* and the International Centers of Excellence for Malaria Research (ICEMR) *(49)*.

Monoclonal antibodies (mAbs). Other tools being used to assist in the preclinical characterization of the human antibody response to vaccines and parasite infection are 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 more potent 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 *(50)*. Improvements in production and manufacturing have reduced some cost barriers to 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.

Adjuvants and vaccine delivery platforms. Most candidate malaria vaccines 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 critical components in the advancement of new vaccines.

Recent years have seen increased investment in adjuvant development. The NIAID 2018 Strategic Plan for Vaccine Adjuvant Research encompassed a range of R&D areas, from fundamental immunology and adjuvant discovery to preclinical and clinical adjuvant development and evaluation *(51)*. This has led to research on adjuvant comparison and characterization *(52)*, molecular mechanisms of combination adjuvants (MMCA) *(53)*, production of adjuvant mimics *(54)*, and adjuvant development for vaccines *(55)*. The Vaccine Adjuvant Compendium (VAC) was also established 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 different vaccine indications (https://vac.niaid.nih.gov/) *(56)*. Similarly, the Vaccine Formulation Institute (VFI) provides a range of adjuvants, technology and expertise to support the optimization of vaccines in preclinical and clinical settings (https://www.vaccineformulationinstitute.org/).

In the area of vaccine delivery platforms, VLPs and vesicle-based technologies have been tested, along with mixed-modality prime-boost immunization regimens using vectored and protein-based components to maximize cellular and humoral immune responses *(57)*.

Mathematical modelling. When informed by data on expected vaccine characteristics, and the epidemiological and health system characteristics in the settings of intended use, mathematical models can provide estimates of potential public health impact and support decision-making and investment planning for product developers, WHO, Gavi and other stakeholders. Modelling can examine the relative importance of different vaccine characteristics for a range of end-points and how estimates may differ across settings, use case scenarios, or deployment strategies (Table 2).

Vaccines with characteristics similar to RTS,S have been modelled to understand the effect of efficacy, duration of protection or vaccine coverage on health outcomes, stratified by transmission intensity and age group. Modelling can help anticipate the potential impact across a range of end-points, from incidence of infection or uncomplicated malaria to severe malaria and deaths. Analysis of the relationship between end-points can be particularly useful for more severe outcomes that are difficult to detect in Phase 3 trials.

Several models have evaluated the potential impact of anti-infective or transmission-blocking vaccines when combined with other malaria control interventions, including seasonal malaria chemoprevention (SMC), mass drug administration (MDA) or vector control. Studies have also aimed to estimate minimum vaccine characteristics (efficacy, half-life of protection, coverage) required to achieve target reductions in infection prevalence across different transmission intensities in seasonal and perennial settings. Models have been used to estimate the potential cost-effectiveness of vaccine candidates across a range of epidemiological settings *(58,59)*.

Modelling has also explored the potential public health impact of transmission-blocking vaccines. For example, based on antibody levels observed for vaccine candidate Pfs25, models have evaluated the impact of duration of antibody response on clinical cases averted, the effect of targeting different age groups, as well as the age groups in which

the burden of malaria is most reduced *(60)*. This study also evaluated the relationship between antibody titres and transmission-reducing and transmission-blocking activity. Modelling has also explored the potential synergy of co-administering pre-erythrocytic and transmission-blocking vaccines to reduce infection prevalence *(61)*.

To inform research and policy decisions as candidates progress through the pipeline, modelling should consider the minimum characteristics required to achieve public health impact based on priority use case scenarios and deployment strategies in different epidemiological settings.

Table 2. Examples of vaccine modelling studies to inform product development and public health decision-making

	Variable	Study references
Vaccine characteristics	Efficacy / Initial efficacy	*58,59,62–64*
	Duration of protection / Half-life	*58–60,62–64*
	Dose regimen and schedule	*59,62*
End-points	Uncomplicated malaria	*58,59,62,65*
	Severe malaria	*58,59,62,65*
	Hospitalizations or deaths	*58,59,65*
	Vaccine preventable disease incidence	*19*
	Incidence or prevalence of infection	*63,64*
	Cost-effectiveness / Disability-adjusted life years (DALYs) averted	*58,59*
Epidemiological setting	Transmission intensity	*58,59,62,64*
	Perennial transmission	*62,64*
	Seasonal transmission	*60,63,64*
Deployment	Coverage	*58–60,63–65*
	Target age group	*60*
	Seasonal administration	*63*
Combined interventions	Seasonal malaria chemoprevention (SMC)	*65*
	Mass drug administration (MDA)	*63,64*
	Vector control	*60,65*
Multi-target vaccines	Pre-erythrocytic, blood-stage, and/or sexual, sporogonic, or mosquito stage vaccines	*61*
Early clinical to Phase 3 end-points	Antibody titres, avidity, efficacy	*66*
	Antibody titres and transmission reduction	*60*

3.2 Malaria vaccine pipeline: status as of August 2022

RTS,S/AS01 pilot implementation and additional studies

In July 2015, RTS,S/AS01 became the first malaria vaccine to receive a positive scientific opinion from the EMA *(10)*. Subsequently, 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 Immunization and the Malaria Policy Advisory Group (MPAG; formerly the Malaria Policy Advisory Committee), WHO recommended pilot implementation in moderate to high malaria transmission settings in sub-Saharan Africa *(67)*. A four-dose schedule of the RTS,S/AS01 vaccine was recommended in children from 5 months of age, with the first three doses given a minimum of four weeks apart and the fourth dose provided approximately 15–18 months after dose three *(68,69)*. This recommendation was based, in large part, on results from a Phase 3 clinical trial conducted at 11 sites in seven African countries, which included a follow-up period of three to four years (depending on age at enrolment) *(70)*. Extended follow-up in three of the trial sites later confirmed that significant protection against clinical malaria was still evident after seven years of follow-up in children receiving three or four vaccine doses *(71)*.

The Malaria Vaccine Implementation Programme (MVIP) was developed to respond to the SAGE/MPAG recommendation for a phased introduction of RTS,S/AS01 through the EPI *(72)*. Vaccinations began in 2019 in Ghana, Kenya and Malawi *(72,73)*. In parallel, Phase 4 studies were implemented by GlaxoSmithKline as part of its risk management plan and post-authorization evaluation programme *(74)*. In October 2021, a full review of the evidence on RTS,S/AS01 by WHO malaria and immunization advisory groups resulted in a WHO recommendation for the widescale use of the vaccine in children living in areas of moderate to high *P. falciparum* transmission.

Additional studies have included evaluation of fractional doses of RTS,S, annual doses and reduced intervals between doses three and four in children in endemic settings (NCT03276962) *(75)*, and a comparative field trial of seasonal vaccination of RTS,S/AS01 with or without SMC in Burkina Faso and Mali (NCT03143218) *(76)*.

Clinical development

Over the past 20 years, new malaria vaccine trials have been registered at a rate of approximately 10 trials per year *(11)*.[1] The R21 anti-sporozoite subunit vaccine candidate (NCT04704830, NCT03580824) *(77–79)* targets the same circumsporozoite protein antigen (CS) as RTS,S, but has different immunogenic properties *(80)* and is combined with Matrix-M adjuvant technology *(81)*. R21 entered Phase 3 development in late 2021 (NCT04704830). PfSPZ is a pre-erythrocytic radiation-attenuated vaccine platform using aseptic, purified, vialled, cryopreserved *P. falciparum* sporozoites and has also completed several Phase 2 studies (NCT03521973, NCT03503058) *(82,83)*. 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) *(34,84)* and SE36, a single recombinant protein-based vaccine candidate targeting the *P. falciparum* serine repeat antigen 5 (SERA5) *(85)*. SSM-VIMT candidates include pre-fertilization antigens, Pfs230 (NCT03917654) *(86)* and Pfs48/45 *(87)*, and post-fertilization antigens, Pfs25 (NCT04271306) *(88)* and Pfs28 *(89,90)*.

1 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/observatories/global-observatory-on-health-research-and-development/monitoring/health-products-in-the-pipeline-from-discovery-to-market-launch-for-all-diseases) *(12)*.

Malaria in pregnancy. Malaria in pregnancy is associated with sequestration of *P. falciparum*-infected erythrocytes that bind to CSA in the placenta via the VAR2CSA protein. Two VAR2CSA antigen-based vaccine candidates have been evaluated in Phase 1 trials: PRIMVAC (NCT02658253) *(91)* and PAMVAC (NCT02647489) *(92)*. Additionally, any vaccines that can prevent *P. falciparum* infection and can be delivered safely to women of childbearing age or early in pregnancy have the potential to reduce the burden of malaria in pregnancy.

Vaccines targeting P. vivax. In 2019, the global burden of *P. vivax* stood at 6.9 million cases *(93)*, 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 suggests that pre-erythrocytic vaccines preventing dormancy, blood-stage vaccines, SSM-VIMTs, and 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. These include the subunit vaccines VMP001/AS01 and VMP002 targeting CSP (NCT01157897) *(94)*, a radiation-attenuated *P. vivax* sporozoite candidate *(37)*, blood-stage vaccine candidates targeting the *P. vivax* Duffy-binding protein (PvDBP) *(95,96)*, and a sexual-stage candidate Pvs25H/Alhydrogel protein vaccine *(97)*.

3.3 Vaccination strategies for malaria control and elimination

Target populations

The development of any malaria vaccine must 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 as long as there is stable malaria transmission. Reductions in transmission also produce changes in the relative contribution of different malaria species, and *P. vivax* has become 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 *(98)*.

A number of factors are commonly considered in malaria risk stratification and may help identify potential target groups for vaccination *(99)*. For example, epidemiological metrics such as parasite prevalence, clinical case incidence, and malaria-specific and all-cause mortality can be used to identify the target age groups experiencing a substantial proportion of malaria disease or infection. 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 depend 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 at the time a vaccine becomes available.

Target age group. In high-transmission areas, infants and children under 5 years old are typically at greatest risk of malaria, while older age groups may become

increasingly at high risk of severe disease and death as the intensity of transmission declines. Even in settings with intense transmission, morbidity from uncomplicated disease may nevertheless be significant in adolescents and adults, as may non-health impacts of malaria disease (e.g. educational outcomes, economic productivity); therefore, they may represent an additional target group for malaria vaccination. In settings with *P. vivax*, adults and adolescents, in addition to infants and small children, are often at risk in moderate- to low-transmission settings *(98)*.

Malaria in pregnancy. Pregnant women are highly susceptible to *P. falciparum* malaria, resulting in substantial maternal, perinatal, and infant morbidity and mortality *(100)*. Primigravid women are at particular risk due to the immunological and physiological changes during pregnancy. For pregnant women living in stable transmission areas, WHO recommends use of insecticide-treated nets (ITNs) while sleeping and chemoprevention through intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP). Women may often develop malaria before receiving their first IPTp dose. As a result, IPTp and ITNs only provide partial protection, and rates of malaria in pregnancy remain high. This, coupled with ongoing challenges with IPTp compliance and coverage (in 2020, 57% of women in 33 African countries received their first IPTp dose, but only 46% and 32% received their second and third dose, respectively *(6)*) suggest that vaccines could provide substantial additional health benefits for women and their babies. Vaccines used in children and adults can potentially be used in pregnant women and women of childbearing age. These vaccines, as well as vaccines targeting pregnancy-specific antigens to prevent placental malaria, would need to either 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 not only to demonstrate the safety and efficacy of vaccines to specifically protect against malaria in pregnancy, but also to enable the inclusion of pregnant women, who may represent an important infectious reservoir, in mass vaccination campaigns. Inclusion of pregnant women in clinical trials can help establish effective dosing during pregnancy and minimize risk to both the mother and infant in all trimesters. Such trials would need to consider definitions for pregnancy-specific end-points (e.g. placental and peripheral parasitaemia) and maternal and infant outcomes (e.g. low birthweight, delivery complications, stillbirth or neonatal death, and maternal anaemia).

Other potential target populations. The epidemiology of malaria in areas such as the Greater Mekong Subregion 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 the Bolivarian Republic of Venezuela, Brazil, Colombia, Ecuador and Peru. 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, presenting major challenges for malaria control and elimination programmes *(101)*. In regions that have already cleared or locally eliminated malaria, vaccination could also target high-risk travellers to prevent reintroduction.

Immunization strategies

Priority immunization strategies will depend on the indication and use case of the vaccine, as well as on 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 immunization programmes using schedules compatible with existing immunization visits is envisaged where infants and young children are the primary risk group. In settings where adolescents and adults may also be at risk, initial vaccine introduction may be through mass immunization campaigns to rapidly cover the susceptible population, followed by the addition of the vaccine to routine immunization 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 prevention campaigns to a broad age range, where the frequency of campaigns will depend on the duration of protection and on population birth and in-migration rates. Transmission-reducing vaccines with long-lasting efficacy may also be considered for routine vaccination of infants and young children after, or in addition to, initial mass campaigns.

For both indications, the use of periodic mass immunization campaigns could reduce the risk of clinical malaria in populations living in malaria-endemic settings, and help to control malaria epidemics and re-importation outbreaks in post-elimination settings.

Ultimately, the aim is to deliver malaria vaccines using strategies that achieve the highest impact. This may involve delivering additional doses before peak transmission seasons or targeting areas with poor access to case management or other 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 a vaccine candidate provides a relatively short period of high-level protection, it could conceivably be useful in seasonal or emergency settings where the required duration of protection may be shorter. This includes a substantial proportion of the highest burden countries in Africa, 80% of which have areas in intensely seasonal transmission settings *(102–104)*. In 2020, 31.2 million children were targeted for SMC in 13 sub-Saharan African countries *(6)*. Additionally, nearly all settings with perennial transmission experience some seasonal increases in transmission and disease. Therefore, the use of seasonal vaccination strategies on top of routine vaccination through the childhood EPI may be useful. 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. It is particularly important to minimize the number of doses required to provide adequate protection in emergency settings, where access to the target population may be difficult, and in seasonal vaccination scenarios. An example of seasonal vaccination is provided by a study evaluating the efficacy of a primary course (three doses) of the vaccine before the rainy season, followed by an additional dose annually, prior to each subsequent rainy season *(105,106)*.

The Coalition for Epidemic Preparedness Innovations (CEPI) was established in 2016 to accelerate vaccine development for emerging infectious diseases and to enable access to vaccines during outbreaks. During outbreaks of major infectious diseases such as Ebola, substantial increases in untreated malaria cases can occur due to declines in health facility attendance and disruptions to community-based malaria control programmes *(107,108)*, highlighting the potential value of malaria vaccination in such settings.

3.4 Special PPC considerations for seasonal vaccination

Parameters	Preferred Product Characteristics	Notes
Indication for use	Seasonal vaccination to reduce morbidity and mortality due to *P. falciparum* and/or *P. vivax* malaria Prevention of clinical malaria, including manifestations of severe malaria, caused by *P. falciparum* and/or *P. vivax*	This is a variation of the PPCs for vaccines to reduce morbidity and mortality. Only differences or important additional considerations are highlighted in this PPC table. Seasonal vaccination may be considered for administration of the primary vaccination series or, more likely, annual booster vaccinations to supplement routine vaccination programmes. See report section Seasonal or emergency situations (p. 26).
Target population	Populations most at risk of malaria in geographical regions where malaria 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 over 5 years of age where substantial disease risk exists in this age group. See report section Vaccination strategies for malaria control and elimination: Target populations and Immunization strategies (pp. 24–26).
Safety	As listed in previous PPC tables above	As listed in previous PPC tables above
Efficacy and duration	High efficacy against infection and/or clinical malaria (as described in strategic goals 1 and 2) is highly desirable, matching the period of malaria risk.	Same as for vaccines to reduce morbidity and mortality

Parameters	Preferred Product Characteristics	Notes
Dose regimen and schedule	Single or minimal number of doses to protect during period of malaria risk	A primary immunization course could be administered at scheduled ages through routine immunization services, or 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). Subsequent doses may be delivered before high-transmission seasons, rather than being strictly age-targeted. See report section Clinical development pathways and evaluation tools: from vaccine efficacy to public health impact (pp. 44–46).
Co-administration	As listed in previous PPC tables above	Seasonal vaccination may be indicated in settings where SMC is implemented. SMC delivers malaria medicines during the peak transmission season, whereas seasonal vaccination would deliver booster doses before the peak transmission season. See report sections Vaccination strategies for malaria control and elimination: use of vaccines with other malaria interventions (p. 36) and Clinical development pathways and evaluation tools: safety considerations (pp. 43–44).
Formulation/ presentation	As listed in previous PPC tables above	As listed in previous PPC tables above
Route of administration		
Product stability and storage		
Programmatic suitability		
Access and affordability		As listed in previous PPC tables above Cost-effectiveness should be considered in the context of other seasonally targeted malaria interventions.

3.5 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 in geographical areas at risk of malaria	This is a variation of the PPCs for vaccines to reduce morbidity and mortality. Only differences or important additional considerations are highlighted in this PPC table. Additional considerations can be referenced in the following WHO reports: • *Vaccination in acute humanitarian emergencies (109)* • *Vaccination in humanitarian emergencies: implementation guide (110)* See report section Seasonal or emergency situations (p. 26).
Target population	Target population experiencing high risk of malaria in complex emergencies, which may include expanded target age groups compared to routine vaccination in endemic settings Displaced persons due to environmental or humanitarian disasters in malaria transmission zones, especially those in crowded camps or settlements This may also include populations not directly affected by the emergency, but living in close proximity to those who are, whether hosting displaced populations or experiencing increased risk due to changing local circumstances or health service delivery. A guiding principle should be equitable access to vaccination for those at equal risk.	Special considerations include the following: • 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 vaccine implementation (e.g. overcrowding; insufficient access to water, sanitation and hygiene; reduced access to health services).
Safety	Same as for 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 do not necessarily need to be generated in emergency situations, and data from evaluations in more stable settings can be considered.

Parameters	Preferred Product Characteristics	Notes
Efficacy and duration	High efficacy against infection and/or clinical malaria (as described in strategic goals 1 and 2) is highly desirable, matching the period of malaria risk.	Due to the difficulties associated with the collection of epidemiological data in complex humanitarian emergency settings, safety and efficacy data do 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. 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 course, less than full course, and fractional dose use). See report section Fractional dosing and dose sparing (p. 32).
Dose regimen and schedule	Single or minimal number of doses particularly valuable 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 may be particularly useful if adequate efficacy is maintained. • For refugee populations, feasibility of administering the immunization schedule of country of origin may need to be considered. See report section Clinical development pathways and evaluation tools: from vaccine efficacy to public health impact (pp. 44–46).
Co-administration	Data should ideally be available on malaria and non-malaria vaccines, as well as on drugs that may be co-administered in emergency situations (e.g. for cholera, measles, meningococcal meningitis, or malaria medicines used in SMC or MDA) to ensure that immunogenicity and safety are maintained and there is no clinically relevant interference.	In many cases, vaccine delivery may also be used as an opportunity to deliver other interventions, be it other vaccines, medicines, ITNs, vitamins or commodities such as soap, jerry cans, shovels, 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 immunization services. Nevertheless, depending on the context, the addition of each additional item to vaccination delivery should be approached cautiously to minimize the risk of overwhelming limited human and logistical resources.

Parameters	Preferred Product Characteristics	Notes
Formulation/ presentation	As listed in previous PPC tables above	As listed in previous PPC tables above
Route of administration	As listed in previous PPC tables above	As listed in previous PPC tables above
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.	As listed in previous PPC tables above
Programmatic suitability	As listed in previous PPC tables above	Distribution may primarily be 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 geographical 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, civil society organizations (CSOs) or stockpiles. International donor stockpiles are managed through an International Coordinating Group on Vaccine Provision (ICG), which reviews country requests for vaccines in 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 key component in malaria elimination programmes both in settings where transmission is moderate or high and in areas where the prevalence of infection is very low or highly localized. All-age vaccination campaigns are likely to be needed 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 MDA, which can clear a large number of infections from a population, vaccines that protect against infection for durations as short as one year could have a substantial impact on delaying resurgence *(111)*.

Fractional dosing and dose sparing. Vaccine efficacy is dependent on the number of doses in a recommended course. The delayed administration of smaller doses (i.e. fractional dosing or dose sparing) may increase vaccine efficacy when a fractional dose is administered later in the primary immunization schedule. Fractional dosing may also help to mitigate vaccine shortages, extend vaccine coverage to a larger number of individuals, and/or improve the cost-effectiveness of vaccines. Fractional dosing strategies have been used for meningococcal vaccine *(112)*, yellow fever vaccine *(113)*, and inactivated poliovirus vaccine *(114)*. In a Phase 2b study, vaccine efficacy of RTS,S fractional dose in children in endemic settings was similar to full-dose RTS,S (NCT03276962) *(115)*. Delayed fractional dosing of the vaccine candidate Rh5.1/AS01$_B$ has also been tested as part of a Phase 1a study in healthy adult volunteers in the United Kingdom of Great Britain and Northern Ireland *(34)*.

In some settings, population movements and erratic access to populations due to security or 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 situations, decision-making on vaccine use needs to balance the best available information on vaccine efficacy at less than the full course with the potential benefit of vaccination for the target population *(109)*. It may be important to determine whether schedules that differ from those used in routine immunization would be better suited to the emergency situation. For vaccines currently in development, evaluating the efficacy of fractional dosing prior to Phase 3 trials could provide valuable data for decision-making at a later date.

Special considerations for P. vivax *vaccine development.* There has been an interest in the control of *P. vivax*, particularly in the Asia Pacific region and Latin America where persistent *P. vivax* presents ongoing challenges *(116,117)*. 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. In studies in Thailand and Papua New Guinea, approximately 80–90% of *P. vivax* cases were due to relapses *(118,119)*. Modelling suggests that vaccines with high efficacy against relapses, by targeting hypnozoites, could lead to substantial reductions in parasite prevalence, even if efficacy against primary infection was low *(120)*.

While the general principles of trial design for *P. vivax* vaccines are similar to those for *P. falciparum*, the dormant phase has implications, particularly in terms of the increased follow-up time required for trial populations and the desirability of distinguishing new infections from relapses. It may be preferable to conduct trials in regions with faster relapsing strains *(121)* where follow-up times can range from nine to 12 months if active and frequent detection of infection is conducted (e.g. every four weeks with PCR). Given the difficulty in endemic settings of confirming whether *P. vivax* episodes are due to new infections or relapses, primary trial end-points should be incidence of infection overall.

In most regions with endemic *P. vivax*, infection is primarily in adolescents and adults, driven by a combination of peri-domestic and occupational transmission *(98,122,123)*. Therefore, vaccines would likely be targeted at high-risk groups such as forest workers or miners. There are only limited settings where transmission in children is high enough to warrant the administration of a *P. vivax* vaccine through routine childhood immunization programmes *(98,123)*. Given that the incidence of severe disease and mortality from *P. vivax* is substantially lower than for *P. falciparum*, trials may need to be conducted primarily in adolescents and adults where the risk of *P. vivax* is highest. Trials could potentially be conducted in children in highly endemic areas where the incidence of infection is sufficiently high to maintain feasible sample sizes *(98)*.

To evaluate the efficacy of pre-erythrocytic *P. vivax* vaccines, unless it is predicted that the vaccine may be therapeutic by acting on established hypnozoites, measuring the incidence of infection as an end-point in Phase 2 trials may require treatment-reinfection designs, whereby radical treatment of liver and blood stages is given after the last vaccine dose but prior to the infection observation period. The 8-aminoquinoline drugs used to eliminate hypnozoites can cause severe haemolytic anaemia in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency *(124)*, a phenotype that is particularly common in *P. vivax*-endemic areas. Therefore, the use of radical cure to improve detection of incident *P. vivax* infections requires careful screening and exclusion of G6PD-deficient volunteers. Study designs including arms with and without radical cure may be useful, but will lead to larger sample sizes. For blood-stage vaccines, a traditional cohort design without radical cure may be suitable. As noted above, if pre-erythrocytic vaccines that target hypnozoites (either by eliminating them from the liver or preventing their development) are expected to reduce relapses and blood-stage parasitaemia, this potential effect may need to be accounted for in clinical trial designs when estimating vaccine efficacy on the incidence of blood-stage infection.

In areas endemic to both *P. vivax* and *P. falciparum*, the effect of coinfection or shifting dynamics of species distribution due to vaccination may need to be monitored in Phase 3 vaccine trials or post-licensure studies. Evidence on cross-protection is conflicting, and some studies have found increased risk of severe disease in mixed *P. vivax*/*P. falciparum* infections *(125–127)*. Potential increases in *P. falciparum* risk among *P. vivax* vaccine recipients should be monitored, and rapid access to early diagnosis and treatment for symptomatic individuals in trial sites is needed. In proof-of-principle studies, the higher incidence of clinical episodes detected through ACD, compared to PCD, can facilitate initial estimates of efficacy and close monitoring of *P. falciparum* disease. Once clinical data indicate no significant increase in *P. falciparum* disease, PCD is preferable for Phase 3 trials to more accurately reflect the public health value of the vaccine as experienced by the health system. Studies in dual-endemic zones may help to determine if there is a need to include *P. falciparum* vaccine components to prevent *Plasmodium* species interaction *(98)*.

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

Parameters	Preferred Product Characteristics	Notes
Indication for use	Reduction of clinical malaria and/or infection due to *P. vivax* malaria	Envisaged as vaccines that target pre-erythrocytic and/or blood-stage *P. vivax* antigens that reduce the frequency of primary infections and/or relapses and can prevent clinical disease and/or transmission Many PPC considerations for *P. vivax* vaccines are similar to those for *P. falciparum* vaccines. Only differences or important additional considerations are highlighted in this PPC table. See report section Special considerations for *P. vivax* vaccine development (pp. 32–33).
Target population	In most endemic regions, vaccination campaigns can be targeted at adolescents and adults, or high-risk occupations such as forest work or mining. Potential to be delivered through routine immunization programmes only in limited areas where infection is primarily in children	In most endemic regions, *P. vivax* risk is primarily in adolescents and adults, driven by peri-domestic and occupational transmission. It is only in limited geographies with moderate to high transmission that *P. vivax* is a predominantly paediatric illness.
Safety	Same as for vaccines to reduce morbidity and mortality due to *P. falciparum* Additionally, monitoring potential increases in the incidence and severity of *P. falciparum* episodes following *P. vivax* vaccination may be needed in areas where both parasites are present. If treatment-reinfection study designs are used, safe treatment with 8-aminoquinolines requires testing for G6PD deficiency.	Same as for vaccines to reduce morbidity and mortality due to *P. falciparum* Additionally, coinfection with *P. vivax* may modulate the incidence and severity of *P. falciparum* illness, and an increase in *P. falciparum* risk among *P. vivax* vaccine recipients could be a potential safety concern.

Parameters	Preferred Product Characteristics	Notes
Efficacy and duration	Vaccine needs to provide sufficiently long protection to cover both initial infection and relapses from long-lasting liver stages. Note the geographical variability in relapsing patterns. If incidence of infection is used as a trial end-point for pre-erythrocytic vaccines, trial duration needs to account for the hypnozoite stage and the effect of latent/recurrent disease. Consider G6PD testing if treatment-reinfection study designs are to be used.	Choice of case definition may differ between proof-of-principle Phase 2 trials and later stage field efficacy studies (large Phase 2b and 3 trials). In proof-of-principle studies, measuring a higher incidence of clinical episodes through ACD can enable better determination of efficacy and close monitoring of *P. falciparum* disease. Once sufficient clinical safety data indicate no significant increase in risk of *P. falciparum* morbidity, PCD is preferable in Phase 3 trials to measure clinical efficacy as experienced by the health system.
Dose regimen and schedule	Same as for vaccines to reduce morbidity and mortality due to *P. falciparum*	Same as for vaccines to reduce morbidity and mortality due to *P. falciparum*
Co-administration	Efficacy trials in dual-endemic zones can enable early assessment of the need for co-administration or inclusion of a *P. falciparum* vaccine component to prevent potential *Plasmodium* species replacement/interaction.	A reduction in the incidence of *P. vivax* may lead to an increase in the incidence of other *Plasmodium* species. Assessment of multiple species during the surveillance period may be needed.
Formulation/ presentation	Same as for vaccines to reduce morbidity and mortality due to *P. falciparum*	Same as for vaccines to reduce morbidity and mortality due to *P. falciparum*
Route of administration		
Product stability and storage		
Programmatic suitability		
Access and affordability		

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 ITNs and/or indoor residual spraying with insecticide, malaria chemoprevention, the use of quality-assured rapid diagnostic tests (RDTs) and effective antimalarial chemotherapy. Routine immunization programmes often achieve higher coverage than other malaria control strategies. The use of multiple interventions and delivery strategies can help maximize the number of children receiving at least one preventive malaria intervention, thus reducing inequities.

Malaria vaccination may be considered in seasonal transmission settings, alongside or instead of SMC if, for example, areas are facing difficulties achieving or sustaining high SMC coverage and compliance, or where drug resistance undermines the effectiveness of SMC. Administration of a single vaccine dose 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 SP and amodiaquine (AQ) *(105)*. In addition to safety and efficacy, data on the expected cost-effectiveness of a malaria vaccine can help inform WHO policy processes and country decision-making. However, caution is required when comparing the cost-effectiveness of different interventions that have been studied in different contexts and at different times, as the results can be misleading.

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

3.7 Clinical development pathways and evaluation tools

Clinical development

Preliminary trials (Phases 1 and 2a) assess safety, immunogenicity, dose regimen and schedule, and formulation. Evidence of efficacy against end-points of interest, including those related to biomarkers of efficacy (e.g. mosquito feeding data for transmission-blocking vaccines) 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 (Phases 2b and 3) are intended to provide robust evidence to support licensure, usually based on demonstration of safety and efficacy using randomized controlled trials with clinical end-points. There is currently no accepted single correlate of malaria vaccine-induced protection. Whereas Phase 1 and 2a trials have typically been conducted in non-immune populations, pivotal studies generate data in the target population.

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 finalization of pivotal trial protocols, so that global guideline considerations can be taken into account. Readers are encouraged to refer to the *WHO Coordinated Scientific Advice procedure (128)* and the *WHO Guidance on clinical evaluation of vaccines (129)* for details on regulatory expectations.

The development of vaccines that combine targets from different stages of the parasite's life cycle requires special considerations, including the clinical development stage at which to individually test the different components of a multi-stage vaccine and when to test the combination.

Trials to demonstrate impact on transmission. Demonstrating an impact on transmission requires study designs that differ from those of trials to establish efficacy against individual-level infection or clinical disease. Cluster randomized trials (CRTs), where the unit of randomization is the community or cluster of individuals, may be used, where the primary measure of efficacy may be the incidence or prevalence of human *Plasmodium* infection. The feasibility of measuring efficacy against clinical end-points will depend on the baseline transmission intensity. In low-transmission settings, low incidence rates are likely to result in prohibitively large sample sizes to achieve adequate statistical power to determine efficacy against clinical end-points. Trials conducted in high-transmission settings will have more statistical power to measure impact on clinical end-points and potentially community-level transmission than trials in lower transmission settings. However, the impact on infection will differ in low-transmission compared to moderate- or high-transmission settings, and the generalizability of trial results between transmission intensities needs careful consideration.

Developers are also encouraged to explore alternative trial designs for proof-of-concept studies, such as licensure based on analytically and biologically validated surrogates of efficacy against transmission, which would need to be followed by demonstration of impact on community-level transmission in post-approval studies *(130)*. The former would require robust and validated assays, approved by regulatory agencies, that can serve as surrogates for transmission reduction in humans. 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 can provide critical additional data. For instance, post-licensure studies may be used to demonstrate the generalizability 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 end-points may also require demonstration of effectiveness in routine use.

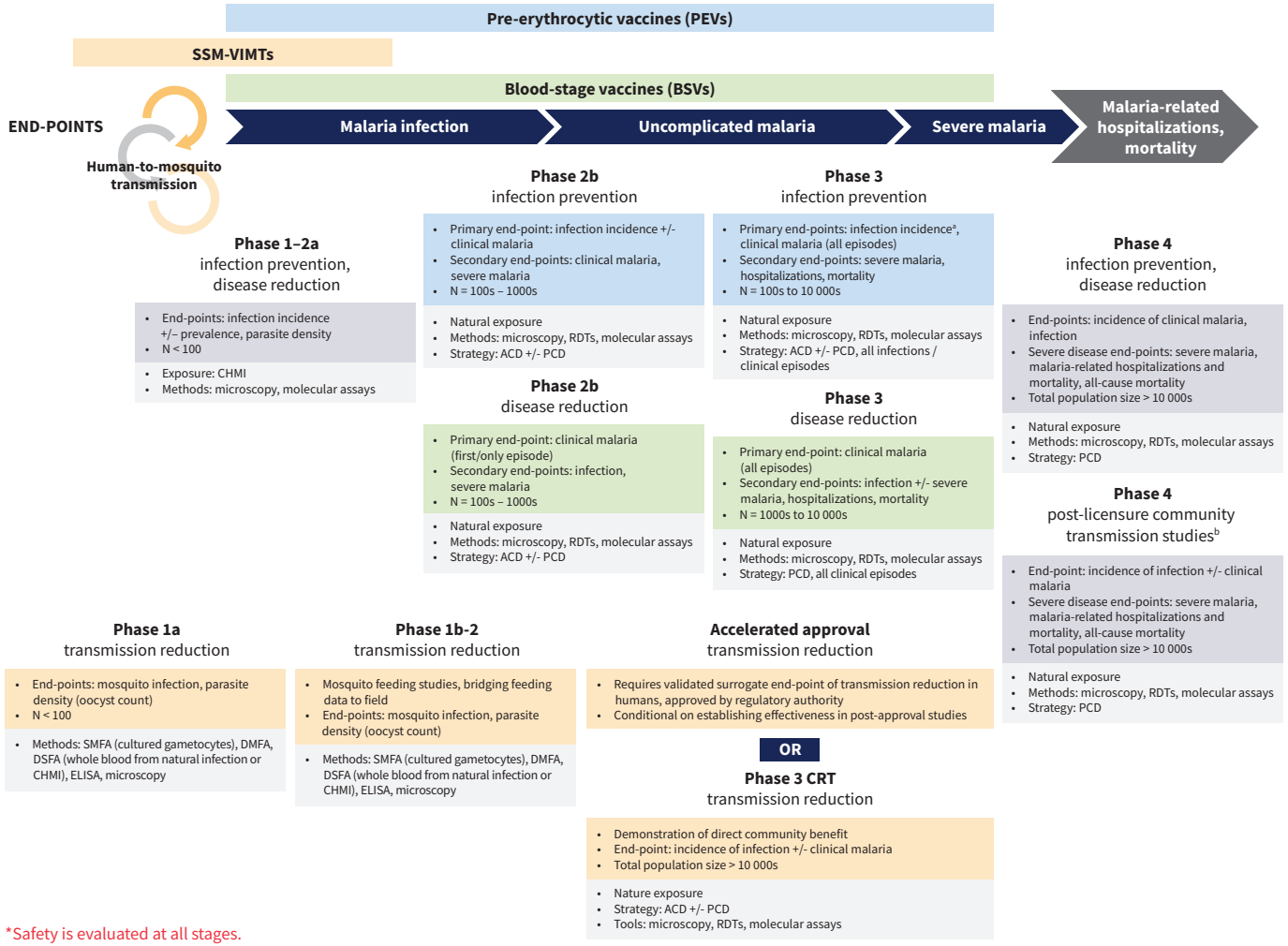
A number of end-points, including severe malaria, malaria-related hospitalizations and mortality, and all-cause mortality, while relevant to understanding the broader public health impact of vaccines, may not be feasible in Phase 3 trials, but may be evaluated in post-licensure studies.

End-points, case definitions and analytical strategies in late-stage clinical development

The optimal approach to measuring vaccine efficacy and public health impact varies according to the evaluation phase, intended use case, and transmission intensity of the study setting. For detailed guidance on the choice of immunogenicity and efficacy end-points, 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 P. falciparum (131)*.

When considering the selection of end-points, it may be helpful to consider a simple model of how the vaccine is expected to work (Fig. 2). End-points closer to the point of biological action tend to be used in early-stage vaccine evaluation, whereas end-points farther 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 or incidence of infection can be informative in early clinical evaluation of candidate 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 end-points in naturally exposed populations.

Fig. 2. Malaria vaccine evaluation end-points and analytical strategies. The figure below illustrates potential clinical development pathways and end-points for different vaccines and indications. However, consultation with relevant regulatory agencies and WHO departments is needed regarding product-specific requirements for licensure and WHO recommendations.



a Use of infection as a primary end-point in Phase 3 would require consultation with regulatory authorities on acceptability for licensure. Developers are strongly encouraged to discuss product-specific evaluation plans and end-points with regulators and WHO.

b Post-licensure studies to measure an effect on community-level transmission may be relevant for multiple vaccine types, including infection-prevention vaccines that have already demonstrated individual-level efficacy and SSM-VIMTs conditionally approved based on surrogate end-points.

ACD: active case detection; CHMI: controlled human malaria infection; CRT: cluster randomized trial; DMFA: direct membrane feeding assay; DSFA: direct skin feeding assay; ELISA: enzyme-linked immunosorbent assay; PCD: passive case detection; RDT: rapid diagnostic test; SMFA: standardized membrane feeding assay; SSM-VIMT: sexual, sporogonic, or mosquito stage vaccine interrupting malaria transmission.

Potential primary and secondary end-points for infection-prevention and disease-reducing vaccines may include:

- **Infection**, through CHMI challenge trials or field studies under conditions of natural exposure. CHMI studies have increasingly been used in early screening of disease-reducing vaccines (see Annex 3, Appendix 1, pp. 195–196, WHO Technical Report Series 980, 63rd report of Expert Committee of Biological Standardization "Controlled human malaria infection trials") *(131)*. For vaccines targeting prevention of infection, efficacy against infection may be used as an end-point in Phase 2 field trials. While data on clinical end-points may be expected in Phase 3 evaluation, use of infection as a primary end-point in Phase 3 could allow for trial efficiencies (e.g. size, duration, cost), but would require early consultation with regulatory authorities on its acceptability for licensure. Developers are strongly encouraged to discuss product-specific evaluation plans and end-points with regulators and WHO.

  In some Phase 2 studies, drug treatment to clear parasites prior to vaccination or before the final dose may be used i) to reduce the immunosuppressive effects of existing *Plasmodium* infections and enhance the immune response to the vaccine, ii) to ensure that any parasitaemia detected in the follow-up period is due to new infections, or iii) as chemoprophylaxis-attenuated whole organism vaccines to prevent disease in the vaccinated individual. 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 implications for product labelling for licensure and its indication for use. Treating study subjects prior to vaccination in Phase 3 should only be used if this will be included on the label as part of the expected mode of deployment to enhance immunogenicity or prevent illness from whole organism vaccines *(131)*.

  Note that the use of malaria drugs described here is distinct from the co-administration of vaccines with mass drug campaigns, including SMC, which is discussed above in the report section "Use of vaccines with other malaria interventions" on p. 36.

- **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°C) at presentation and a parasite density threshold that delivers an acceptable level of sensitivity and specificity *(132)*. 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 5000/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 or only episodes of malaria may also be evaluated, especially in Phase 1/2a trials; however, this is less relevant than the impact on all episodes of malaria to understand the potential public health benefit of disease-reducing vaccines and is the preferred end-point in Phase 3 evaluation.

  The case detection system also has an important bearing on the interpretation of vaccine efficacy. Either ACD or 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, at least in a subset of participants. PCD will generally be preferred in Phase 3 trials to measure the public health impact on reducing the burden on health facilities *(131)*. The results of study end-points detected through PCD systems will be

impacted by a number of factors, such as distance of trial participants from the health facility, treatment-seeking behaviour, and differences in clinical characteristics of cases or clinical diagnosis. Clear descriptions of any PCD systems used in a trial, including potential limitations or variations at study sites, should be well documented. Important differences in PCD systems between studies or sites may confound the comparison of results between locations. Potential confounding factors in ACD systems used in a trial, such as the frequency of follow-up visits, should also be clearly described.

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

Primary and secondary end-points will be different for transmission-reducing vaccines.

- **Incidence of human infection at the community level** is likely the earliest measurable end-point reflecting reduction in transmission. In contrast to disease-reducing vaccines, the use of ACD will be important for measuring a primary infection end-point. Reduction of community-level incidence of infection could also be evaluated in a representative sample of the community included in Phase 4 implementation studies. Post-licensure effectiveness studies measuring incident human infections at the community level may be relevant for highly efficacious infection-prevention vaccines if given to a substantial proportion of the population with the intention of transmission reduction. Such vaccines would likely have already demonstrated individual-level efficacy in Phase 3 studies.

- **Clinical malaria and other clinical end-points** such as malaria-related hospitalizations could be considered as secondary end-points.

- **Human-to-mosquito transmission** end-points (e.g. prevalence of mosquito infection following DMFAs or DSFAs) are playing an increasing role in the evaluation of sexual stage and mosquito antigen vaccines. Research is ongoing to understand the relationship between antibody concentration and transmission-blocking activity. Any candidate measure will require sufficient analytical and biological validation, as well as approval by regulatory authorities, if such data are to be used as surrogate end-points for transmission reduction in humans. If these measures are used for licensure, post-licensure effectiveness studies will likely be needed to confirm a reduction in the incidence of infection or clinical malaria at the community level *(130)*.

Analytical strategies 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 need to evaluate the effect of a candidate on the incidence of infection or clinical disease. Early clinical studies may evaluate the effect on rates of first or only episodes per participant, whereas analysis of the rates of all (i.e. including multiple) malaria episodes is preferred in late-stage development. This has greater public health relevance, but needs to account for the lack of independence of multiple clinical episodes within individuals.

Improved standardization and documentation of end-points and key study parameters is needed to enhance the comparability of results from different studies. Factors that have the potential to affect estimates of efficacy include the study population (location, prior exposure status, age), timing of vaccinations in relation

to seasonal variation in malaria transmission, case-ascertainment methods, follow-up time points, case definitions (clinical criteria, laboratory criteria), follow-up approaches and analytical methods. Annex 1 illustrates example data standardization templates that could be used for CHMI or field studies under conditions of natural exposure.

Trial design considerations

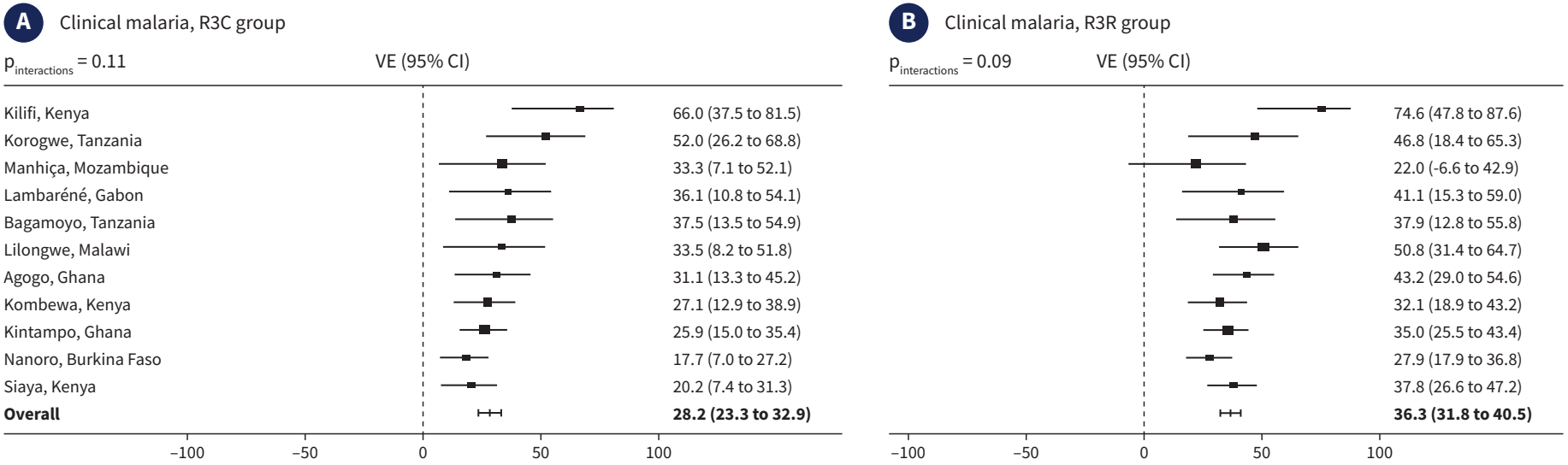
Comparator arms for second-generation vaccines. Interventions used in malaria control programmes are continuously evolving. Following the recommendation for broad use of a first-generation malaria vaccine, trial designs may need to consider licensure and use of the first-generation vaccine in the country where the trial is planned. The choice of comparator and trial designs considered appropriate will depend on the context in which a vaccine candidate is intended for use, the view of local ethical committees, the needs of regulators to support licensure, and the opinion of public health stakeholders involved in decision-making for implementation. Readers are referred to the report of the 2013 WHO Consultation on the Use of Placebos in Vaccine Trials *(133)* and Annex 2, Table A2.1 of this report, which summarizes potential comparator arms for superiority and non-inferiority trials.

Standard of care. The RTS,S Phase 3 trial illustrated how the improved quality of case management required to capture the primary end-point (clinical malaria) may compromise a trial's ability to measure more severe clinical end-points, such as mortality. Access to both outpatient and inpatient care was improved, as was the quality of clinical and laboratory care (e.g. availability of essential medicines, oxygen and blood, and increased clinical staffing). Data from the Health and Demographic Surveillance Survey (HDSS) in the trial site in Siaya, Kenya, estimated a 70% reduction in all-cause mortality associated with enrolment in the RTS,S trial, regardless of study arm *(134)*. Study investigators have noted in published literature that the high standard of care provided to all trial participants may have limited the ability of the trial to detect an effect on secondary outcomes, including mortality *(70)*. While these end-points may provide important information on public health impact, their evaluation may be more feasible in post-licensure studies.

Non-vaccine malaria control interventions. Study designs will need to carefully document any control measures, such as the use of ITNs, indoor residual spraying, chemoprevention programmes, or access to diagnosis and treatment, so that the context in which the vaccine's efficacy was measured can be established. Study reports should document the comparability of the trial arms with respect to these factors. Where imbalances exist, for example in vector control efforts or access to case management, well designed clinical trials should be able to control for the potential confounding effects. The longer term public health consequences of the simultaneous use of a malaria vaccine and other control measures could be evaluated in post-licensure studies *(131)*.

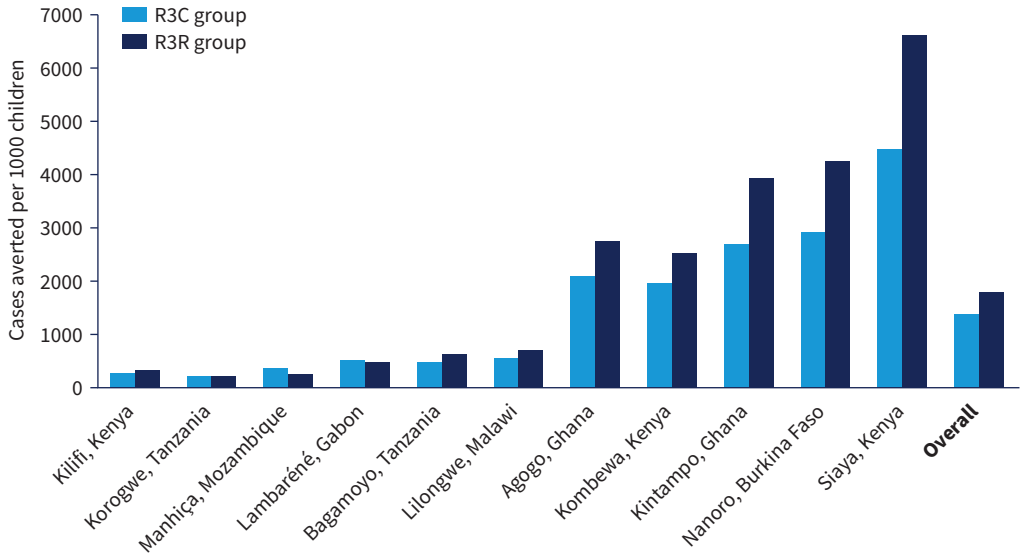
Vaccine efficacy and transmission intensity. Vaccine efficacy and cases averted have been shown to differ according to transmission intensity, as observed in the RTS,S/AS01 Phase 3 trial. Vaccine efficacy was highest in the site with the lowest malaria transmission (reaching 75% during 48 months of follow-up) and was lower in areas of moderate to high transmission. Nevertheless, the highest impact was seen in areas of moderate to high transmission, reaching thousands of cases averted per 1000 children vaccinated during four years of follow-up in areas of moderate to high transmission (Figs. 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).

Fig. 3. RTS,S/AS01 vaccine efficacy against clinical malaria by study site in children aged 5–17 months during 48 months of follow-up post-immunization. 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 three.



Source: RTS,S Clinical Trials Partnership. doi: 10.1016/S0140-6736(15)60721-8 *(70)*.

Fig. 4. Cases of clinical malaria averted in children aged 5–17 months during 48 months of follow-up post-immunization, 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 fourth dose.



Source: RTS,S Clinical Trials Partnership. doi: 10.1016/S0140-6736(15)60721-8 *(70)*.

Studies should be conducted in settings with the range of transmission intensities and seasonal variation in which the vaccine is intended for use. The sponsor may choose to perform separate studies in different geographical areas, or to conduct one large multi-centre study. If the latter approach is adopted, a predefined stratification of enrolment by area could be used to support secondary analyses of efficacy by area or by transmission pattern *(131)*.

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. It is critical that clinical studies include high-quality data on safety in the relevant populations and age groups (including high-risk and immunocompromised groups such as HIV-infected children or adults), with reporting according to international standards and accepted case definitions. In the case of transmission-blocking vaccines, the individual-level risk–benefit assessment differs for vaccines with no direct effect on either infection or disease in individual recipients, compared to vaccines that confer direct protection to the vaccinated individual in addition to indirect effects on transmission 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 (hepatitis B, diphtheria, tetanus, pertussis, poliovirus, measles, yellow fever). The potential of co-administered vaccines to influence the immunological effects of the candidate malaria vaccine should also be examined.

If malaria or other chemoprevention strategies are routinely used in a target population, the potential for clinically relevant interference between the vaccine and co-administered drugs should be evaluated, for example, drugs used for malaria chemoprevention or treatment for non-malaria pathogens, such as helminths.

Finally, vaccine developers should be cognizant of the potential for 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 to inform the management of any potential deferred increases in morbidity. Key issues related to the potential for malaria rebound were considered by a WHO technical consultation in March 2022 *(135)*.

From vaccine efficacy to public health impact

Vaccine efficacy is usually defined as 100*(1- (rate in vaccine recipients/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. VPDI, or the vaccine-attributable rate reduction, measures the absolute difference in disease incidence between vaccinated and unvaccinated groups *(19)*. 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 randomized clinical trials, VPDI can be calculated in CRTs 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 that reduces infections in individuals will reduce transmission and potentially benefit people who do not receive the intervention. In addition to the severe disease caused directly by infection, malaria may increase the risk and severity of disease from coinfections *(136,137)*. A *Plasmodium* infection may not necessarily cause death by itself, but the presence of comorbidities may increase the risk of severe malaria 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 admissions and all-cause mortality better assess the total potential impact of a vaccine.

In addition to selection of suitable trial end-points 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 be ascertained through contemporaneous control arms in standard randomized controlled trials (RCTs) and CRTs, where children randomized to the control arms would receive a comparator vaccine or placebo 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 also overall value for money *(138,139)*. This includes cost-effectiveness, which will be highly dependent on transmission intensity and baseline disease burden, existing standards of care and local costs. Opportunity costs to other malaria interventions or other vaccination and health services should 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 in malaria control programmes. Equity is another important component of value for money. Routine immunization programmes have frequently been shown to reach higher coverage than is achieved by many existing approaches to malaria control, which could help reduce inequities in access to malaria control interventions. A 2020 analysis of Demographic Health Survey (DHS) and Malaria Indicator Survey (MIS) data from 20 African countries showed that among the 33 million children who do not use ITNs, 23 million (70%) are reached by routine immunization programmes. Malaria vaccination for children not using ITNs could avert an estimated 9.7 million clinical malaria cases per year and an additional 10.8 million cases among children already using an ITN *(140)*.

While the development of highly efficacious long-lasting vaccines (e.g. targeting 90% vaccine efficacy or above) remains a strong public health priority, it is increasingly appreciated that vaccines with moderate 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 *(141)*, 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) *(142)*. New vaccines with similar efficacy to RTS,S would provide added value in meeting the expected demand and help create 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 immunization 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 EPI. By contrast, the use of vaccines in seasonal immunization campaigns or during short risk periods will need to prioritize high efficacy with a duration matched to the period of risk, minimize the number of doses and ensure ease of programmatic delivery outside clinical settings. Vaccines to prevent malaria in pregnancy should ideally be administered before pregnancy and last throughout pregnancy or include a booster vaccination during pregnancy. Single-dose regimens would be particularly valuable for emergency situations, where follow-up of displaced or mobile populations may be challenging. For vaccines to interrupt transmission, the potential need to vaccinate a wider age range and population will require particularly 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 MDA or SMC.

Table 2. Relative importance of different vaccine characteristics by use case scenario. The table below is an illustrative example of how trade-offs between characteristics may need to be considered in the context of different use case scenarios and vaccine candidates. Note that it is not the product of a formal evidence review process. The relative importance of product characteristics will differ between use case scenarios and between vaccine candidates (e.g. for a highly efficacious vaccine, a greater number of doses may be more acceptable).

Relative level of importance	High	Moderate	Low			
	PPCs					
Use case scenario	**Efficacy**	**Duration**	**Number of doses**	**Dose schedule**	**Co-administration**	**Delivery**
Infection prevention Routine immunization (high-efficacy pre-erythrocytic and/or blood-stage vaccines)	Efficacy > 90% against blood-stage infection at the individual level	Long duration of protection preferred (> 1 year)	Number of primary doses feasible and acceptable to deliver through routine health contacts	Schedule may vary to align with local immunization infrastructure and preferences.	Envisioned to be delivered with other childhood EPI vaccines. Data to ensure safety and immunogenicity of malaria and non-malaria vaccines maintained	Storage, distribution and route of administration should be feasible in routine health facilities by health care workers.
Disease reduction Routine immunization (moderate- to high-efficacy pre-erythrocytic and/or blood-stage vaccines)	Efficacy > 90% against clinical malaria preferred, but efficacy > 45% with longer duration also have potential for public health impact.	Long duration of protection preferred (> 1 year), particularly for vaccines with lower vaccine efficacy	Number of primary doses feasible and acceptable to deliver through routine health contacts	Schedule may vary to align with local immunization infrastructure and preferences.	Envisioned to be delivered with other childhood EPI vaccines. Data to ensure safety and immunogenicity of malaria and non-malaria vaccines are maintained	Storage, distribution and route of administration should be feasible in routine health facilities by health care workers.
Transmission reduction Mass immunization campaigns (high-efficacy pre-erythrocytic and/or blood-stage vaccines, SSM-VIMTs, or multi-target combination vaccines)	High efficacy against incidence of infection and/or clinical malaria at the community level	Long duration of protection preferred (> 1 year), particularly for vaccines with lower vaccine efficacy	Fewer doses preferred compared to routine immunization for ease of delivery during vaccination campaigns	Schedule should be feasible to deliver through vaccination campaigns or through EPI if delivered with vaccines for disease reduction.	Potential delivery with vaccines targeting different parasite stages (pre-erythrocytic or blood-stage vaccines combined with SSM-VIMTs)	Minimal cold chain requirements preferred and route of administration suitable for vaccination campaigns
Seasonal administration Mass immunization or primary doses via routine immunization with seasonal boosters via campaigns	High efficacy against clinical malaria for duration of malaria transmission season	Duration should be matched to malaria risk period. Long duration of protection would facilitate delivery of primary doses via routine immunization.	Number of doses should be feasible to deliver through routine health contacts or prior to transmission season.	Primary doses should be feasible to deliver through routine health contacts or prior to transmission season.	Co-administration depends on whether delivered through routine health contacts or mass immunization campaigns.	Storage, distribution and route of administration should be suitable for use in vaccination campaigns or routine health facilities if delivered through EPI.
Emergency situations Mass immunization campaigns	High efficacy against clinical malaria required for short campaigns	Duration should be matched to malaria risk period.	Minimal doses preferred due to follow-up challenges	Primary doses should be feasible to be rapidly delivered with minimal follow-up.	Highly likely to be delivered with other vaccines or drugs during complex emergencies	Minimal cold chain requirements preferred and route of administration suitable for use in emergency settings
Malaria in pregnancy† Routine health contacts or mass immunization campaigns	High efficacy for duration of malaria in pregnancy risk period	Duration should be matched to malaria in pregnancy risk period.	Feasible and acceptable to deliver through routine health contacts, including antenatal care	Potentially short window between first vaccine opportunity and birth/delivery	Potential co-administration with IPTp	Storage, distribution and route of administration should be feasible in routine health facilities or antenatal care clinics by health care workers.

PPC DESCRIPTIONS

Efficacy: High efficacy against incidence of infection or clinical malaria at individual or community level;
Duration: Long duration of efficacy (> 1 year);
Number of doses: Minimum number of primary doses; single dose preferred, but more than one dose likely needed for long-lasting immunity;
Dose schedule: Short primary dosing schedule;
Co-administration: Need for co-administration studies with other vaccines and drugs (malaria and non-malaria); data to ensure that safety and immunogenicity are maintained;
Delivery: Minimal need for cold chain for storage and distribution (2–8°C preferred), not less than -20°C; subcutaneous or intramuscular injection preferred (intravenous not recommended);
Safety: Safety is classified as very high priority for all use case scenarios;
Supply: Reliable production and manufacturing is needed for all use case scenarios to ensure sufficient vaccine supply for mass immunization.

† Prevention of infection, clinical malaria and/or placental malaria in pregnant women or women of childbearing age

EPI: Expanded Programme on Immunization; IPTp: intermittent preventive treatment of malaria in pregnancy; SSM-VIMT: sexual, sporogonic, or mosquito stage vaccine interrupting malaria transmission

3.8 WHO prequalification

Vaccines that are procured by UN agencies or financed by agencies such as Gavi require WHO prequalification. The WHO PQ process provides an international assurance of quality, safety, efficacy and suitability for LMIC immunization 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 EMA for centralized marketing authorization in Europe, will be required prior to consideration for 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; such an NRA should have been assessed as functional by WHO. The PQ procedure is described in detail in the document *Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies* (WHO/BS/10.2155) *(17)*.

3.9 Programmatic suitability

In addition to meeting quality, safety and efficacy requirements, it is important that developers and manufacturers understand WHO's preferences for parameters that have a direct operational impact on immunization programmes. Low programmatic suitability of new vaccines may impair their overall public health impact, for example, if they present challenges for vaccine introduction and achievement of adequate uptake and coverage. Additionally, introduction of vaccines that have higher volumes, cold chain capacity or disposal demands may have a negative impact on the existing operation of immunization programmes. 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 development.

The PSPQ Working Group was formed in 2010 to oversee the standardization of programmatic suitability requirements for prequalification. Subsequently, the document *Assessing the programmatic suitability of vaccine candidates for WHO prequalification* was developed in 2012 *(143)* and revised in 2014 *(4)*. This document defines the characteristics that determine programmatic suitability for developing country public-sector immunization programmes. It also describes key vaccine characteristics for PSPQ and the process for assessing compliance with these characteristics.

Vaccine characteristics are organized 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 PQ 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 innovative" characteristics are those for which there is no specific guidance and they are not otherwise specified as "mandatory" or "critical." Such vaccines will be referred to the PSPQ Standing Committee 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 immunization 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.

3.10 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 seven years for some vaccines. The use of new vaccine platforms, such as mRNA vaccines, may reduce manufacturing timelines, but development 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, shortening processing times and lowering overall operational costs. Consequently, manufacturing has become more feasible in countries traditionally lacking the resources required to run plants *(144)*. As a result, vaccine production is increasingly undertaken in LMICs, which can provide affordable vaccines at scale, thus facilitating global access. Prioritizing manufacturing in malaria-endemic countries could enable long-term investment in regions where the vaccine will be used, strengthening the global infrastructure and human capital for vaccines against malaria and infectious diseases. The Developing Countries Vaccine Manufacturers Network (DCVMN) was established in 2000 with the mission to increase the availability and affordability of quality vaccines to protect against known and emerging infectious diseases. DCVMN manufacturers have contributed over 30 WHO-prequalified vaccines, and about 70% of global EPI vaccine supplies are met by the DCVMN for diseases such as rotavirus, Japanese encephalitis, pneumonia, meningitis, and other neglected tropical diseases *(145,146)*.

A key part of vaccine development is establishing a well-characterized and repeatable production process. Many components of the product profile, including product cost, are determined early in the development process, given that vaccines are complex biologicals and are more difficult to characterize precisely than small-molecule agents. Consistent, replicable manufacturing steps are critical to regulatory approval of a commercially available vaccine. It is important to establish a well-characterized production process in Phase 1 *(147)*. Variations in production process and vaccine components can affect many aspects of the product profile, including efficacy, safety, dosing, cost and stability. Major changes in the production

process can jeopardize the ability to progress from Phase 1 to Phase 2. Generally, building commercial-scale manufacturing capability is started early in Phase 2 *(147)*. Therefore, issues related to scale-up, final formulation, release specifications and product presentation must be resolved. Commercial products are subject to stability and bridging studies to link any changes from pilot scale to commercial scale, often as part of Phase 3 studies. Ideally, Phase 3 studies are conducted using product from the final production facilities. 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 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; prioritization 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 need to be considered, so that new vaccine introduction can be sustained without adversely affecting other services. As the number of vaccines increases, 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 delivery 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 events following immunization (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 countries and LMICs) for malaria vaccines makes investment in Phase 3 efficacy trials and commercial production and manufacturing 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, highlights that early consideration of late-stage development challenges is important, including long-duration funding commitments to cover R&D, engaging with public health officials in endemic countries to determine acceptable vaccine costs, and negotiating cost-effective vaccine production agreements and the use of advanced market commitments to guarantee vaccine demand *(148,149)*. 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 *(150)*. 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 four years during Phase 3 trials, RTS,S was able to avert more than 4000 clinical malaria cases per 1000 vaccinees (receiving four doses) in high-transmission settings such as Nanaro, Burkina Faso and Siaya, Kenya. With an estimated incremental cost-effectiveness ratio (ICER) of US$ 25 (range US$ 16–222) per clinical case averted *(141)*, the value of RTS,S is comparable to several other vaccines and in the range of other malaria interventions. While the RTS,S vaccine is not as inexpensive as 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 established and functioning routine EPI services compared to other malaria prevention tools. As described above, a 2020 analysis of survey data from 20 African countries showed the incredible reach of routine immunization programmes, presenting an opportunity to reduce inequities in access to life-saving malaria control interventions. Malaria vaccine visits are also a platform to deliver further health interventions and messages (e.g. reminding carers that children should sleep under ITNs and should be brought promptly for testing and treatment of fever). Therefore, 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 *(151)*. Historically, malaria and poverty have been directly and indirectly linked. In a 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 compared to non-malarious countries *(152,153)*. A more recent analysis of data from 180 countries between 2000 and 2015 indicates 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 *(154)*. 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 pushing already low-income households into extreme poverty *(152,155,156)*. Analysis of data from Brazil, Colombia, Mexico and the United States of America has estimated that persistent childhood malaria reduces adult income by 50% *(157)*. The range of socioeconomic impacts of malaria prevention should be considered as part of the full public health value of malaria vaccines and can help to inform policy, prioritization and decision-making.

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ANNEX 1. CLINICAL DEVELOPMENT DATA STANDARDIZATION TEMPLATES

Standardization of trial data collection can enable comparisons between studies. Tables A1.1 and A1.2 illustrate key variables to measure at harmonized follow-up time points to reflect the dynamics of efficacy. These data can aid the interpretation of results across different CHMI studies and field trials.

Table A1.1. Example data template for controlled human malaria infection (CHMI) studies

Vaccine candidate[a]	Vaccine regimen[b]	Challenge & inoculation schedule[c,d]	Challenge strain	Study population			Infection end-point			Vaccinated		Controls		Vaccine efficacy (incl. primary end-point)[h]
				Location	Exposure	Age range & sex	Measure-ment[e]	Assay[f]	Follow-up	Number protected, PMR (BSVs), or infectivity (SSM-VIMTs)[g]	Number not protected	Number protected, PMR (BSVs), or infectivity (SSM-VIMTs)[g]	Number not protected	
			Pf7G8	USA	Malaria naive	18–65 yrs (males)			21 days					

a Description of vaccine candidate should indicate life cycle stage targeted (pre-erythrocytic, blood stage, sexual and/or mosquito stage).

b Vaccine regimen should include dose and schedule.

c Challenge and inoculation schedule should specify timing in relation to last vaccine dose.

d Route of inoculation should specify intravenous/intramuscular/intradermal sporozoite injection, mosquito bite or blood-stage inoculation.

e Measurement description should indicate definition of end-point (e.g. slide/PCR positivity, parasite density).

f Assay (e.g. PCR, microscopy)

g PMR: parasite multiplication rate (blood-stage vaccines), or infectivity (SSM-VIMT transmission-blocking vaccines). Number protected should indicate measure of infection used to define protective efficacy. End-points will differ depending on the vaccine type. Pre-erythrocytic vaccines will primarily measure the number protected; blood-stage vaccines will measure parasite multiplication rate; and transmission-blocking vaccines will measure infectivity. All should compare respective end-points between vaccinated and control groups.

h Vaccine efficacy should indicate primary end-point used to define protective efficacy. Measure of vaccine efficacy will vary by vaccine type – e.g. individuals protected (pre-erythrocytic vaccines), reduction in parasite density (blood-stage vaccines), reduction in infectivity (SSM-VIMT transmission-blocking vaccines).

Table A1.2. Example data template for field trials under conditions of natural exposure

Vaccine candidate[a]	Trial registration number	Vaccination schedule (incl. timing w/ season)[b]	Malaria control measures in place	Study population		End-point			Vaccinated				Controls				Vaccine efficacy (incl. primary end-point)[d]
				Location	Age range & sex	End-point	Method	Follow-up[b]	Sample size	PYAR[c]	Number of events	Incidence rate	Sample size	PYAR[c]	Number of events	Incidence rate	
						Infection	ACD	3 months									
								6 months									
								12 months									
								18 months									
						Clinical malaria	ACD	3 months									
						Clinical malaria	PCD	6 months									
								12 months									
								18 months									

a Vaccine candidate, including life cycle stage targets (pre-erythrocytic, blood stage, sexual and/or mosquito stage)

b Timing of vaccination schedule with malaria transmission season and duration of follow-up should enable vaccine efficacy (including number of events by study arm) to be considered in the context of the period of malaria risk.

c PYAR: person-years at risk

d Vaccine efficacy should indicate primary end-point used to define protective efficacy. Measure of vaccine efficacy will vary by vaccine type – e.g. individuals protected (pre-erythrocytic vaccines), reduction in parasite density (blood-stage vaccines), and validated surrogate end-point or reduction of community transmission (SSM-VIMT transmission-blocking vaccines).

ANNEX 2. POTENTIAL COMPARATOR ARMS FOR SUPERIORITY AND NON-INFERIORITY TRIALS

A new vaccine may include the biological activity of both the first- and second-generation vaccine as a combined formulation, which could be compared to the first-generation vaccine. Comparison of the co-administration of the first- and second-generation vaccines against the first-generation vaccine and/or control (e.g., placebo) is also possible. Non-inferiority trials are often used to evaluate new products that may bring advantages (e.g., simpler dose and schedule, ease of administration, improved safety and tolerability profile). An acceptable non-inferiority margin will be determined based on scientific, clinical and public health opinion and needs. Consultations with the WHO Coordinated Scientific Advice procedure (1) and regulatory agencies are strongly recommended when planning and prior to finalization of designs for pivotal trials. This may advance timelines by avoiding the need for repeat trials if global policy considerations were not adequately addressed in Phase 3 trials.

Table A2.1. Considerations of different trial design options for second-generation malaria vaccines (modified from *(2)*)

Field efficacy trial options	Second-generation vs. control	Second-generation vs. first-generation	First- and second-generation vs. first-generation	First- and second-generation vs. first-generation vs. control
Estimate of efficacy	Absolute efficacy	Relative efficacy	Relative efficacy	Absolute and relative efficacy
Type of assessment	Superiority to control (e.g., placebo)	Non-inferiority or superiority to first-generation	Superiority to first-generation	Superiority to first-generation and to control (e.g., placebo)
Limitations and considerations	May be considered unethical to randomize to placebo, especially if first-generation is available and recommended in country	Large sample sizes may be needed, depending on the outcome measure. Non-inferiority design would not clearly show progress towards absolute efficacy goal, but could make alternative vaccines available.	Large sample sizes may be needed. First- and second- 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 randomize to placebo, especially if first-generation vaccine is available and recommended.
	Efficacy relative to first-generation vaccine would not be estimated with confidence.	Efficacy relative to placebo would not be estimated with confidence.	This design would not demonstrate efficacy of the second-generation vaccine independent of the first-generation vaccine. Efficacy relative to placebo would not be estimated.	This design would not demonstrate efficacy of the second-generation vaccine independent of the first-generation vaccine.

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World Health Organization

For further information please contact:

Global Malaria Programme
World Health Organization
20, avenue Appia
CH-1211 Geneva 27
Switzerland
Email: GMPinfo@who.int

9789240057463