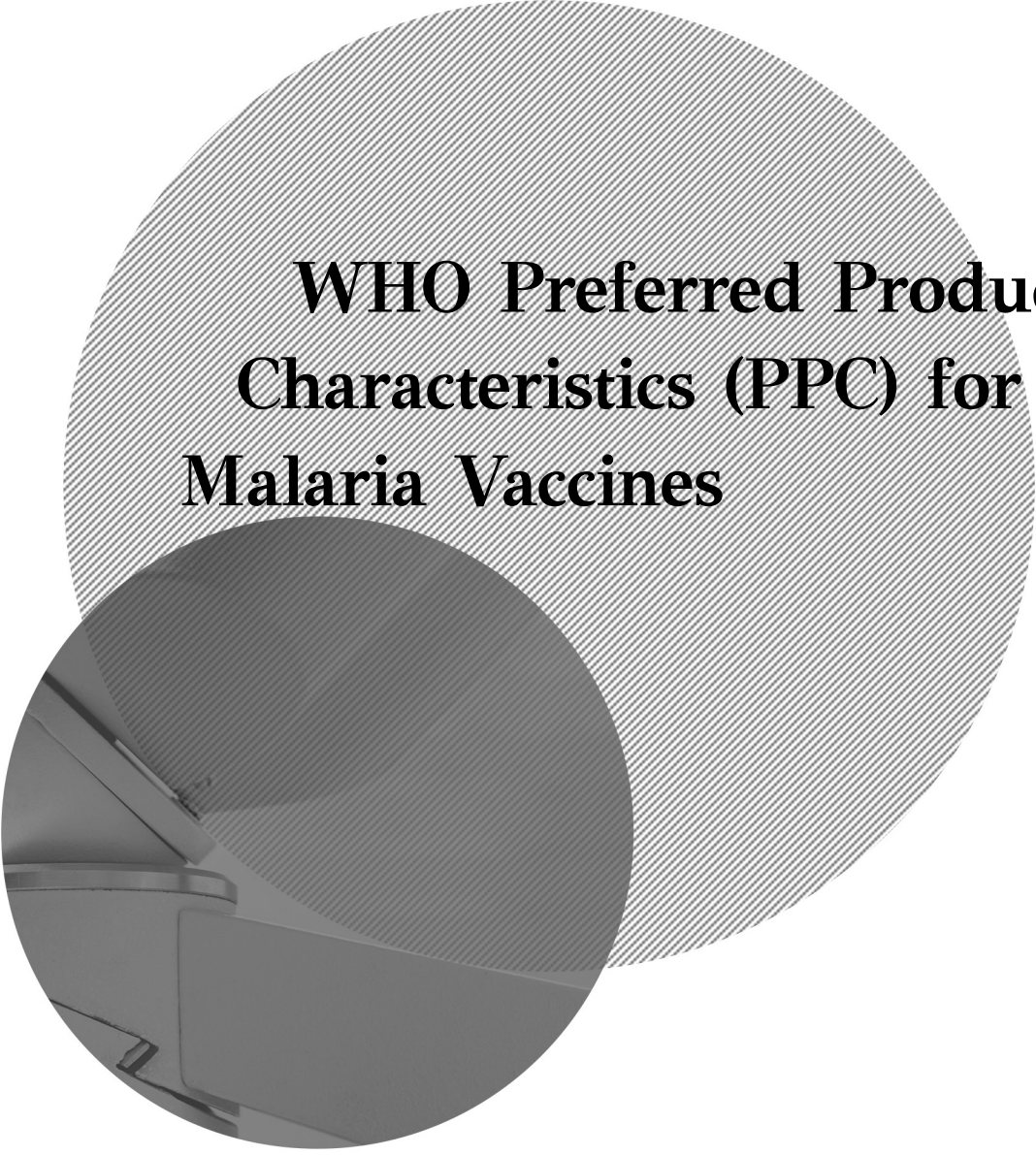


WHO Preferred Product Characteristics (PPC) for Malaria Vaccines





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1. Background and purpose

Preferred product characteristics (PPCs) describe WHO preferences for parameters of vaccines, in particular its indications, target groups, possible immunization strategies, and features of clinical data desired related to safety and efficacy. These preferences are shaped by the unmet public health need in a priority disease area for which WHO encourages vaccine development. In keeping with its mandate, WHO preferences reflect its desire to promote the development of vaccines with high public health impact and suitable for use in low to middle-income countries.

PPCs are meant to provide early guidance for the development of new products or the improvement of existing ones. Each PPC addresses early stage vaccine R&D generally at least 5-10 years from vaccine availability, and will be reviewed and updated if necessary at least every 5 years. PPC are not static exit criteria, but are structured in such a way so as to drive innovation towards meeting public health needs.

Although the parameters in PPCs are commonly found in another product development tool often developed by industry known as target product profile (TPP), PPCs provide guidance tailored with the public health perspective. As the name suggests, PPCs focus on the preferred characteristics, while industry TPPs often specify minimally acceptable in addition to preferred criteria.

PPCs do not provide new guidance on other characteristics often described in TPPs such as vaccine presentation, packaging, thermostability, formulation and disposal, as this area is well-addressed by existing WHO processes such as the WHO Vaccine Presentation and Packaging Advisory Group (VPPAG) and the WHO Prequalification (PQ) process. The VPPAG interacts with manufacturers on questions related to presentation and packaging and has developed a preferred product profile on these aspects. (<http://www.who.int/immunization/policy/committees/vppag/en/index2.html>)

The WHO PQ process which assesses vaccine quality, safety, efficacy and suitability for use in low and middle-income countries has developed criteria called Programmatic Suitability for Prequalification (PSPQ) criteria to review vaccines submitted for prequalification. (http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf)

In addition to the documents related to PSPQ and VPPAG referred to above, malaria vaccine developers should be familiar with “Guidelines on the quality, safety and efficacy of recombinant malaria vaccines targeting the pre-erythrocytic and blood stages of *Plasmodium falciparum*”¹.

Thus WHO encourages developers to consult the above links, in addition to the PPCs for guidance covering many aspects of TPPs, particularly if they intend to seek WHO Policy Recommendation and Prequalification for their products.

1.1 Target audience for WHO PPCs

The primary target audience is any entity intending to eventually seek WHO policy recommendation and prequalification for their products. Knowledge of WHO preferences can be useful to all those involved in malaria vaccine development, including academic groups from pre-clinical development onwards.

The PPCs are intended to encourage innovation and the development of vaccines that perform in settings most relevant to the global unmet public health need. At the same time, changes in scientific and technological feasibility could affect the PPCs. Each PPC document will be reviewed and, where necessary, revised at least every 5 years. In addition, changes to the Malaria Vaccine Technology Roadmap Strategic Goals may prompt revision of WHO PPCs for malaria vaccines. It is important to note that if a vaccine does not meet the PPC criteria, it could still be assessed by WHO for possible policy recommendations in the standard way.

1.2 Malaria Vaccines, A Strategic Priority for WHO

Malaria vaccine PPCs are aligned to the strategic priorities of WHO and partners as articulated by the two updated Malaria Vaccine Technology Roadmap goals². The geographical distribution and burden of disease of *Plasmodium falciparum* and *Plasmodium vivax* malaria make these two pathogens high priority targets for vaccine development. In 2013, WHO’s principal advisory group on immunization, SAGE (Strategic Advisory Group of Experts) stated that “malaria vaccine development remains a global public health imperative”. The changing epidemiology of malaria and the call for eradication of the malaria parasite as a public health goal in recent years has led the global malaria vaccine community, in 2013, to update the *Malaria Vaccine Technology Roadmap*, which provides a blueprint for developing malaria vaccines. The current update calls for the development of vaccines targeting *Plasmodium falciparum* and *Plasmodium vivax*, by 2030 that address two unmet priority public health goals:

- Roadmap strategic goal 1: Malaria vaccines with a protective efficacy of at least 75% against clinical malaria, suitable for administration to appropriate at-risk groups in malaria-endemic areas³.

¹ http://who.int/entity/biologicals/vaccines/Malaria_Guidelines_TRS_980_Annex_3.pdf.

This document is part of a class of documents known as WHO written standards used by National Regulatory Authorities to guide assessment of dossiers for licensure of vaccines. Written standards are also used by the WHO Prequalification team to guide PQ assessments of vaccines.

² http://www.who.int/immunization/topics/malaria/vaccine_roadmap/en/

³ Duration of protection will be assessed over at least two years, with a booster dose required at most once during the two year period.

-
- Roadmap strategic goal 2: Malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection. This will enable elimination in multiple settings. Vaccines to reduce transmission should be suitable for administration in mass campaigns.

This guidance presents PPCs that correspond to these goals.

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

1.3 Context of available WHO recommended malaria interventions

Malaria vaccines will be tested and deployed in conjunction with other WHO recommended malaria control measures. These include effective artemisinin combination anti-malarial chemotherapy, use of quality-assured rapid diagnostic tests, long-lasting insecticide-treated bednets and other vector control measures, including indoor residual spraying with insecticide. In addition drug-based prophylaxis is recommended by WHO in certain settings and target groups. In the future, the recommended malaria control measures may also include a first-generation malaria vaccine.

Even if a first-generation malaria vaccine becomes available, it seems likely that the efficacy and duration of protection will be modest and there will remain a pressing need to develop second generation vaccines with higher efficacy to further reduce malaria cases and deaths. Furthermore, control measures are increasingly threatened by the development of resistance to drugs and insecticides, and so authorities in most malaria-endemic countries will view a safe and highly effective second generation malaria vaccine as a high priority for possible introduction.

2. Vaccines preventing malaria disease (Roadmap strategic goal 1)

2.1 Target Groups and Immunization Strategies

Despite the changing epidemiology of malaria, and the scaling up of control interventions, *Plasmodium falciparum* malaria continues to be a major cause of morbidity and mortality in infants and young children in many countries.

In addition to biological characteristics of the parasite and its hosts and intervention measures that influence disease burden and epidemiology, ecological, social and economic factors can play an important role. Thus, accurately predicting what the epidemiology of malaria will be in five or ten years is difficult. However, in settings in which malaria transmission falls, the pattern of immunity associated with persistent exposure to malaria will change and, in particular, the risk of disease is likely to shift to older children. The development of disease-reducing malaria vaccines will have to take account of potential epidemiological changes, including the likelihood that it will be necessary to target other age groups. In addition, falling rates of transmission of the dominant malaria species *Plasmodium falciparum* could result in the dominance of other malaria species, in particular, *Plasmodium vivax*, in some areas.

With these developments in mind, target groups for roadmap strategic goal 1 include:-

- 1) Populations living in areas with significant malaria transmission, with the following differences according to transmission intensity.
 - In high transmission areas, infants and young children are at greatest risk, with the age groups at highest risk for severe disease and death being inversely related to the intensity of transmission. Vaccine administration through routine immunizations programmes using schedules compatible with existing immunization visits is envisaged in these settings, with completion of the primary immunization series latest by 9 months of age in high transmission areas. If efficacy wanes, booster doses may be necessary and clinical trial data should allow assessment of the need for and timing of booster doses. Should morbidity be significant in older children and adults, they may also represent a target group.
 - In settings with lower transmission, the age groups at risk may also include older children and adults. Initial vaccine introduction may be through mass immunization campaigns to cover the susceptible population rapidly, followed by addition of vaccine to routine immunization programmes in young children, depending on the duration of protection induced by the vaccine.

-
- The absence of clinically relevant interference between the malaria vaccine and other vaccines that may be administered concomitantly should be confirmed in co-administration studies. Choice of vaccines for these studies should be driven by the vaccines in use at the intended target age group in the target populations. In general, there are most concerns about inactivated/subunit vaccine interfering with other inactivated/subunit vaccines, and live vaccines interfering with other live vaccines. If drug prophylaxis is routinely administered in any target population, another consideration would be clinically relevant interference between vaccine and drug prophylaxis.
- 2) Protection of primigravid women through immunization of women of child-bearing age.
 - Primigravid women are at substantial risk of death from malaria in many countries, as previously immune women become susceptible again from early in their first pregnancy. Women of child-bearing age in endemic areas would also benefit from protection against malaria during second and subsequent pregnancies. Therefore the target group here is women of child-bearing age in order to protect pregnant women.
 - Chemoprophylactic measures are recommended for malaria in pregnancy but this does not remove the need for potential vaccination.
 - Vaccines whose molecular targets allow that they may be used both against malaria in pregnancy and malaria in children and adults are preferred to those which can only be used against malaria in pregnancy.
 - 3) 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.
 - 4) Non-immune individuals who are visiting or temporarily employed in malaria-endemic areas.
 - Non-immune individuals who visit malaria-endemic areas for leisure or are temporarily employed in these areas (including seasonal workers, deployed international organization or military personnel) are also at risk.
 - Chemoprophylaxis is available but issues related to compliance, drug resistance and adverse events create a demand for a highly effective malaria vaccine.
 - 5) Mass immunization campaigns, in addition to the use of vaccine in routine immunization schedules, may have a role for highly effective disease-reducing vaccines as a way of rapidly protecting susceptible populations and achieving accelerated disease control.
 - Periodic mass immunization campaigns to reduce the risk of clinical malaria in populations living in malaria-endemic areas where significant transmission is expected to continue.
 - Mass immunization to control malaria epidemics and re-importation outbreaks in post-elimination settings.

2.2 Endpoints and case definitions for evaluating disease-reducing malaria vaccines

The design of malaria vaccine trials requires understanding of the complex relationships between the observable clinical end-points, immunity specific to the life-cycle stage of the malaria parasite in the human host and the corresponding molecular biological target of the vaccine in question.

Readers are referred to the background and clinical section of “Guidelines on the quality, safety and efficacy of recombinant malaria vaccines targeting the pre-erythrocytic and blood stages of *Plasmodium falciparum*” for guidance on choice of immunogenicity and efficacy endpoints, case definitions and analysis methods. This available WHO guidance applies to vaccine development for Roadmap strategic goal 1, but not necessarily for strategic goal 2.

Brief highlights from the above document and other WHO consultation documents are included here.

- The recommended primary efficacy endpoint for Phase 2b to Phase 3 trials is incidence of all episodes of clinical malaria.
- An episode of clinical malaria should include measured fever ≥ 37.5 degrees centigrade at presentation and a parasite density threshold with acceptable specificity and sensitivity for the definition of fever due to malaria (this threshold may vary according to the endemicity of malaria in different settings, and may be any detectable parasites in low transmission settings and in infants).
- In addition the case detection system in use should be specified and forms part of the case definition. Active or passive case detection may be appropriate for Phase 2b trials whereas passive case detection will generally be preferred for Phase 3 trials.
- An appropriate analysis method should be applied which takes into account the lack of independence of multiple clinical episodes of malaria within individuals.
- Severe malaria, malaria hospitalizations, malaria-related deaths and all-cause mortality should be secondary endpoints.
- Capture of co-morbidities, using specific case definitions, is encouraged to allow for analysis of any impact of vaccination on co-morbidities.
- It is possible that high efficacy against infection, rather than disease, demonstrated in field trials could be used as a surrogate efficacy endpoint in development of second generation malaria vaccines. This could potentially be included in subsequent versions of this document if data supportive of such use is submitted to WHO.
- Controlled human malaria infection challenge trials have an increasingly important role, particularly in the early screening of disease-reducing vaccines (see Annex 3, Appendix 1, page 195-6, WHO Technical Report Series 980, 63rd report of Expert Committee of Biological Standardization “Controlled human malaria infection trials”⁴).

⁴ http://www.who.int/biologicals/vaccines/Malaria_Guidelines_TRS_980_Annex_3.pdf

2.2.1 *Duration of protection and booster doses*

Although an estimate of efficacy might be made after a year of follow-up post-vaccination in a pivotal trial, and this might be adequate for licensure, it would be essential to continue follow-up for at least 2 years, and preferably for longer, to obtain data on the duration of protection and long-term safety, including to confirm the absence of rebound pathology and increased susceptibility following the waning of vaccine-induced immunity. Data on the duration of protection and long-term safety will be critically important for public-health decision-making. Given that booster vaccinations may well be necessary to extend protection, Phase 2b-3 randomised controlled trials design may benefit from evaluation of boosters in a randomised fashion.

2.3 **Trial design considerations for second generation malaria vaccines**

Following licensure of a first generation malaria vaccine in some countries, various options will remain for trial designs in any given setting depending on factors including licensure of the first generation vaccine in the country where the trial is planned, whether the first generation malaria vaccine is recommended and in use locally and other factors. Readers are referred to the report of the 2013 WHO Expert Consultation on the Use of Placebos in Vaccine Trials⁵. The decision on whether the control arm receives the first generation malaria vaccine rests with the national regulatory authorities and local ethics committees overseeing the trial conduct.

Currently, with no accepted regulatory correlate of vaccine-induced protection, licensure of malaria vaccines will be based on the demonstration of safety and efficacy through the conduct of randomized controlled trials with clinical endpoints.

Whether superiority or non-inferiority trials are appropriate will depend on the type of vaccine being compared as well as the needs of the regulatory and public health stakeholders. A superiority trial design compares the incidence of the primary efficacy endpoint between those receiving either the new vaccine or a comparator (which can be either a placebo, control non-malaria vaccine or the currently licensed malaria vaccine). A non-inferiority trial is designed with the objective of showing that the new vaccine is not “unacceptably worse” than the currently licensed vaccine with which a margin of maximum acceptable difference must be agreed. Table 1 shows some of these field trial design options.

A potential approach to achieve the desired target of malaria vaccines with superior efficacy and durability could be the combination of vaccines that target different stages of the parasite. Thus Table 1 also shows two situations that could result from this approach in the two right hand columns. One situation could be where a single second generation vaccine which includes the biological activity of the 1st generation vaccine and a 2nd generation vaccine in a combined presentation would be compared with the 1st generation vaccine. Second could be the comparison of an approach that combined co-administration of the first generation vaccine with a second generation vaccine, against the 1st generation vaccine and placebo.

⁵ http://apps.who.int/iris/bitstream/10665/94056/1/9789241506250_eng.pdf?ua=1

Properly designed non-inferiority trials are considered justified in the context of development of new products which may bring advantages such as reduced cost, fewer doses, a simpler schedule, ease of administration, delivery and storage or an improved safety and tolerability profile. The determination of the non-inferiority margin will have to be carefully justified, taking into account scientific, clinical and public health opinion and needs. Table 2 shows indicative sample size calculations for superiority or non-inferiority designs based on efficacy margins of 5% and 10% that have previously been used for vaccines against other diseases. Superiority trials where a new vaccine is compared to existing vaccines will require larger sample sizes than placebo-controlled trials, as will small margins for demonstration of non-inferiority. Regulatory agencies should be consulted when planning all pivotal trials and, in the case of non-inferiority trials, particularly to ensure that the justification of the margin meets regulatory expectations in licensure settings. Interactions with WHO are strongly recommended prior to finalization of design of pivotal trials. This may advance timelines by avoiding the need to perform repeated Phase 3 trials because global policy considerations were not adequately addressed in early Phase 3 trials.

Table 1: Considerations of different trial design options for second generation malaria vaccines*

Field efficacy trial options	2nd generation vs placebo	2nd generation vs 1st generation	1st and 2nd generation vs 1st generation	1st and 2nd generation vs 1st generation vs placebo
Estimate of efficacy	Absolute efficacy estimated.	Relative efficacy estimated.	Relative efficacy estimated.	Absolute and relative efficacy estimated.
Type of assessment	Superiority to no treatment.	Non-inferiority to 1st generation or superiority to 1st generation.	Superiority to 1st generation.	Superiority to 1st generation and to no treatment.
Limitations and Considerations	May be considered unethical to randomize to placebo, if 1st generation vaccine is available and recommended in country.	Large sample sizes may be needed. Non-inferiority design would not clearly show progress towards the 75% effective goal, but could make alternative vaccines available.	Large sample sizes may be needed. 1st and 2nd 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, if 1st generation vaccine is available and recommended. This design would not demonstrate efficacy of the 2nd generation vaccine independent of the 1st generation vaccine.
	Efficacy relative to 1st generation vaccine would not be estimated with confidence	Efficacy relative to no treatment would not be estimated with confidence.	This design would not demonstrate efficacy of the 2nd generation vaccine independent of the 1st generation vaccine. Efficacy relative to no treatment would not be estimated with confidence.	

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

Table 2: Examples of total sample sizes required for field studies of second-generation vaccine to demonstrate non-inferiority or superiority (assuming intention-to-treat and calculated using Z-test with continuity correction)*

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

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

3. Vaccines to reduce and interrupt malaria transmission

3.1 Transmission reducing malaria vaccines: target groups and immunization strategies

The vaccines will preferably be suitable for administration in mass campaigns to all ages including women of child-bearing age, infants and the elderly. Naturally acquired immunity to the sexual stages of the malaria parasite does develop in high transmission settings by adulthood; exclusion of the elderly from immunization campaigns may still enable sufficient transmission reduction in those settings. It may also be possible that infants (less than 12 months of age) can be omitted, although this would not be preferred as infants do contribute to transmission and it would preclude the option of routine immunization before 12 months of age.

Decision about immunization strategies for such vaccines will be dependent on factors such as malaria transmission intensity, species composition, other malaria interventions in use, duration of protection, co-formulation, the stage of malaria elimination that any given programme has reached. It is envisaged that the chances of malaria elimination will be greatly increased if the vaccine is combined with tailored packages of other malaria interventions according to the local malaria epidemiological situation. Possible immunization strategies may include:-

- 1) Reducing transmission or preventing re-introduction through periodic mass preventive campaigns. The frequency of such 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 of infants/young children may be appropriate after an initial mass campaign.
- 2) Managing outbreaks through reactive campaigns to stop transmission.

Key complementary measures that may form part of malaria elimination programmes in the future, together with malaria vaccines, include: dynamic surveillance with ongoing generation of data for targeting of preventive and treatment measures; molecular malaria diagnostics of sufficient quality, affordability and high-throughput to allow identification of remaining infection foci; use of vector control measures; treatment of all malaria cases with effective artemisinin-combination therapies, as outlined in WHO Global Malaria Programme policy.

3.2 Malaria transmission and endpoints for vaccine evaluation

The transmission reduction PPCs are applicable to any malaria vaccine product with the primary indication of reduction of person-to-person transmission, regardless of what life-cycle stage the vaccine product is targeting. Although there are candidate vaccines that specifically target human to mosquito transmission such as sexual stage and mosquito antigen vaccines known within the malaria vaccine community as “transmission-blocking vaccines”, highly efficacious vaccines targeting the pre-erythrocytic stages would also be capable of reducing or blocking transmission. In theory highly efficacious blood stage vaccines may also reduce or block transmission.

Whatever the biological target of the vaccine, the earliest measurable clinical end-point reflecting reduction in transmission is incidence of human infection (at the community level). Specific and sensitive validated assays will likely be required to capture low parasite density infections, using molecular tests.

Clinical malaria and other clinical end-points such as malaria hospitalization could be considered as secondary end-points.

For “transmission-blocking vaccines” (sexual stage/mosquito (SSM) antigen vaccines), end-points that measure human to mosquito transmission (eg. prevalence of mosquito infection, direct or indirect membrane feeding assays) are being considered. Sufficient analytical and biological validation of any candidate measure will need to be demonstrated if such data are to be accepted by regulators as a surrogate for efficacy of new interventions. If such measures were developed and accepted for licensure of SSM vaccines, effectiveness studies would be required to confirm transmission reduction to be performed in conjunction with national authorities in malaria endemic countries. It is likely that WHO recommendations for use will require either supportive efficacy or effectiveness data to be available.

The use of malaria vaccines are envisioned within the greater context of malaria control and elimination efforts. The WHO and its key partners are developing and implementing a new Global Technical Strategy for the control and elimination of malaria and will make malaria-related policy decisions under the mechanism of the Malaria Policy Advisory Committee. The role of malaria vaccines indicated for malaria transmission reduction will occur within the context of this larger global framework. In addition, further innovation is a central aspect of the Global Vaccine Action Plan (GVAP), which also specifically highlights malaria as one focus of attention for vaccine R&D. WHO’s SAGE committee on immunisation assesses progresses according to GVAP with reporting to the World Health Assembly.

3.3 Clinical Development considerations

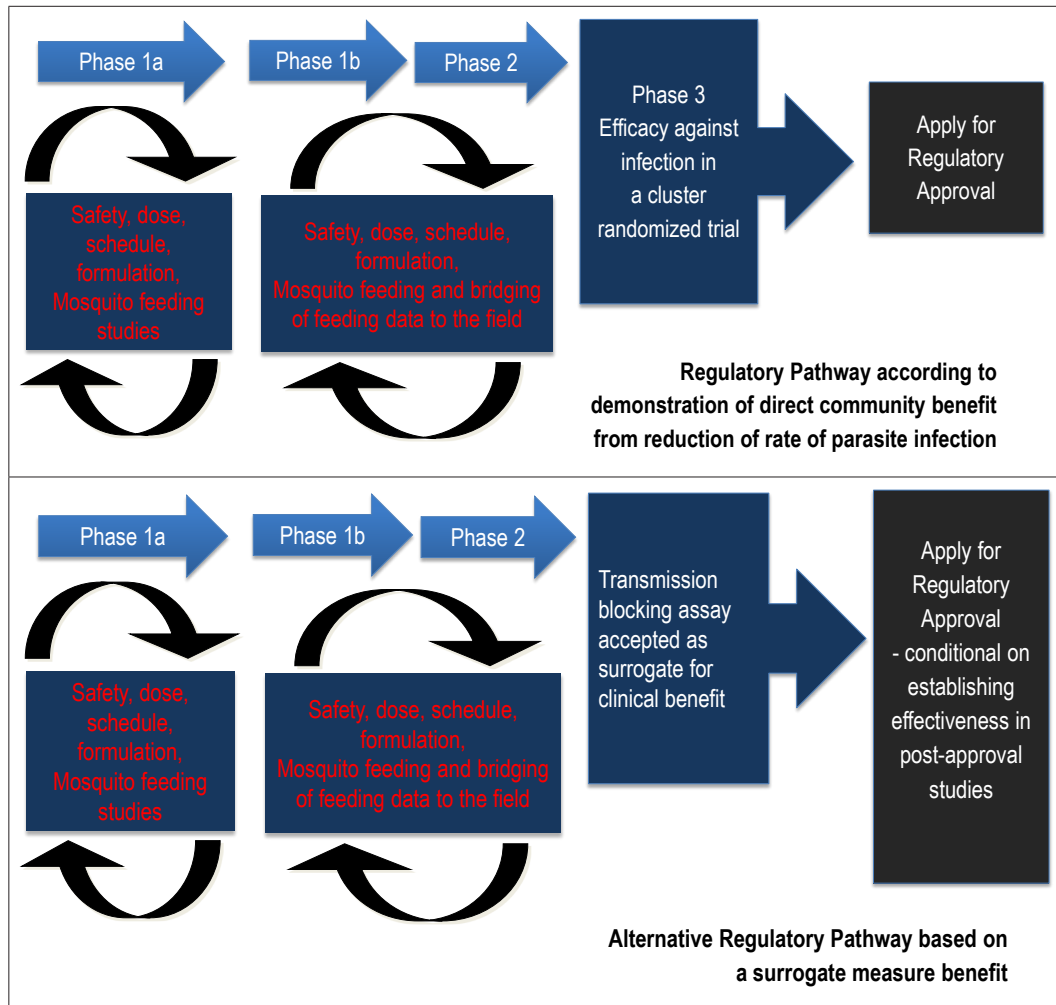
Clinical development of a potential malaria vaccine will first require a series of initial clinical trials that will assess safety, immunogenicity and appropriate dose and schedule of the candidate product. Evidence of preliminary efficacy against endpoints of interest including those related to biomarkers of efficacy could be obtained at this stage.

Establishing an impact on transmission will require a trial design that is different from efficacy trials establishing clinical benefit alone. Any transmission reduction effect will be influenced by both the efficacy of the product and vaccination coverage achieved in terms of proportion of the human infectious reservoir. The efficacy/effectiveness measured in clinical trials in terms of effect on infection or clinical malaria may be dependent on the baseline transmission intensity because of the nonlinear relationship between malaria transmission and clinical malaria.

The unit of randomization in a double-blind, controlled trial will be the community or cluster of individuals and the primary measure of efficacy will be rates of human malaria infections. Such cluster-randomized trials will be a substantial undertaking, necessitating collection of baseline information essential for their design and planning. In addition to the consideration of the feasibility of conducting such trials in the field, developers are encouraged to fully explore alternative trial designs for proof-of-concept, particularly those that validate the use of surrogate biomarkers in the clinical development pathway.

There are some concerns as to the feasibility of conducting several cluster randomized trials in different transmission settings if required for licensure. This highlights the importance of full assessment of possible surrogate biomarkers that have been proposed for candidate vaccines that target human to mosquito transmission, such as sexual stage and mosquito antigen vaccines known as “transmission-blocking” vaccines. Vaccine developers and regulatory agencies are also encouraged to engage in early dialogue regarding the possible regulatory pathways that could be considered for such vaccines. A possible pathway is illustrated in Figure 1.

Figure 1: Clinical evaluation and possible regulatory pathways for transmission-blocking vaccines.



It may be advisable to consult WHO prior to finalisation of key clinical proof-of-concept and pivotal studies in this area.

As yet, no clinical trial data are available on vaccines that interrupt malaria transmission to determine the efficacy thresholds that would be required to have a clinically beneficial impact on transmission and achieve elimination. Thus this PPC does not set firm efficacy thresholds and WHO will keep this area under review.

The need to administer the vaccine to a wide age range, including women of child bearing age, has implications for the clinical development pathway. In addition, immunogenicity data is required if vaccination is to be combined with vaccination against other pathogens. Such data should provide confidence that immunogenicity of both the malaria and non-malaria vaccine are preserved in co-administration.

There may be a valuable role for mathematical modelling of malaria transmission to inform product development decisions, and to inform clinical trial design. One important question that models may inform is the sensitivity of any transmission reductions effects to vaccine coverage. It is recommended that where models are used there is transparency about key assumptions driving predictions and the uncertainties related to model structure and parameterisation. Comparison of the predictions of models with different assumptions and underlying structures are likely to be valuable in assessing the key drivers of numeric predictions from the models.

The range of acceptable safety may be narrower for vaccines designed to achieve strategic goal 2 (transmission reduction) with no direct effect on either infection or disease for the individual, compared to vaccines with the usual direct effects in addition to indirect/transmission effects.

4. WHO Prequalification

Vaccines that are procured by United Nations agencies and for financing by other agencies, including the GAVI Alliance, require WHO Prequalification. The WHO prequalification (PQ) process acts as an international assurance of quality, safety, efficacy and suitability for low and middle-income country immunization programs. WHO encourages vaccine developers and manufacturers to be aware of the WHO prequalification process, even at the early stages of development and to discuss the product and the regulatory requirements with the WHO prequalification staff early in the process. Regulatory pathways can impact eligibility for prequalification. Registration by a national regulatory authority (NRA), or European Medicines Agency in the case of the centralized procedure for marketing authorization in Europe, will be required prior to any consideration of prequalification. Furthermore the prequalification process requires regulatory oversight by the NRA of Record, which is usually the NRA of the country where the vaccine is manufactured or the NRA of the country of finishing and distribution, and such an NRA should have been assessed as functional by WHO. Vaccine developers should check that the planned NRA of Record for the prequalification procedure is considered functional by WHO.

The prequalification procedure is described in detail in the document *Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies* (WHO/BS/10.2155) available here: http://www.who.int/entity/immunization_standards/vaccine_quality/pq_revised_procedure_final_1may2012.pdf.

5. Malaria Vaccine Preferred Product Characteristics

The following tables present the PPCs for the disease reducing and the transmission reducing malaria vaccines. The tables address indication and target population, safety and efficacy and registration and prequalification.

**Table 3a: Preferred Product Characteristics:
Disease-Reducing Malaria Vaccines**

Indication & Target Group	
Parameter	Preferred Characteristic
Indication	<p>Indications: Prevention of clinical malaria, including manifestations of severe malaria, caused by either <i>P. falciparum</i> and/or <i>P. vivax</i>. The vaccine would be indicated primarily for malaria disease control, rather than elimination.</p>
Target population	<p>Infants and young children aged 5 years and under, in most settings</p> <p>Comment: Vaccines that are highly effective at preventing clinical malaria (>75%) can be considered for use in other high-risk groups (depending on available efficacy and safety data in this population) such as:-</p> <ul style="list-style-type: none"> • Non-immune individuals migrating to, or living temporarily in, areas of malaria transmission. • Women of child-bearing age and pregnant women living in areas of malaria transmission • Where substantial disease burden occurs in children aged over 5 years or adults, these also form part of the target population
Safety & Efficacy	
Parameter	Preferred Characteristic
Safety	<p>The safety and reactogenicity of the vaccine is comparable to or better than WHO recommended vaccines in use in low and middle-income countries. Data should allow assessment of deferred increases in morbidity as vaccine-induced immunity wanes. For vaccines within the EPI schedule, absence of clinically important interference with EPI vaccines will have to be documented.</p> <p>Comment:</p> <ul style="list-style-type: none"> • WHO prequalification and policy recommendations include risk-benefit assessment in malaria endemic settings and safety will be assessed in the context of the data on benefit for each vaccine, as well as risk. • It is critical that clinical studies include high quality data on safety in the relevant populations and age groups, with reporting according to international standards and accepted case definitions. Greater standardisation of data collection and reporting of safety and reactogenicity data in pre-licensure clinical trials is strongly encouraged. • Vaccine developers and vaccine financing agencies are referred to the Global Vaccine Safety Initiative (GVS). Pharmacovigilance systems strengthening is a high priority as outlined in the GVS and thus consideration of safety data generation as part of Phase 4 studies and pharmacovigilance systems is strongly encouraged.
Efficacy	<p>The vaccine should reduce incidence of all clinical malaria episodes by at least 75% for no less than one year and preferably at least two years. Booster doses should be required no more frequently than annually.</p> <p>The duration of protection is as important as the short-term efficacy for the primary target group of children under the age of 5 years in medium to high transmission malaria endemic countries. Thus, the initial efficacy and duration of protection will be considered together. Clinical data should allow assessment of the requirement for and timing of booster doses. The public health impact, in terms of cases averted, will be an important element in the public health assessment. Baseline incidence of disease and the vaccine efficacy taken together yield the cases averted. The following efficacy measures are recommended:-</p> <ul style="list-style-type: none"> • Primary efficacy measure: incidence of all episodes of clinical malaria. • See section 2b for further guidance
Registration & Prequalification	
Parameter	Preferred Characteristic
Registration and Prequalification	<p>The vaccine should be WHO pre-qualified according to the process outlined in <i>Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies</i> (WHO/BS/10.2155).</p>

**Table 3b: Preferred Product Characteristics:
Transmission Reducing Malaria Vaccines, development timeline:
first product targeted between 2025 and 2035**

Indication & Target Group	
Parameter	Preferred Characteristic
Indication	Prevention of person to person malaria transmission through a mosquito vector at the community level. The vaccine would be indicated for malaria control, elimination and/or prevention of re-introduction post-elimination depending on clinical data submitted.
Target population	<p>Children aged 12 months and above and adults, including women of child-bearing age.</p> <p>Comment: For sexual stage and mosquito antigen vaccines, the infectivity reservoir for transmission to Anopheline mosquitoes in malaria endemic areas extends from infancy through childhood to adults. While the per person infectivity is highest in young children, older children and adults remain infectious to mosquitoes, and thus represent a major contributor to transmission from humans to mosquitoes.</p> <p>Comment: Although inclusion of infants aged less than 12 months may not be essential, their inclusion is highly likely to confer additional transmission reduction at the population level.</p> <p>Comment: Although inclusion of pregnant women may not be essential, their inclusion is highly likely to confer additional transmission reduction at the population level.</p> <p>Comment: The top end of the age range for inclusion in mass campaigns is not clear as of 2014.</p>
Safety & Efficacy	
Parameter	Preferred Characteristic
Safety	<p>For vaccines with no direct effect: the safety and reactogenicity profile of the vaccine is comparable to other vaccines with highly favourable safety and reactogenicity profiles</p> <p>For vaccines with direct effects in addition to transmission effects: The safety and reactogenicity of the vaccine is comparable to or better than WHO recommended vaccines in use in malaria endemic countries.</p> <p>Comment:</p> <ul style="list-style-type: none"> • WHO prequalification and policy recommendations include risk-benefit assessment and safety will be assessed in the context of the data on benefit for each vaccine, as well as risk. • It is critical that clinical studies include high quality data on safety in the relevant populations and age groups, with reporting according to international standards and accepted case definitions. Greater standardisation of data collection and reporting of safety and reactogenicity data in pre-licensure clinical trials is strongly encouraged. • Vaccine developers and vaccine financing agencies are referred to the Global Vaccine Safety Initiative (GVSII). Pharmacovigilance systems strengthening is a high priority as outlined in the GVSII and thus consideration of safety data generation as part of Phase 4 studies and pharmacovigilance systems is strongly encouraged.
Efficacy	<p>The vaccine should reduce malaria transmission resulting in the reduction of incident human malaria infections at the community level.</p> <p>The following efficacy measures are recommended:-</p> <ul style="list-style-type: none"> • Primary efficacy measure: incidence of new human infections, including an analysis method that takes into account interdependence of events within individuals • Secondary efficacy measure: incidence of all episodes of clinical malaria, taking into account interdependence of events within individuals • Tertiary efficacy measure: prevention of mosquito infection, using analytically validated techniques <p>The duration of efficacy is as important as the short-term efficacy. Thus, the initial efficacy and duration of protection will be considered together.</p> <p>Clinical data should allow assessment of the requirement for and timing of booster doses.</p> <p>The public health impact, particularly of the potential for elimination will be an important element in the WHO assessment.</p>

Registration & Prequalification	
<i>Parameter</i>	<i>Preferred Characteristic</i>
Registration and Prequalification	The vaccine should be WHO pre-qualified according to the process outlined in <i>Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies</i> (WHO/BS/10.2155).

6. Considerations on Programmatic suitability

In addition to meeting quality, safety and efficacy requirements, it is also important that developers and manufacturers understand WHO's preferences for parameters that have a direct operational impact on immunization programs. Low programmatic suitability of new vaccines could result in delaying introduction and deployment. In addition, introduction of new vaccines that have higher volume, cold chain capacity or disposal demands have had a negative impact on existing operations of immunization programs. Therefore early stage consideration of presentation and packaging parameters is encouraged. Deferring these considerations may lead to additional costs and delays required for reformulation later in the development pathway.

Recognising the need to encourage early consideration of these issues, WHO has published several documents that describe WHO preferences for vaccine presentations and packaging and programmatic suitability. These documents include:-

- Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification (WHO/IVB/12.10) (http://www.who.int/immunization_standards/vaccine_quality/ps_pq/en/index.html)
- Vaccine Presentation and Packaging Advisory Group (VPPAG). Generic preferred product profile (gPPP), Version 2.1, August 2009 (http://www.who.int/immunization_delivery/systems_policy/VPPAG_Generic_PPP_and_Workplan.pdf)

Malaria vaccine developers and manufacturers should refer to the current version of these documents to gain an understanding of these parameters and the relevant recommendations to ensure that their target product and development program meet WHO preferences. An understanding of these preferences will hopefully ensure not only the development of highly efficacious and safe products that have characteristics desirable for low and middle-income country settings but also facilitate and enable a successful outcome for vaccine developers from the WHO Programmatic Suitability for Prequalification Process.

Beyond the minimum requirements for consideration of WHO PQ, vaccine developers should be aware of the call from immunization programmes in resource poor settings that innovation related to programmatic suitability aspects such as ease of administration and thermostability will lead to great advances in these areas. Advances that are foreseen in the next decade include, firstly, greater availability of needle-free administration for vaccine delivery in low income countries, and secondly thermostability so greatly improved that vaccines can be stored at ambient temperatures and a refrigerated cold chain will no longer be needed for some vaccines. The economic benefits of ambient temperature storage of a meningitis vaccine have been evaluated⁶. Research and collaboration between academics, vaccine and delivery device developers, together with dialogue and engagement of regulators and WHO to facilitate such advances could be transformative for immunization programmes and is strongly encouraged.

⁶ Lydon P et al. Bulletin of the World Health Organization 2014;92:86-92. who.int/bulletin/volumes/92/2/13-123471.pdf

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