

Malaria Vaccine Advisory Committee (MALVAC) meeting on Preferred Product Characteristics for malaria vaccines

Report of a meeting, 27–28 October 2020

1. SUMMARY

On 27–28 October 2020, the World Health Organization (WHO) Initiative for Vaccine Research and Global Malaria Programme convened a meeting of the Malaria Vaccine Advisory Committee (MALVAC) to review priority issues in product development in malaria vaccine research and development (R&D). Experts reviewed major use case scenarios for malaria vaccines, including the reduction of morbidity and mortality, and the reduction of malaria transmission. Other potential use case scenarios were also discussed, including seasonal vaccination, vaccination to prevent malaria in pregnancy, and vaccines targeting non-*Plasmodium falciparum* species such as *P. vivax*. MALVAC members discussed how best to update and build on the previously developed malaria vaccine Preferred Product Characteristics (PPCs) (1), bearing in mind advances in the field and lessons learned from the development and evaluation of the RTS,S/AS01E vaccine. These advances include new approaches in study design and clinical development, and innovations in surrogate biomarkers, assay development, and other evaluation technologies. These topics were particularly relevant given that, as of October 2020, two vaccine candidates were approaching late-stage development.

Key conclusions of the meeting included:

- **Vaccine efficacy should be considered in the context of other characteristics, which together determine the overall potential public health benefit.** Although previous malaria vaccine PPCs specified a target vaccine efficacy of 75%, vaccines with a considerably lower efficacy may also have the potential to deliver substantial public health benefit if used in high-burden settings and when other characteristics are considered, such as improved duration of efficacy, dose regimens, or delivery mechanisms. Malaria vaccine PPCs should, therefore, reflect a balanced approach to assessing overall vaccine impact, taking into account multiple vaccine characteristics as well as the use case scenario in which it will be deployed.

- **Optimal target populations for vaccination may vary by transmission setting and use case scenario.** The target age range for vaccination may extend beyond young children in a number of settings and scenarios. This includes areas where a significant burden of clinical malaria also exists in older children or where a wider age range in the population remain infectious, contributing to ongoing transmission. Further consideration was needed of how best to determine target ages and populations.
- **The development of transmission-blocking vaccines may require novel development paths, study designs or surrogate endpoints.** Traditional cluster randomized trials for vaccines targeting transmission reduction at the community level may have limited study power in low transmission settings. Alternatives discussed included trials in moderate transmission settings, proof-of-concept study designs such as controlled human malaria infections, and surrogate endpoints such as membrane feeding assays. However, these would likely require validation and further consultation with regulatory bodies on data requirements.
- **Seasonal administration of malaria vaccines is an important potential use case scenario.** Given recent studies on the use of RTS,S/AS01E with seasonal malaria chemoprevention, specific guidance on the future application of vaccines for this purpose may be useful. The importance of some vaccine characteristics, such as the criteria for vaccine efficacy, duration of protection and dose regimen, may warrant review for vaccines delivered seasonally. A seasonal use case would be a subset of vaccines targeting the reduction of clinical malaria.
- **Where the incidence of *P. falciparum* malaria declines, increasing dominance of non-*P. falciparum* malaria may emerge and require the development of *P. vivax* vaccines.** These vaccines may require specific R&D guidance. Several *P. vivax* vaccines currently in the R&D pipeline may potentially be used in malaria-endemic regions. These vaccines could be used independently or in combination with *P. falciparum* vaccines and would benefit from guidance specifying criteria that may differ from *P. falciparum* vaccines, for instance requiring duration of efficacy that is sufficient to protect against relapses. This requires further review based on the epidemiology of *P. vivax* in endemic areas, such as differences in immune status with age at varying transmission levels, and the approach to deployment (that is, mass vaccination campaigns or short duration time-limited vaccination).
- **Access and affordability should be considered at an early R&D stage.** Consideration of the scalability of commercial manufacturing to meet anticipated demand, and the delivery of vaccines within existing country health systems, will be critical in order to maximize public health impact. While PPCs may not be able to address these issues directly, the early engagement of relevant WHO departments to consider these challenges would support innovation by vaccine developers.

2. BACKGROUND

While there has been a significant decrease in malaria burden over the last 20 years, recent data from 2015–2019 indicate that reductions in mortality and clinical incidence have stalled, underlining the need for new tools to help meet global control and elimination targets. RTS,S/AS01E is a successful step towards an effective first-generation malaria vaccine and is currently undergoing pilot implementation in moderate to high transmission sites in Africa in order to assess its potential suitability for wide-scale introduction (2). Given the demonstrated feasibility of prevention through vaccines, continued development of second-generation and future malaria vaccines that can

provide higher levels of protection and reduce transmission will be a valuable addition to existing tools for malaria control and prevention.

At a WHO consultation by MALVAC held on 16–17 July 2019, experts had discussed current challenges and opportunities in malaria vaccine R&D and options to improve end-to-end development pathways. The MALVAC meeting convened on 27–28 October 2020 aimed to review priority issues in product development in malaria vaccine R&D. Specific meeting objectives were:

1. to update on developments since the MALVAC meeting held in July 2019;
2. to discuss and begin to develop updated PPCs for malaria vaccine priority use case scenarios;
3. to develop plans to provide ongoing advice to product developers, including guidance on study designs and clinical development pathways;
4. to provide an update on horizon scanning of the malaria vaccine R&D pipeline for integration with the WHO Global Health Observatory.

The meeting began with introductory presentations on the WHO policy pathway for new malaria products, the WHO framework for developing PPCs, and ongoing horizon scanning activities on the malaria vaccine R&D pipeline. The Committee was asked to review high-level potential malaria vaccine use case scenarios, followed by a detailed review of specific PPCs for i) vaccines to reduce morbidity and mortality ii) vaccines to reduce malaria transmission and iii) other potential use case scenarios, including seasonal vaccination, malaria in pregnancy, vaccines for emergency situations, and vaccines targeting *P. vivax*. Meeting participants were asked to consider how to develop data-driven PPC criteria to guide the R&D of vaccines to best meet WHO public health priorities for malaria.

Policy pathway for new malaria products and WHO framework for PPCs

An overview was presented of the policy pathway for new malaria products (3) and the WHO framework for developing PPCs, providing background on the motivation for developing malaria vaccine PPCs. In order to develop malaria products that can address unmet public health needs, the WHO Global Malaria Programme aims to describe the preferred characteristics of desirable tools and conduct horizon scanning of the development pipeline. These activities should identify opportunities to accelerate the development of relevant tools and encourage product developers and funders to align around a common aim. The WHO Global Malaria Programme also seeks to reduce the time from evidence review to policy recommendations, through improved coordination with WHO Prequalification and other relevant WHO departments.

There is a standardized WHO approach for the development of PPCs and target product profiles, which are intended to inform product developers, regulatory agencies, procurement agencies, and funders of R&D and to facilitate the development of products that address the most urgent public health needs. The existence of a WHO product profile provides a strong indication that products meeting the criteria are highly desirable for public health. The process of developing a WHO PPC includes the scientific development of a draft PPC document via an expert working group, as well as a public consultation stage. After undergoing further amendments and expert consultation, as needed, a final PPC is endorsed and disseminated. A WHO PPC for vaccines is expected to include the following criteria: indication (obligatory), target population (obligatory), safety, efficacy, formulation/presentation, dose regimen, co-administration, route of administration, product stability and storage, and access and affordability. As of September 2019, 196 product profiles are publicly available on the WHO Special Programme for Research and Training in Tropical Diseases product profile directory, of which 31 were specific to malaria (4).

Malaria vaccine R&D horizon scanning

The WHO Global Malaria Programme is conducting horizon scanning of the malaria R&D pipeline. An overview of the work plan was presented, which aims to provide a publicly available resource on the pipeline and to identify any gaps between the current pipeline and the strategic goals set forth through the PPC. This can form the basis for engaging developers and funders to focus research in areas of unmet need. The information included to date builds on data from the current WHO Global Observatory on Health R&D website (5), which spans products (drugs, vaccines, and diagnostics) across all WHO diseases, including malaria. The Observatory is based on the AdisInsight database (6), which collates information from company websites, clinical trial registries and annual reports from pharmaceutical and biotechnology companies; products are only included when at least one developer is commercially driven. To capture information most relevant to malaria vaccine stakeholders, the horizon scanning exercise is collating data from additional sources, such as previous versions of the Malaria Vaccine Pipeline Tracker and the MESA Track database on *P. vivax* vaccine R&D (7). Work is ongoing to develop a bespoke webpage for the malaria vaccine data, with data visualizations to summarize the current R&D landscape, such as breakdowns by *Plasmodium* species, target antigen, or life cycle stage of delivery platform. The malaria vaccine pipeline information will be shared regularly with MALVAC to help ensure that it is complete and up to date.

3. EXPERT DISCUSSION SESSIONS

A series of detailed discussion sessions were held over the course of two days, during which experts reviewed PPC criteria for priority use case scenarios. The key discussion topics for each use case scenario are summarized below. In addition, a general aim should be to try to “future proof” vaccines, to minimize the possibility that escape variants develop and spread.

Use case scenario one: malaria vaccines to reduce morbidity and mortality

Despite the scaling up of malaria control interventions, *P. falciparum* malaria continues to be a major cause of morbidity and mortality in infants and young children in many countries, and the development of vaccines against malaria disease and death remains an unmet public health priority. The development of disease-reducing malaria vaccines will need to take into account a number of factors. These include not only the biological characteristics of the parasite and its host, but also potential changes in transmission patterns and the associated burden and age pattern of the clinical manifestations of the disease.

There was general agreement that although morbidity and mortality reduction will tend to be the focus of malaria control programmes in countries with moderate to high disease burden, vaccines designed for this indication would also have potential application across all transmission settings.

For vaccines targeting reduction in morbidity and mortality, the following areas were highlighted as priorities for consideration and future review:

- **Measuring public health impact beyond vaccine efficacy.** While a previous PPC specified a target vaccine efficacy of 75%, there was general agreement that a vaccine with lower efficacy could have considerable public health benefit in settings with a high disease burden. Lower vaccine efficacy may also be offset by other characteristics, such as a longer duration of protection, reduced number of doses (and thus ease of achieving high coverage) or improved programmatic suitability, such as cold chain requirements or cost. The Committee was cognizant that a balance needs to be achieved in order

to encourage the development of vaccines that may have substantial impact despite lower efficacy, while also supporting the continued development of vaccines targeting 75% efficacy or above. Although it was considered desirable to have a rationale for any target efficacy included in the PPC, it was noted that care should be taken not to disincentivize funders and product developers from efforts to develop the most highly efficacious vaccines possible.

- **Defining the target age range across transmission settings with differing patterns of clinical disease.** In many settings with stable malaria transmission, the burdens of severe and fatal malaria are predominantly seen in children under 5 years of age. Less severe manifestations may, however, be common throughout childhood and in adults. Similarly, as transmission declines in a setting, an increasing proportion of uncomplicated malaria disease will occur in children over 5 years of age and in adults (8). However, the most severe manifestations will still occur predominantly in children under 5 years of age. Hence, an efficacious malaria vaccine will most readily prevent severe disease and death when targeting young children. However, there will also be potential to reduce (predominantly uncomplicated) disease if older individuals are targeted. The cost effectiveness of the vaccine will thus vary according to the age group targeted and differential potential to prevent disease of different severity. Non-health benefits, such as improved educational outcomes or enhanced economic productivity, may become more important in age groups older than those bearing the brunt of severe malaria. The target age range will have implications for trial design as well as country implementation, influencing whether vaccines can be delivered as part of the routine Expanded Programme on Immunization schedule for young children or through mass immunization campaigns in wider age groups.
- **Facilitating WHO-wide guidance to developers on addressing vaccine access and affordability.** It was noted that the scope of access and affordability extends beyond price, with developers facing important challenges in ensuring adequate vaccine supply (that is, scalable commercial manufacturing) and delivery (that is, avoiding excessive strain on existing country health systems). Experts noted that, although access and affordability are essential components of meeting public health needs, addressing these issues in detail may be beyond the scope of the PPCs developed by MALVAC. However, the PPCs should encourage early consideration of these issues and encourage product developers to access guidance from relevant WHO departments early in the vaccine development process.

Other topics discussed included criteria for vaccine formulation and presentation, route of administration, and product stability and storage. It was suggested that such characteristics could be considered together, in the overall cost of vaccine administration. It was also suggested that modelling studies could help inform decisions about which regimens to test to achieve optimal boosting of immune responses and protection.

Malaria vaccines will be tested and deployed in many settings where other WHO-recommended malaria control measures are being used, such as vector control and chemoprevention, as well as non-malaria vaccines. Evaluation of potential interactions with other interventions, including co-administered vaccines, should be considered.

Use case scenario 2: malaria vaccines to reduce transmission

Vaccines interrupting malaria transmission (VIMTs) are also a strategic priority for WHO. These vaccines aim to reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection in the community. This encompasses products targeting multiple life-cycle stages, including i) sexual-, sporogonic- and/or mosquito-stage antigens to interrupt transmission and ii) highly efficacious pre-erythrocytic or blood-stage vaccines capable of reducing transmission. Although VIMTs will have particular application in malaria elimination settings, there was general

consensus that they may have utility across multiple transmission settings, particularly if used in conjunction with other measures to prevent clinical malaria.

For vaccines targeting transmission reduction, the following areas were highlighted as priorities for consideration and future review:

- **Target age range.** As with vaccines targeting clinical malaria, definition of the target age range for vaccination may vary by setting and delivery strategy. In contrast to clinical malaria, where the burden falls predominantly in younger children, individuals can remain infectious to mosquitoes into adulthood, representing a major contribution to transmission from humans to mosquitoes. However, the upper limit of the age range for inclusion in mass vaccination campaigns is not immediately clear. Further discussion is needed on appropriate methods to determine optimal age ranges. For instance, using prevalence of infection or other measures (such as membrane feeding assays) to identify which populations are contributing most to transmission. Target populations would need to be defined by geographical location.
- **Phase 3 trial designs to demonstrate community-level transmission reduction.** Evaluating the effectiveness of vaccines in reducing community-level transmission in cluster randomized trials is challenging. In low transmission settings, such studies would require prohibitively large sample sizes to achieve adequate study power. Although trials conducted in areas of moderate transmission may more readily achieve measurable effects, there may be a need to conduct trials in all settings where the vaccine is intended for use. Trials would also potentially need to cover a very wide age range, including women of child-bearing age, and be conducted at multiple sites in order to demonstrate safety and efficacy. For these reasons, the commercial feasibility of developing a stand-alone VIMT may be limited, and so development of a combination vaccine with sexual- or mosquito stage, pre-erythrocytic and/or blood stage antigens may be of interest. It is yet to be determined at which R&D stages the different targets of a multi-component vaccine would be evaluated independently versus combined. Overall, approaches to clinical development of VIMTs require further consultation with regulatory bodies regarding acceptable endpoints and study designs.
- **Surrogate endpoints.** In situations where the feasibility of conducting cluster randomized trials is limited, the use of proof-of-concept study designs such as controlled human malaria infection studies (9) has been explored, particularly those that utilize surrogate biomarkers. For example, the application of endpoints measuring human-to-mosquito transmission (such as prevalence of mosquito infection, direct or indirect membrane feeding assays) was discussed. As with the aforementioned trial design issues, further consultation with regulatory bodies is needed as to the type of data that would be required. In contrast to burden-reducing vaccines, there has been limited discussion on the need for a target efficacy level for VIMTs. It has been suggested that these could be informed by modelling that evaluates the efficacy needed to achieve sufficient interruption of transmission.
- **Access and affordability.** Achieving scalable manufacturing capacity to meet supply requirements was highlighted as a particular challenge for VIMTs if the coverage of the population includes a large age range, and hence a very large catch-up cohort, and numerous vaccination cohorts.

Additional use-case scenarios for malaria vaccines

In addition to vaccines targeting the reduction of morbidity and mortality and the reduction of transmission, Committee members were asked to consider additional use-case scenarios that may warrant specific PPCs to be developed, or modification of the burden- or transmission-reduction PPCs. Suggested use-case scenarios that were

considered included vaccines for seasonal administration, vaccines for emergency situations, vaccines for pregnant women, and vaccines for *P. vivax*.

The following areas were highlighted for consideration:

- **Seasonal vaccination.** Seasonal administration of malaria vaccines is a potentially important use case scenario given the large number of children living in intensely seasonal transmission settings and the high mortality in these populations. In 2012, it was estimated that approximately 39 million children under the age of 5 live in areas of sub-Saharan Africa where seasonal malaria chemoprevention is deemed appropriate, where 33.7 million episodes of malaria and 152 000 deaths among children due to malaria are reported in 2008 (10). A phase 3 trial of the use of RTS,S/AS01E in combination with seasonal malaria chemoprevention had recently been conducted and delivered striking results (11). Nearly all settings with perennial transmission also experience seasonal increases in transmission and disease. Therefore, the use of seasonal vaccination combined with routine vaccination through the childhood Expanded Programme on Immunization or other year-round malaria control interventions are potential strategies. Experts indicated that, although some of the desired efficacy and dose regimen attributes may be different for a seasonal vaccination use case, the PPC for seasonal vaccines could be considered to be a variation of the PPC for vaccines aimed at reducing morbidity and mortality. For example, vaccines providing high levels of efficacy for only a few months may be more acceptable in seasonal transmission settings than in settings with perennial transmission, if they could be readily administered on a recurrent (for example annual) basis.
- **Malaria in pregnancy.** The scope of vaccines for malaria in pregnancy could include both the use of standard vaccines developed to prevent clinical malaria in the general population, when administered to women before or during pregnancy, as well as vaccines targeting pregnancy-specific antigens, for example those expressed in placental malaria. Pregnancy-specific vaccines may have limited demand as a stand-alone intervention but may have potential to be combined with multi-target vaccines in the future.
- **Vaccines deployed in emergency situations.** Experts raised the issue that, while the PPC criteria for vaccines used in emergency situations may be no different, the relative importance of each characteristic may be weighted differently. For example, the number of doses may become a more critical consideration, with a preference for fewer doses, and rapid onset of protection may be crucial. A malaria vaccine for use in emergencies may need to target a broad age range if non-immune migrants, who are at risk of severe disease and death at all ages, are affected. A key question is whether there would be a need for special regulatory approval for vaccines delivered in emergency situations, requiring additional data from vaccine developers. Consultation on these regulatory requirements with relevant WHO departments should help inform the criteria for this use case scenario, but, as with vaccines for seasonal vaccination, could be considered to be a subset of PPCs for vaccines to reduce morbidity and mortality.
- **Vaccines targeting *P. vivax* malaria.** In areas of declining transmission, large reductions in the once dominant *P. falciparum* species will result in increasing proportions of other malaria species, particularly *P. vivax*. Given that vaccines are being developed to target this species independently, PPCs specific for *P. vivax* vaccines could be beneficial, or *P. vivax*-specific criteria can be highlighted within PPCs for vaccines targeting morbidity and mortality or for reducing transmission. Due to the co-endemicity of *P. vivax* with *P. falciparum* in most areas, the development of multi-species vaccines is likely to be preferable to a single-species vaccine.

4. CONCLUSIONS

There was general consensus that preferred characteristics for malaria vaccines should reflect a balanced approach to assessing public health impact, weighed in the context of the delivery strategies and epidemiological settings in which they will be deployed. Malaria vaccines targeting a wide efficacy range have the potential to deliver meaningful public health benefit if combined with other favourable characteristics, such as improved dosing regimens or delivery platforms. Similarly, optimal target populations may differ by transmission setting and use case scenario, depending on who contributes most significantly to disease burden or ongoing transmission. Ongoing changes in malaria epidemiology should be considered, accounting for potential shifts in high-risk populations by the time vaccines become available. Demonstrating a reduction in transmission may require innovations in development pathways including alternative study designs or surrogate endpoints. Although it may be technically feasible to develop a stand-alone transmission-blocking vaccine, the eventual deployment of such a vaccine was considered more challenging.

A number of special use cases were highlighted. Seasonal administration is a particularly important use case to consider, as illustrated by the recent study of RTS,S/AS01E with seasonal malaria chemoprevention. As incidence of *P. falciparum* malaria declines, it will be increasingly important to ensure that available vaccines target *P. vivax*.

Updating the technical guidance for malaria vaccine development will require further review in several areas. Clarity is needed on how best to determine the target ages and populations across a diversity of epidemiological settings. Alternative study designs to demonstrate transmission reduction have been explored by researchers and innovative development pathways will need to be considered and require validation in consultation with regulatory bodies on data requirements. Specific guidance on the future use of vaccines for seasonal administration, in emergency situations, targeting *P. vivax*, or to prevent malaria in pregnancy will be increasingly important to support vaccine developers and malaria control programmes. Lastly, challenges related to access and affordability, although outside the immediate scope of malaria vaccine PPCs, will be critical. Support from relevant WHO departments should help vaccine developers to consider and address these challenges at an early R&D stage.

MALVAC aims to integrate the latest research and expertise from vaccine developers and manufacturers, malaria control programmes, regulatory agencies and funding bodies to promote the deployment of first-generation vaccine candidates and support the development of second-generation and future malaria vaccines. Fostering a strong R&D environment to enable the successful development of malaria vaccines is multi-faceted, ranging from studies on the immune mechanisms of malaria protection and its impact on vaccine efficacy, identification of potential surrogate endpoints, and bridging of vaccine and adjuvant research. Additionally, the lack of a dual-readout (targeting

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