WHO working group on late-stage development for malaria vaccines to reduce disease burden: phase 3 considerations on the path to licensure and wide-scale implementation

Report on a virtual meeting, 12 and 19 April 2021

SUMMARY

On 12 and 19 April 2021, a World Health Organization (WHO) working group on late-stage development of malaria vaccines to reduce disease burden was convened by the WHO Department of Immunization, Vaccines and Biologicals (IVB) and the Global Malaria Programme (GMP). The goal of the working group was to review priority phase 3 research and development (R&D) considerations for the path to licensure and wide-scale implementation of vaccines. Experts reviewed key issues related to preclinical and phase 1 and 2 studies, phase 3 trial design, and manufacturing and production for wide-scale implementation.

Working group 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, evaluation and pilot implementation of RTS,S/AS01 – the first malaria vaccine to receive a positive scientific opinion from the European Medicines Agency and a WHO recommendation for wide-scale use in children living in regions with moderate to high transmission. Scientific advances include new approaches used in study design and clinical development, and innovations in surrogate biomarkers, assay development and other evaluation technologies. These topics are particularly relevant as vaccine candidates approach late-stage development.

Key conclusions of the meeting included the following:

- Lessons learned from phase 3 trials and the Malaria Vaccine Implementation Programme (MVIP) for RTS,S/AS01 can help guide the clinical development path for other malaria vaccine candidates. These lessons relate to trial design, post-licensure studies, and supply considerations and challenges. As well, the experience with RTS,S provides insight into the potential public health impact (informed by modelling) that can be achieved through wide-scale implementation of malaria vaccines.
• Vaccine developers are encouraged to consult with regulators and relevant WHO departments throughout the development process to align with existing WHO target product profiles or PPCs and to ensure generation of relevant evidence for WHO review processes. For example, the WHO Coordinated Scientific Advice procedure, which draws on experts from the relevant WHO technical departments and the Prequalification Team, provides guidance to applicants on the suitability of development plans and study designs to generate relevant data to meet WHO standards for assessing the public health value of a proposed product.

Prerequisites for progression to phase 3 evaluation

• Before pivotal trials, data on safety and immunogenicity should be demonstrated in the target population for which the vaccine is intended. Also required is some biological indication that the vaccine may be efficacious in the target population (e.g. prevention of infection following natural exposure or controlled human malaria infection – CHMI). These data would be evaluated in phase 1 and 2 studies. Where possible, the target population should align with the population involved in phase 3 trials for which the vaccine would be recommended (e.g. phase 2 trials in children).

• Correlates of protection as surrogate end-points to demonstrate vaccine efficacy are unlikely to be necessary or sufficient for licensure. Currently, no clear or universal vaccine-induced correlates of malaria protection have been established. It is nevertheless important to characterize the dynamics of immune responses, and to collect data and samples in phase 3 trials that would be needed to investigate possible vaccine-induced correlates of protection.

• Improved standardization and documentation of end-points and key study parameters are needed to enable comparisons between results from different studies or different vaccines and to indicate the appropriateness of extrapolation to non-study populations in other settings.

• Pre-vaccination parasite clearance with drug treatment in phase 3 studies may have implications for product labelling and indications for use. Pre-vaccination clearance facilitates evaluation of vaccine efficacy by ensuring that any infections detected during follow-up are new – rather than pre-existing or recrudescent. Preliminary evidence also suggests that pre-vaccination clearance may enhance immune responses to some vaccines. Given this potential confounding effect, pre-vaccination parasite clearance should only be included in phase 3 studies if it will be included in the vaccine label (when the vaccine is deployed) or if there is compelling evidence that immunogenicity and protective efficacy are significantly improved with treatment.

• Heterologous challenge strains used in CHMI studies may affect interpretation of results and the level of transferability of efficacy to field conditions. CHMI studies will need to take into account whether strains used in heterologous challenge are representative of the parasite diversity expected in settings where vaccines are intended for use. Improved characterization and development of additional parasite strains that are genetically and geographically distinct from the NF54 strain of Plasmodium falciparum would be useful for future studies.

Phase 3 trial design considerations

• The recommended primary efficacy end-point for phase 2b and 3 trials to support licensure is incidence of uncomplicated clinical malaria. Data on more
severe end-points (e.g. severe malaria, malaria-related hospitalizations and mortality, all-cause mortality) are necessary for demonstrating broader public health impact; however, these aspects are difficult to measure with precision in phase 3 trials because of the very large sample sizes needed and the ideal healthcare conditions under which the trials are conducted. These end-points may be more amenable to evaluation in post-licensure studies. The findings from such studies can be used to support policy review and decision-making, or to revise vaccine guidelines, if appropriate.

- **Selection of vaccines used in comparator study arms will need to be considered following a recommendation for broad use of a first-generation malaria vaccine.** The choice of appropriate comparator and trial designs will depend on the context in which a candidate vaccine is intended for use, the view of local ethics committees, the needs of regulators to support licensure, and the opinion of public health stakeholders involved in decision-making for implementation.

- **Use of optimized versus routine delivery, and the quality and coverage of malaria control interventions, including case management, may vary between settings.** Whether malaria control measures are provided as part of the study or through local distribution channels and health systems, investigators should aim to maximize access, coverage and quality of interventions and care throughout the study. Study design and analysis will need to anticipate the effect of delivery of non-vaccine interventions and standard of care on study end-points.

- **Evaluation of vaccine efficacy will need to account for the routine use of other malaria control interventions in the study setting.** Studies should carefully document existing control measures, such as the use of insecticide-treated nets, indoor residual spraying or chemoprevention programmes, and access to quality diagnosis and treatment (which may affect baseline incidence of clinical malaria), so that the context in which vaccine efficacy was measured can be established.

- **Improved quality of care and malaria case management available in clinical trials, especially trials evaluating efficacy against clinical malaria episodes, reduces progression to more severe disease.** This affects the ability to evaluate efficacy of vaccines against more severe clinical end-points, such as severe malaria, or malaria-related hospitalizations or mortality. These end-points provide important information on public health impact. However, the effects of a vaccine using these endpoints may be imprecisely measured in phase 3 studies, and more precise evaluation may be necessary in post-licensure studies.

- **Trial site selection should reflect the settings for which the vaccine is intended for use.** Studies will often need to be conducted in both seasonal and perennial malaria settings, and across a range of incidence and prevalence of disease. Well-designed clinical studies should document safety, immunogenicity and efficacy in different populations (e.g. geographical locations) and transmission settings, to enable evaluation of the transferability of study results to other settings. Overall, study sites should be representative of the areas in which the vaccine is intended to be deployed.

- **Active case detection (ACD) may be appropriate in phase 2b trials, but passive case detection (PCD) is generally preferred for phase 3 trials to measure end-points that are more relevant to public health impact.** Study results based on PCD will be affected by several factors, such as distance of trial participants from the healthcare facility and treatment-seeking behaviours.
Clear descriptions of any ACD and PCD systems used in a trial, and the potential implications of variations between study sites should be well documented to aid interpretation of studies in different settings.

**Transition from phase 3 to wide-scale implementation**

- **Development of manufacturing processes needs to be advanced in parallel with clinical development programmes, depending on the investment available and level of risk tolerance.** The primary risk in delaying such development is the possible need to repeat stability testing and clinical trials because of significant changes that may occur in the manufacturing process – these may affect the quality, safety or efficacy of the vaccine compared with the product evaluated in the original clinical studies.

- **As early as phase 1 studies, vaccine composition, manufacturing process and presentation decisions can critically affect the production process and costs.** Vaccine developers are encouraged to explore options early in development and consult with relevant WHO departments for guidance through the WHO Coordinated Scientific Advice procedure.

- **Availability of more than one efficacious vaccine can facilitate sustainable supply and a healthy market.** Despite commitments by several stakeholders to supply the RTS,S/AS01 vaccine, a vaccine supply gap is anticipated for the next 5–10 years, making the availability of more than one vaccine with at least similar efficacy to RTS,S/AS01 desirable for a healthy market. Vaccine manufacturing capacity and supply must be considered with early engagement of pharmaceutical companies, Gavi, WHO and other stakeholders.

- **The lack of a dual market presents challenges in assuring sustainable supply and the ability to meet potential demand. Innovative financing mechanisms are needed.** Malaria vaccines will be targeted towards resource-poor countries and public immunization programmes, and R&D business models must take this into account, including uncertainty in demand and price setting.

**BACKGROUND**

Despite progress since 2010 in reducing malaria morbidity and mortality, trends since 2015 have shown stagnation in malaria control, underlining the need for new tools to help meet global control and elimination targets. In October 2021, RTS,S/AS01 was the first malaria vaccine to be recommended by WHO for wide-scale use to prevent *Plasmodium falciparum* malaria in children living in regions with moderate to high transmission. Development of second-generation malaria vaccines is underway. They have the potential to provide similar or higher levels of protection as an alternative, or in addition, to RTS,S/AS01.

Up-to-date guidance from WHO for the evaluation of malaria vaccines approaching late-stage clinical trials can help product developers ensure delivery of a complete data package to support policy and regulatory review. More than one malaria vaccine will likely be required in the long term. Lessons from the RTS,S/AS01 phase 3 trials and pilot implementation can help to optimize development timelines for vaccines currently in the pipeline, and avoid setbacks on the path to licensure and wide-scale roll-out. Delivery of a complete data package can be expected to smooth the policy and regulatory reviews of new vaccines, although there is no guarantee that a positive recommendation by WHO or licensure will follow.
Under the auspices of the Malaria Vaccine Advisory Committee (MALVAC), the WHO Department of Immunization, Vaccines and Biologicals, and the Global Malaria Programme convened a working group on 12 and 19 April 2021 to consider requirements for phase 3 trials of malaria vaccines. The key areas for discussion were:

- prerequisites for progression to phase 3 trials (safety, immunogenicity, target population, dosing, surrogate end-points);
- phase 3 trial considerations (safety and efficacy end-points, duration of follow-up, trial site selection, ancillary studies); and
- transitioning from phase 3 to wide-scale implementation (regulatory issues, manufacturing, production, phase 4 monitoring).

Specific meeting objectives were to:

- summarize key lessons learned from RTS,S/AS01 clinical development and pilot implementation that can inform clinical development pathways for malaria vaccines;
- agree on recommendations for phase 3 study designs for malaria vaccines;
- inform malaria vaccine preferred product characteristics (PPCs); and
- agree on key clinical development issues, guided by PPCs developed by MALVAC and lessons learned from RTS,S/AS01 and the Malaria Vaccine Implementation Programme, that should be addressed by product developers.

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 research and development (R&D) pipeline. Presentations were then given on lessons learned from the RTS,S phase 3 trials and the Malaria Vaccine Implementation Programme, key studies and results to date, and plans for future phase 3 trials for two malaria vaccine candidates approaching late-stage clinical development: R21 and PfSPZ.

Meeting participants were asked to consider how to develop data-driven PPC criteria to guide the development of vaccines to best meet WHO public health priorities for malaria. The meeting focused specifically on clinical development of vaccines to reduce malaria morbidity and mortality, which is the most likely indication for use for the most advanced malaria vaccine candidates currently in the pipeline. Although vaccines to reduce malaria parasite transmission are also a WHO strategic priority, these will require different trial designs and continued consultation with regulatory agencies to determine feasible clinical development pathways.

**Malaria vaccine PPCs and R&D horizon scanning**

An overview of the policy pathway for new malaria products (2) and the WHO framework for developing PPCs was presented, providing background on the motivation for developing malaria vaccine PPCs. To develop malaria products that address unmet public health needs, the Global Malaria Programme and the Department of Immunization, Vaccines and Biologicals aim 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.
An overview of the current malaria vaccine R&D pipeline was presented by the Global Malaria Programme. The aim is to provide a publicly available resource that identifies any gaps between the current pipeline and the strategic goals set forth through the PPCs. This can form the basis for engaging developers and funders to focus research in areas of unmet need. Data are collated from the WHO Global Observatory on Health R&D (3), as well as additional sources such as previous versions of the Malaria Vaccine Pipeline Tracker and the MESA Track database on \textit{P. vivax} vaccine R&D (4). Work is ongoing to develop a webpage for the malaria vaccine R&D pipeline data. The database will be reviewed periodically to ensure that it is complete and up to date.

**MALARIA VACCINE PIPELINE: CHALLENGES AND OPPORTUNITIES**

**Lessons learned from RTS,S/AS01**

An overview and summary of lessons learned from the RTS,S/AS01 phase 3 pivotal efficacy trials and the Malaria Vaccine Implementation Programme were presented. In July 2015, RTS,S/AS01 was the first malaria vaccine to receive a positive scientific opinion from the European Medicines Agency (5). 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 former Malaria Policy Advisory Committee (MPAC; now the Malaria Policy Advisory Group – MPAG), WHO recommended pilot implementation in settings with moderate to high malaria transmission in sub-Saharan Africa (6). The Malaria Vaccine Implementation Programme was developed to respond to the SAGE/MPAC recommendation of a phased introduction of RTS,S/AS01 through the Expanded Programme on Immunization (EPI) in selected areas in three malaria-endemic countries (7). Analyses from the pilot implementation were reviewed in October 2021 by SAGE and MPAG, and RTS,S/AS01 was recommended for wide-scale use in children in areas of moderate to high transmission in sub-Saharan Africa.

The experience of the RTS,S/AS01 pilot programme demonstrated the notable reach and speed of vaccine uptake that may be possible through the established EPI system. Even with the moderate efficacy shown in the phase 3 trial (39% against clinical malaria over 4 years of follow-up in children receiving the first of their four doses between the ages of 5 and 17 months), RTS,S/AS01 has the potential to deliver considerable public health impact. During the 4-year follow-up in the phase 3 trial, RTS,S/AS01 averted more than 4000 clinical malaria episodes per 1000 vaccinees (receiving four doses) in settings with high disease burden, such as Nanoro (Burkina Faso) and Siaya (Kenya). With an estimated incremental cost-effectiveness ratio (ICER) of $25 (range $16–222) per clinical case averted (assuming a cost of $5 per dose) (8), the value of RTS,S/AS01 is comparable to that of other vaccines in the EPI programme and other malaria control interventions. Pilot implementations have shown that malaria vaccines can achieve more rapid scale-up and higher coverage through established and functioning routine EPI services than other malaria prevention tools. Malaria vaccine visits also present an opportunity to use a well-developed platform to deliver other malaria control and health interventions and messages. For example, training for new vaccine introduction for the RTS,S/AS01 vaccine emphasizes the need to remind parents at each visit that children should sleep under insecticide-treated nets, and should be brought promptly for testing and treatment of any fever episodes. The effectiveness of an intervention during routine delivery is likely to differ from the efficacy documented in clinical trials because of differences in implementation. Regional expertise and engagement are needed to understand and convey the full public health value of the intervention.

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1 Since April 2019, the Malaria Vaccine Implementation Programme has implemented vaccinations through the EPI system in Malawi, Ghana and Kenya. As of April 2021, more than 1.7 million doses had been administered through the programme (https://www.who.int/initiatives/malaria-vaccine-implementation-programme).
Several aspects of the RTS,S/AS01 phase 3 trial design may have affected the study results. The primary end-point was clinical malaria, and sufficient funding allowed measurement of the effect on this end-point with high precision in the trial. Study participants were provided with improved access to higher-quality health care, including outpatient and inpatient care, with additional clinical and laboratory equipment provided for the trial; this ensured reliable supplies of essential medications, oxygen and blood, and increased clinical staffing. In Siaya, Kenya, there was an estimated 70% reduction in mortality associated with enrolment in the RTS,S/AS01 trial, regardless of the study arm to which children were randomized (9). Study investigators noted that the high standard of care provided to all trial participants may have limited the ability of the trial to detect an effect on mortality and some other severe outcomes, although a substantial impact on severe malaria was detected (10).

Based on the experience with RTS,S/AS01, several considerations for clinical development were highlighted, which may help to inform trial design for future vaccines. First, vaccine efficacy may vary by transmission setting, and public health impact will depend on the local incidence of malaria. Therefore, inclusion of settings with a range of transmission intensities and epidemiological characteristics is important if the vaccine is intended for broad use. Additionally, caution should be used when comparing results across trials or with historical data, given that factors such as the choice of end-points and trial designs often vary between studies. Where trials are conducted and how vaccination is implemented will also define the approved indications for use (e.g. transmission intensity, dosing schedule, seasonal administration, fractional dosing). Therefore, some aspects of programmatic suitability can be addressed earlier in clinical development and help provide relevant data for the guideline development and regulatory review processes. The optimal dosing schedule should be determined before phase 3. Other programmatic questions can be addressed during phase 3/2b studies, such as safety and efficacy in malnourished children, HIV-infected individuals and low-birthweight babies; co-administration with other vaccines or malaria drugs; ease of use; acceptability to parents and healthcare workers; and demonstration that novel schedules (e.g. seasonal administration, fractional dosing) can be administered effectively.

Several risks and uncertainties influence the commercial feasibility of guaranteeing supply of vaccines and adjuvants. These primarily relate to uncertainties around future vaccine demand and the required manufacturing capacity, future vaccine price (linked to unclear future demand), availability of long-term investments and funding, feasibility of delivery and funding for post-marketing commitments (e.g. for the European Medicines Agency and African national regulatory authorities). The lack of a dual market presents additional challenges for sustainable supply. Vaccine supply must be addressed, and early engagement with pharmaceutical companies, Gavi, WHO and other stakeholders is needed. Large-scale pilot implementation studies should be avoided, if possible, given the high costs, lack of established financing mechanisms, and delays in delivery to the wider target population.

Next-generation vaccines: plans for future phase 3 trials

Two malaria vaccines are approaching late-stage clinical development. Study investigators for the R21 Matrix-M anti-sporozoite subunit candidate and the PfSPZ whole sporozoite vaccine presented overviews of key studies and findings to date, as well as plans for future phase 3 trials, regulatory strategies and manufacturing.

R21 is an anti-sporozoite subunit candidate vaccine, targeting the same circumsporozoite protein antigen as RTS,S/AS01, but aiming to increase efficacy with different immunogenic properties (11) and combined with Matrix-M adjuvant technology (12). Key studies so far include a phase 1/2a study using controlled human malaria infection (CHMI) with sporozoite challenge in healthy United Kingdom
volunteers (VAC072, NCT03970993); a phase 1b age de-escalation, dose escalation study conducted in Kilifi, Kenya, to assess safety and immunogenicity in adults, young children and infants (VAC073, NCT03580824); and a phase 1b/2b randomized controlled trial in Nanoro, Burkina Faso, in 450 children aged 5–17 months (VAC076, NCT03896724). In the Nanoro trial, efficacy was shown with vaccinations administered from May to August 2019, mainly just before the malaria season, and booster vaccinations in June 2020. A multicentre phase 3 randomized controlled trial (NCT04704830) to evaluate the efficacy of 5 µg R21/50 µg Matrix-M against clinical malaria in children is underway at five sites across four African countries: Burkina Faso, Mali, Kenya and Tanzania. Manufacturing plans have been developed with the Serum Institute of India for vaccine doses and with Novavax for the Matrix-M adjuvant.

PfSPZ Vaccine is a pre-erythrocytic radiation attenuated vaccine platform using aseptic, purified, vialled, cryopreserved *P. falciparum* sporozoites. Whole sporozoite-based vaccines aim to induce immune responses to a broad antigenic repertoire. A total of 20 trials have been completed or are underway, including 13 in Africa. Phase 1 studies using CHMI in malaria-naïve adults have been conducted in Europe (NCT02704533) and the United States (NCT02015091, NCT02215707). In Africa, phase 1 studies in malaria-exposed adults have been conducted in Mali (NCT01988636, NCT03510481), Tanzania (NCT03420053, NCT02132299), Burkina Faso (NCT02663700) and Equatorial Guinea (NCT02418962, NCT03590340); phase 1 and 2 studies in children and infants have taken place in Tanzania (NCT02613520), Kenya (NCT02687373) and Equatorial Guinea (NCT02859350). Phase 2 trials are currently being conducted in adults in Mali (NCT03989102) and Indonesia (NCT03503058), and in children in Gabon (NCT03521973). Phase 3 clinical trials are being planned in Equatorial Guinea, targeting residents in malaria-endemic areas, and in Germany and the United States, for travellers to endemic areas.

**EXPERT DISCUSSION SESSIONS**

A series of detailed sessions were held over the course of 2 days, where experts discussed key considerations for various stages of clinical development of malaria vaccines, including:

- prerequisites established during preclinical, phase 1 or phase 2 studies to progress to late-stage trials;
- phase 3 trial design considerations; and
- transition to wide-scale implementation.

A summary of the key topics for each discussion session is presented below.

**Session 1: Prerequisites for progression to phase 3 studies**

Phase 1 and 2 vaccine studies are typically designed to provide sufficient data on safety and immunogenicity to support the selection of one or more candidate formulations for evaluation in pivotal phase 3 trials. Before phase 3, early-stage clinical trials generally assess safety, immunogenicity, dose and schedule (e.g. different dose intervals, fractional dosing), formulation, and inclusion of adjuvants. Initial evidence of efficacy against end-points of interest, including those related to biomarkers of efficacy, can also be obtained at this stage.

The following areas were highlighted as priorities for consideration in early-stage clinical development before phase 3 trials.

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• Immunogenicity data and biological plausibility of efficacy in phase 1 and 2 studies. An initial indication of immunogenicity and likely efficacy in the target population should be demonstrated before phase 3 trials. What is assessed may depend on the intended mode of action of the vaccine. For example, an efficacious pre-erythrocytic vaccine would be expected to prevent blood stage infection and hence reduce infection following either CHMI or natural exposure. Reductions in infection are likely to translate into reductions in clinical episodes and severe disease, the last two being the true targets of the vaccine. Efficacy against these end-points may be demonstrated in phase 3 and 4 studies. It is important that end-points are measured in the same target population (e.g. age group) as that which will be involved in phase 3 trials and for which the vaccine is ultimately intended.

• Surrogates and correlates of protection and vaccine efficacy. Correlates of vaccine efficacy have been difficult to identify because of the biological complexity of the malaria parasite life cycle, and the immunology and epidemiology of the disease. No clear or “universal” vaccine-induced correlates of protection against malaria infection or clinical malaria have been established. As well, because of the distinct localization of life cycle stages, immune responses may be organ-specific, and different correlates of protection may be appropriate for vaccines targeting different stages or antigens. Associations have been observed between protective immunity and a wide range of variables, but findings have not been consistent across studies. Additionally, studies have not shown consistent immunological correlates of vaccine-induced protection in CHMI and against naturally acquired infections as identified in field trials. Research is ongoing to identify correlates of protection using computational data science approaches in systems biology and vaccinology (13, 14). With current knowledge, the use of surrogate end-points for disease-reducing vaccines is unlikely to provide the basis of licensure, but may be useful as supporting evidence characterizing immune responses.

• CHMI studies and heterologous challenge strains. CHMI models for malaria vaccine research have been hugely advantageous, informing vaccine formulation, dose, route and schedule. CHMI allows vaccine efficacy to be assessed with smaller sample sizes and shorter timeframes than are possible under conditions of natural exposure. A major challenge for malaria vaccine candidates will be the ability to induce strain-transcending protective efficacy.2 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 before field trials. Although only a limited number of defined *P. falciparum* strains3 are currently available for use in CHMI, research is ongoing to better understand how representative these are of the antigenic diversity in malaria-endemic areas (16).

• Future CHMI studies would benefit from improved characterization and development of parasite strains that can consistently produce gametocytes and sporozoites, can be cloned to produce a genetically homogeneous parasite population, are sensitive to commonly used antimalarials, and are genetically and geographically distinct from NF54. More importantly, interpretation of data from CHMI and generalizability of efficacy to field conditions will need to consider not only whether homologous or heterologous challenge is used, but whether strains used in heterologous challenge are representative of the parasite diversity expected in settings where the vaccine is intended for use.

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2 In RTS,S/AS01 phase 3 trials, protective efficacy was found to be greater against *P. falciparum* infections with a circumsporozoite protein genotype matching the vaccine strain, arising from the allele-specific nature of the vaccine-induced immune response (15).

3 NF54, West African; 3D7, clonal line derived from NF54; 7G8, clonal line of Brazilian IMTM22 isolate; NF135. C1, clone derived from Cambodian isolate; HMP02, Ghana, blood stage challenge only.
Session 2: Phase 3 trial design considerations

Pivotal trials (phase 2b and 3) are intended to provide robust evidence to support licensure, usually based on demonstration of safety and efficacy in randomized controlled trials with clinical end-points, particularly in the absence of an accepted single correlate of vaccine-induced protection. Whereas phase 1 and 2a trials tend to be conducted in non-immune populations, pivotal studies generate data in the target population. 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 before the finalization of pivotal trial protocols so that global guideline considerations can be taken into account.

For phase 3 trial design, the following areas were highlighted as priority considerations.

- **Choice of phase 3 trial end-points to support licensure and policy recommendations.** The recommended primary efficacy end-point for phase 2b and 3 trials to support licensure is incidence of all episodes of uncomplicated clinical malaria. Data on more severe end-points (e.g. severe malaria, malaria-related hospitalizations and mortality, all-cause mortality) are useful for demonstrating broader public health value but are more difficult to measure in phase 3. Severe end-points are less common than uncomplicated disease and thus require considerably larger sample sizes. However, reductions in clinical malaria can be expected to translate into reductions in more severe outcomes. The effectiveness against more severe outcomes may be more amenable to evaluation in post-licensure and phase 4 studies to support policy recommendations and decision-making. In some epidemiological settings with high malaria burden, measurement of hospital admissions with malaria may be feasible as a secondary end-point in phase 3 trials.

A balance is needed in phase 3 trials between collecting the minimum data required to support risk–benefit assessment for licensure and addressing relevant implementation questions. This may help to avoid costly or excessive post-licensure studies or monitoring, which could delay vaccine delivery to populations in need.

- **Data standardization and comparability.** Standardization and documentation of end-points and key study parameters are needed to enable reliable comparisons between studies and candidates. Factors that have the potential to affect estimates of efficacy include the study population (location, prior exposure status, age), case-ascertainment methods (active case detection, passive case detection), follow-up time points, case definitions (clinical criteria, laboratory criteria) and analysis methods. For vaccines that may have rapidly declining efficacy, an important consideration is the timing of vaccine administration in relation to seasonal variation in transmission intensity.

Caution is needed when comparing results between trials when target populations and follow-up times differ. Standardization of follow-up times used in vaccine trials – both CHMI and field studies under conditions of natural exposure – would improve comparability between study results (e.g. incidence of infection 21 days post-CHMI, episodes of clinical malaria at 6 and 12 months follow-up under conditions of natural exposure).

- **Pre-immunization parasite clearance.** In some phase 2 studies, drug treatment to clear parasites before vaccination or before the final dose may be used to reduce the immunosuppressive effects of existing malaria parasite infections and enhance the immunogenicity of the vaccine, and/or ensure that any parasitaemia detected in the follow-up period is due to new infections. However, use of pre-vaccination parasite clearance in phase 3 studies may have major implications for product labelling for licensure and the indication
for use. This would add considerable complexity to implementation as part of routine programmes. Therefore, the pros and cons of treating study subjects before vaccination in phase 3 studies should be carefully evaluated; such treatment would likely result in a recommendation for pre-immunization treatment as part of routine deployment (17).

- **Comparator study arms.** Following a recommendation for the broad use of a first-generation malaria vaccine (RTS,S/AS01), trial designs for new vaccines may need to consider the regulatory status and deployment of existing vaccines in the country where the trial is planned. Where a first-generation vaccine is already being deployed, a placebo-controlled trial may be judged unethical, and product developers may need to consider a trial comparing the existing vaccine with the new vaccine and whether a superiority or non-inferiority trial is appropriate. Consultations with WHO, regulatory agencies and ethics committees are strongly recommended when planning pivotal trials.

- **Evaluation of vaccines with and without other malaria control interventions.** Malaria vaccines will likely be tested and deployed in conjunction with other WHO-recommended malaria control measures, such as vector control with long-lasting insecticide-treated mosquito nets or indoor residual spraying with insecticides, malaria chemoprevention, use of quality-assured rapid diagnostic tests and effective antimalarial chemotherapy. These will vary according to study location. They will affect baseline disease incidence or force of infection, and the potential for the vaccine to further reduce malaria infections and disease. Variation in vaccine efficacy has been observed between settings with differing levels of disease burden (18). Study designs will need to carefully document any control measures so that the context in which the vaccine’s efficacy was measured is clear. Phase 3 trials also need to document the comparability of the trial arms with respect to these factors. Well-designed clinical trials can aim to control for confounding effects from imbalances in malaria control activities between study arms. Longer-term public health consequences of the simultaneous use of malaria vaccines and other control measures would be well suited for post-licensure studies. Post-licensure studies can establish vaccine effectiveness in settings in which other malaria control measures may be less well applied than in a phase 3 trial.

- **Standard of care for malaria case management.** The experience with the RTS,S/AS01 phase 3 trials has highlighted that improved quality of care can reduce the incidence of more severe clinical end-points, such as severe malaria, or malaria-related hospitalizations and mortality. This will impede the accuracy and precision of measuring vaccine efficacy against these end-points. In Siaya, Kenya, there was an estimated 70% reduction in mortality associated with enrolment in the RTS,S/AS01 trial, including among children in the control arm. Study investigators noted that the high standard of care provided to all trial participants may have limited the ability of the trial to detect an effect on mortality and other severe outcomes (10). Although these severe end-points may provide important information on public health impact, their evaluation is likely to be more feasible in post-licensure studies.

- **Use of optimal vs. routine delivery and coverage of malaria control interventions.** Sponsors and investigators will need to liaise with national malaria control programmes to determine whether malaria control measures are supplied as part of the study or through local distribution channels and health systems. Ultimately, investigators should aim to maximize access, coverage and quality of interventions and care that are nationally recommended and known to reduce malaria morbidity and mortality. In both study design and analysis, investigators will need to account for the effect of delivery and coverage of quality health care, including non-vaccine
interventions for malaria and other health interventions, on the measurement of vaccine efficacy.

- **Trial site selection.** The trial sites should reflect the settings in which the vaccine is intended for use. Studies should be conducted in settings with a range of transmission intensities and seasonal patterns, representative of the situations under which the vaccine might be deployed if found efficacious. Well-designed clinical studies should document potential differences between populations (e.g. geographical locations) with varied levels of disease burden, seasonal patterns, and host factors that could affect immune responses. The sponsor may choose to perform separate studies in different geographical areas, or to conduct one large study that includes study sites considered likely to provide representative data. Studies should also consider the number of sites in sample size calculations that can support generalizability of study results to all settings in which a licensed vaccine would be intended for use. If the efficacy of the vaccine is expected to vary in different settings, the trial size should be sufficiently large to enable accurate estimates of setting-specific efficacies.

- **Active and passive case detection.** The case detection system also has an important bearing on the interpretation of vaccine efficacy. Either active case detection (ACD) or passive case detection (PCD) can be used. ACD requires regular home visits and checking the blood for parasites in participants with measured fever or a history of fever. PCD is the detection of outcomes in participants seeking care, usually with symptoms, from health facilities or community health workers. 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 to test for parasites in the blood if participants have fever or history of fever may be appropriate. However, PCD will generally be preferred for phase 3 trials to measure the public health impact of the vaccine on the healthcare system, even if ACD may identify higher numbers of malaria cases and more accurately estimate the burden of malaria in the community as a whole (17).

  The results of study end-points detected through PCD systems will be affected by a number of factors, such as distance from the healthcare facility, treatment-seeking behaviour, availability of diagnosis and treatment commodities, and differences in clinical characteristics of cases. Therefore, clear descriptions of PCD systems, including potential limitations or variations, at study sites should be well documented. Important differences in PCD systems between studies or sites can cause significant confounding, making comparison of results between locations difficult. Potential confounding factors in the ACD system, such as frequency of follow-up, should also be clearly described. Analytical methods should account for individuals treated with antimalarials by excluding a defined period during which the drug is being metabolized (e.g. 14–28 days, depending on the drug used) from person time at risk.

- **Measuring age shifts or potential “rebound” in malaria.** Vaccine developers should be cognisant of the potential for vaccines to interfere with the development of naturally acquired immunity, as may occur with other prevention approaches such as chemoprophylaxis (19, 20). If vaccine-induced protection wanes over time, individuals may experience a period during which they are at increased risk of malaria compared with similarly aged individuals who did not receive the vaccine and acquired immunity naturally. This may warrant extended follow-up of study participants to quantify the extent of any such effect and to manage any potential deferred increases in morbidity. The relevance of malaria rebound extends beyond vaccines to all efficacious malaria prevention tools. Key issues related to the malaria rebound phenomenon will be considered by a separate WHO technical consultation.
Session 3: Transition from phase 3 to wide-scale implementation

Vaccine development after phase 3 trials and licensure will require adequate supply, effective delivery and wide-scale community acceptance of the vaccine. There should be discussion with national authorities as to when and how a vaccine found to be efficacious in a phase 3 trial will become available for use in the country. This is a general expectation for pivotal trials of any vaccine.

The following points were highlighted for consideration.

- **A key part of vaccine development is establishing a well-characterized and repeatable production process.** Many components of the product profile, including key determinants of product cost, are determined very 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.

- **Establishing production processes.** It is important to establish a well-characterized production process in phase 1 (21). Variations in production process and vaccine components can affect many aspects of the product profile, including efficacy, safety, dosing, cost and stability. Therefore, major changes in the production process can jeopardize the ability to progress from phase 1 to phase 2.

- **Establishing commercial-scale manufacturing capability.** Generally, building commercial-scale manufacturing capability is started early in phase 2 (21). 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.

- **Vaccine delivery requires management and coordination of diverse stakeholders across a range of complex activities.** The context of a country’s overall strategy for health promotion and disease 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.

- **Health systems impact of malaria vaccine introduction.** Alignment with existing delivery mechanisms and potential trade-offs with other vaccine distribution or malaria control intervention programmes need to be considered so that introduction of the new vaccine can be sustained without adversely affecting other services. As malaria control improves, heterogeneity in malaria risk is increasingly apparent. This leads to the need for subnational targeting of appropriate mixes of interventions to maximize malaria control in each subnational setting and optimize impact across the country (22). 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 wastage rates, and other logistics management. Decisions about deployment of a malaria vaccine should therefore be taken by national malaria control programme and EPI staff as part of the planning for comprehensive malaria control.
• **Availability of more than one efficacious malaria vaccine should help ensure sustainable supply.** An analysis of malaria vaccine demand estimated that more than 650 million vaccine doses may be needed from 2021 to 2035. Gavi may consider support of up to 490 million doses, and GlaxoSmithKline (GSK) is committed to supplying up to 15 million doses per year until 2028 (conditional on confirmed procurement). A product transfer of RTS,S/AS01 to Bharat Biotech is expected to increase supply by 2028, but the adjuvant AS01 will continue to be supplied by GSK, requiring a potential increase in production capacity of AS01 with external funding. Despite these complicated arrangements, a vaccine supply gap is still anticipated, making the availability of more than one vaccine with efficacy similar to, or better than, RTS,S/AS01 crucial to meet projected demand.

• **The lack of a dual market presents challenges in assuring sustainable supply and the ability to meet potential demand.** Malaria vaccines will be targeted towards resource-poor countries and markets, and R&D business models must take this into account, including uncertainty in demand and price setting. To avoid supply gaps and delays in scaling up, stakeholders must be engaged early. Innovative financing mechanisms are needed to reduce the risk and uncertainty currently faced by industry developers and manufacturers of malaria vaccines.

**CONCLUSIONS**

To achieve wide-scale implementation of new malaria vaccines, a range of issues that can affect downstream feasibility and costs must be considered – not only when designing phase 3 trials, but as early as phase 1 studies. WHO aims to provide strategic guidance to help developers navigate the clinical development pathway and smooth the policy review process. This includes providing a framework for the key data required to support policy review and facilitate comparison between candidates. The WHO Coordinated Scientific Advice procedure (23) brings together experts from the relevant WHO technical departments and the Prequalification Team and provides guidance to applicants on the suitability of the development plan and study designs for generating relevant data to meet WHO standards for assessing the public health value of a proposed product. This includes questions related to quality, non-clinical and clinical/epidemiological aspects of new products. WHO aims to reduce the time from evidence review to making recommendations by ensuring coordination between relevant departments and organizations, such as WHO Prequalification, SAGE, MPAG, the African Vaccine Regulatory Forum, Gavi and other stakeholders.
REFERENCES


## ANNEX 1. MEETING AGENDA

### Monday, 12 April 2021: Malaria vaccine pipeline: challenges and opportunities

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Presenter(s)</th>
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<tbody>
<tr>
<td>12:30–12:40</td>
<td>Welcome and introductions</td>
<td>Dr Regina Rabinovich</td>
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<td></td>
<td>Opening remarks</td>
<td>Dr Pedro Alonso</td>
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<tr>
<td>12:40–13:00</td>
<td>Background</td>
<td>Dr David Schellenberg</td>
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<tr>
<td></td>
<td>• MALVAC and GMP policy process</td>
<td>Dr Lindsey Wu</td>
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<td></td>
<td>• Current malaria vaccine pipeline and innovations</td>
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<td></td>
<td>• Summary of malaria vaccine PPCs</td>
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<td>13:00–13:45</td>
<td>Lessons learned from RTS,S</td>
<td>Dr Mary Hamel</td>
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<tr>
<td>13:45–15:30</td>
<td>Next-generation vaccines: plans for future phase 3 trials</td>
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<tr>
<td>13:45–14:30</td>
<td>PfSPZ attenuated candidate malaria vaccine</td>
<td>Dr Steve Hoffman</td>
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<tr>
<td>14:45–15:30</td>
<td>R21 candidate malaria vaccine</td>
<td>Professor Adrian Hill, Dr Umesh Shaligram</td>
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### Discussion of key development pathway issues (closed sessions)

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<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>15:30–16:50</td>
<td>Session 1: Prerequisites to phase 3 studies</td>
<td>Professor Umberto D’Alessandro</td>
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<tr>
<td></td>
<td>• Correlates/surrogates of protection, safety and efficacy, immunogenicity, dosing, pre-immunization parasite clearance</td>
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<td>16:50–17:00</td>
<td>Concluding remarks, Day 1</td>
<td>Dr Regina Rabinovich, Dr Pedro Alonso</td>
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### Monday, 19 April 2021: Discussion of key development pathway issues continued (closed sessions)

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<tr>
<th>Time</th>
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<tbody>
<tr>
<td>12:30–14:30</td>
<td>Session 2: Phase 3 design</td>
<td>Dr Kwaku Poku Asante</td>
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<td></td>
<td>• Primary and secondary efficacy end-points, safety, site selection, trial duration, needs for measuring rebound, study arms, duration of efficacy</td>
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<tr>
<td>14:40–16:10</td>
<td>Session 3: Transition from phase 3 to wide-scale implementation</td>
<td>Dr Marian Wentworth</td>
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<tr>
<td></td>
<td>• Regulatory and prequalification strategies, manufacturing and production for scale-up</td>
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<tr>
<td>16:10–16:30</td>
<td>Concluding remarks and next steps</td>
<td>Dr Regina Rabinovich, Dr Pedro Alonso</td>
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## ANNEX 2. LIST OF PARTICIPANTS

### Working group committee members

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution and Address</th>
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<tbody>
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