World Health Organization

WHO meeting on preferred product characteristics for monoclonal antibodies for malaria prevention

Meeting report, 3, 11 and 29 November 2021

1. SUMMARY

On 3, 11 and 29 November 2021, the World Health Organization (WHO) Initiative for Vaccine Research and the Global Malaria Programme convened a Scientific Development Committee to review key issues in product development for monoclonal antibodies (mAbs) for malaria prevention. Experts reviewed and discussed the current landscape of malaria mAbs research and development, priority use case scenarios, and key product development considerations. The aim of the meeting was to develop preferred product characteristics (PPCs) for malaria mAbs.

Key conclusions of the meeting include the following:

- The priority use case for malaria mAbs is the reduction of morbidity and mortality in infants and children – the age group at highest risk of severe disease. mAbs able to maintain a high level of protection for the duration of a transmission season or high-risk period (e.g. 3–6 months) can be a potential alternative to chemoprevention in infants and children.
- Other use case scenarios may be of interest in the future as research and development on malaria mAbs evolves. Prevention of infection in pregnant women and/or women of childbearing age will be of particular interest if increased drug resistance leads to a reduction in the effectiveness of chemoprevention in pregnancy.
- Target efficacy and duration of protection should be defined and evaluated (e.g. 80% efficacy against clinical disease for three months). This will enable better trial standardization and comparability across studies. Protection for up to six months would be highly desirable if needed to cover the period of malaria risk in a given setting. Efficacy maintained after a single dose for the duration of the malaria risk period is preferred. The need for additional doses to cover the risk period can be evaluated based on evidence from clinical studies.

- Clinical studies should assess the impact of anti-drug antibodies (ADAs) that may interfere with efficacy or lead to adverse reactions if repeat administration of mAbs is expected, either annually or during a single transmission season.

- Non-interference between malaria vaccines and mAbs that target the same antigen should be considered. The risk of interaction with vaccines may be low with passive immunization of mAbs, but early immunological studies may be needed to rule out potential safety concerns.

- Primary and secondary end-points to evaluate the efficacy of malaria mAbs in reducing clinical disease may include prevention of infection in controlled human malaria infection (CHMI) or Phase 2 studies. In Phase 2b and 3 trials, incidence of clinical malaria is preferred as a primary end-point, while incidence of infection could potentially be measured as a secondary end-point.

- The choice of comparator arms will depend on the context in which a candidate mAb is intended for use, the view of local ethical committees, the needs of regulators to support licensure and the opinions of public health stakeholders involved in decision-making for implementation.

- Manufacturing considerations must be addressed early in development so that production of licensed products can be scaled to cover the target population in need without significant delay. If a product's indication includes a large target population and/or repeat administration requiring high volumes, it may be challenging for the scale and speed of manufacturing processes to meet demand at a cost suitable for low- and middle-income countries (LMICs).

- WHO has published guidance documents on regulatory considerations for biotherapeutics; however, at the time of the meeting, guidance on the prequalification of preventive mAbs had not yet been issued. WHO is in the process of drafting guidance on the manufacturing and quality control of mAbs and mAb fragments, as well as on regulatory considerations for the preclinical and clinical evaluation of mAbs specifically for infectious diseases.

2. BACKGROUND

Alongside the development of new malaria vaccines and chemoprevention drugs, there have been recent advances in the development of mAbs for malaria prevention. Passive immunization with mAbs through direct administration of functional antibodies can overcome some of the limitations of vaccines by providing immediate protection. Malaria mAbs can potentially be used as prophylaxis for several months, providing short-term prevention to vulnerable populations. Furthermore, the simplified dosing regimen offered by preventive mAbs may circumvent some of the coverage and compliance issues faced by seasonal malaria chemoprevention, vector control and intermittent preventive treatment of malaria in pregnant women.

Technical innovations in candidate identification, optimization and manufacturing have reduced the time required to isolate, characterize and produce antibodies, increasing the possibility of developing more affordable mAbs. New methods have also been designed to increase the potency of mAbs and extend their half-life. As of 2022, several candidate malaria mAbs are being evaluated in Phase 1 and 2 clinical trials.

To support this quickly developing area of research and development, the WHO Global Malaria Programme and the Department of Immunization, Vaccines and Biologicals convened a Scientific Development Committee to develop PPCs for mAbs used for prevention of malaria.

Specific meeting objectives were to:

1. review the landscape of malaria mAbs and mAb PPCs for other pathogens;
2. agree on a set of PPCs for malaria mAbs;
3. ensure alignment with WHO guidance on mAb development and PPCs for mAbs for other pathogens (HIV, respiratory syncytial virus, coronavirus disease) and complementarity with PPCs for malaria vaccines and chemoprevention.

The meeting began with introductory presentations on the WHO policy pathway for new malaria products, the WHO framework for developing PPCs, and an overview of PPCs that have been developed for other malaria interventions and infectious disease mAbs. Several experts were invited to give an overview of the current research and development landscape of malaria and infectious disease mAbs, which included presentations on discovery and preclinical research, ongoing and planned clinical trials, and innovations in mAb production and manufacturing.

Key considerations in product development were discussed, including priority use case scenarios, target age groups and populations, translatability of preclinical and CHMI models to clinical studies, trial design end-points and parameters, regulatory pathways, and production and manufacturing to enable wide-scale implementation. Members of the Scientific Development Committee were asked to consider how to develop PPCs to guide the development of mAbs that best meet WHO public health priorities for malaria. See Annex 1 for the meeting agenda and Annex 2 for a list of participants.

3. WHO PPCS FOR MALARIA AND INFECTIOUS DISEASES

An overview of the policy pathway for new malaria products *(1)* and the WHO framework for developing PPCs was presented, providing background on the motivation for developing PPCs for malaria mAbs. To develop malaria products that address unmet public health needs, the Global Malaria Programme describes the preferred characteristics of desirable tools and conducts horizon scanning of the development pipeline. These activities help to identify opportunities to accelerate the development of relevant tools and encourage product developers and funders to align around a common aim.

4. PIPELINE OF MALARIA MONOCLONAL ANTIBODIES: CHALLENGES AND OPPORTUNITIES

4.1 Discovery and preclinical research

Most malaria mAb candidates target sporozoite antigens, particularly the circumsporozoite protein (CSP) antigen due to its immunodominance on the sporozoite surface and its high conservation. The focus on the pre-erythrocytic stage is due to the small number of parasites (10–100 sporozoites), allowing for a favourable mAb-to-parasite ratio to achieve neutralization of the pathogen. Successful elimination of parasites in this critical stage can prevent onward infection, disease and transmission.

Efforts are also being made to identify antibodies targeting other life-cycle stages. High efficacy can be challenging to achieve in the blood stage; not only are parasite numbers up to 10-fold higher, but there is also greater parasite genetic variability than in the pre-erythrocytic stage. There is, however, potential for combination use of pre-erythrocytic stage and blood-stage antibodies to block breakthrough parasites downstream. Blood-stage mAbs could have high efficacy if the number

of parasites entering the blood was dramatically reduced first with pre-erythrocytic stage mAbs. However, improved preclinical models are still needed to test the efficacy against blood-stage infection. mAbs targeting the sexual stage with longer duration of protection than drugs such as primaquine may also be promising. However, an improved understanding of the risks associated with mAb administration is needed, given that sexual-stage mAbs used alone would not provide direct benefit to the immunized individual.

Work is ongoing to identify and develop new malaria mAbs. New technology platforms, such as the Berkeley Lights Beacon, has enabled large-scale high-throughput single B-cell sorting to screen for parasite-stage or antigen-specific antibodies. Methods to generate more potent second-generation mAbs include the use of human B-cell knockout mice, yeast display platforms to evaluate a range of single amino-acid mutations in existing mAb candidates, or modifications to the antibody fragment crystallizable (Fc) region to increase effector functions *(2)*.

There are currently efforts to standardize in vitro and in vivo preclinical assays to enable improved evaluation of mAb candidates. However, challenges remain in the translatability of preclinical models to human studies. In vitro assays against functional activity are currently used to prioritize and select candidates for in vivo studies, but improved assays are needed (e.g. with a greater dynamic range) to better predict in vivo responses in mouse models. The use of humanized mouse models (FRG-huHep) infected with wild-type *Plasmodium falciparum* is one method that has been used to improve the translatability of preclinical results to CHMI. Results from field studies currently underway may help to better understand the comparability of studies conducted under CHMI versus natural exposure with respect to factors such as minimum dose or antibody concentration required for protection. Overall, harmonization of assays and study designs across research groups can enable better comparability between studies and laboratories.

4.2 Clinical evaluation

Most mAbs for malaria prevention are currently in the discovery and optimization phase, but there are three malaria mAb candidates currently being tested in clinical trials. These include two anti-CSP antibodies (CIS43LS and L9LS) that target sporozoites, and one antibody (TB31F) targeting the gametocyte surface protein Pfs48/45 to block human-to-mosquito transmission.

CIS43LS is based on the human mAb CIS43, modified to include LS (leucine and serine) mutations in the Fc region to increase antibody half-life. CIS43 was isolated from a clinical trial participant protected against CHMI following immunization with an attenuated *P. falciparum* whole-sporozoite vaccine (Sanaria), the serum of which also exhibited high anti-*Pf*CSP antibodies and in vitro functional inhibition of sporozoite invasion of hepatocytes *(3)*. Passive transfer of CIS43 showed sterilizing protection in two mouse models of malaria infection – direct venous infection with a transgenic *P. berghei* strain expressing *Pf*CSP (*Pb*-*Pf*CSP) and challenge via infectious mosquito bites, including in human liver-chimeric mice (FRG-huHep) *(4)*. CIS43 preferentially binds to a unique junctional epitope between the N-terminus and the central repeat domains of the *Pf*CSP protein *(4)*. Subsequently, LS mutations were introduced into the Fc region of CIS43 (CIS43LS) to increase antibody half-life. In vivo mouse models showed that CIS43LS had comparable protective efficacy to CIS43, while pharmacokinetics studies in non-human primates showed increased antibody half-life in skin *(5)*. Therefore, this modified CIS43LS candidate, designed to optimize the durability of protection in vivo, was selected for further evaluation in human clinical trials.

In 2020, CIS43LS was tested in a Phase 1 dose-escalation trial in healthy malaria-naïve adults to assess safety, efficacy and pharmacokinetics following CHMI

(NCT04206332) *(6)*. None of the nine participants receiving CIS43LS (by intravenous administration) showed parasitaemia 21 days post-CHMI, compared to five of the six control participants. Additionally, serum concentrations were sustained for six months after a single dose, with an estimated serum concentration half-life of 56 days. This study also sought to estimate the serum concentration required for protective efficacy against malaria in naïve adults and to evaluate the efficacy of subcutaneous administration. Building on these findings, additional CIS43LS clinical trials began in 2021, and results are expected in 2022. In early 2021, a Phase 2 dose-escalation trial also began in Mali (NCT04329104) to evaluate the safety, protective efficacy and pharmacokinetics of CIS43LS administered intravenously in adults under conditions of natural exposure in a seasonal setting *(7)*.

A second-generation anti-CSP mAb candidate, L9LS (also isolated from individuals vaccinated with attenuated *P. falciparum* sporozoites) has been found to be protective in mice with 2- to 3-fold increased potency compared to CIS43. A Phase 1 CHMI dose-escalation study was conducted in 2021 to evaluate the safety, protective efficacy and pharmacokinetics of L9LS by intravenous and subcutaneous administration in malaria-naïve adults (NCT05019729) *(8)*. Additionally, at the time of the meeting, two Phase 2 studies were planned for 2022 to evaluate the safety, protective efficacy and pharmacokinetics of L9LS in seasonal and perennial settings in Africa: a randomized trial evaluating efficacy of two subcutaneous administrations over 12 months in infants and children aged 5 months to 5 years in a perennial setting in Kenya (NCT05400655) *(9)* and a dose-escalation randomized trial evaluating the efficacy of a single subcutaneous administration in children aged 6 to 10 years in a seasonal setting in Mali (NCT05304611) *(10)*, both evaluating L9LS compared to placebo.

The most advanced transmission-blocking mAb candidate is TB31F, a humanized form of the rat mAb 85RF45.1, targeting the male gametocyte surface protein Pfs45/45. In 2020, a Phase 1 dose-escalation study evaluated the safety, pharmacokinetics and functional activity of TB31F administered intravenously and subcutaneously in healthy malaria-naïve adults in the Netherlands (NCT04338689) *(11)*. Serum concentration half-life of TB31F was estimated to be 20.5 days and greater than 80% transmission-reducing activity at a concentration of 3.3 ug/mL, measured as reduction in oocyst intensity using standard membrane feeding assays.

4.3 Manufacturing and production

In addition to ensuring safety and demonstrating efficacy, manufacturing considerations must be addressed early in development so that production of licensed products can be scaled to cover the target population in need without significant delay. Several factors are key to low-cost rapid mAb development and manufacturing.

A candidate mAb should ideally be selected for or engineered to be easily expressed and have low viscosity. This involves substantial upfront biophysical characterization and in silico analysis to determine product suitability for manufacturing and formulation, which can result in a differential cost of development even for candidates with similar potency. Potential factors influencing the cost of development include the ability to engineer a product to remove manufacturing hurdles, such as unwanted post-translational modifications or characteristics affecting formulation stability (e.g. propensity for aggregation, conformational stability, colloidal stability, protein–protein interactions, non-specific binding, etc.).

Potency, dose and volume also affect the manufacturing process and final cost of goods. High-dose volumes can make subcutaneous or intramuscular administration unfeasible, particularly in young children and infants *(12)*, and less suitable for wide-scale use in LMICs. At the same time, high-concentration formulations can result in increased viscosity and aggregation, presenting processing challenges such as the

filtration required to concentrate the product or lower recovery, and excessive loss of the final product *(13)*. Therefore, formulation studies should be closely linked to downstream manufacturing considerations.

If a product's indication includes a large target population and/or repeat administration requiring high volumes, it may be challenging for the scale and speed of manufacturing processes to meet demand at a cost suitable for LMICs. Traditionally, commercial mAbs are produced in mammalian Chinese hamster ovary (CHO) cell lines engineered to produce large quantities of antibodies (1–5 g/L), grown in large bioreactors, then purified and formulated through batch production *(14)*. While CHO cells can produce fully functional proteins well tolerated in humans, they require long production times and are costly.

Therefore, a variety of antibody expression systems and delivery platforms have been considered to accelerate clinical development, increase yields and reduce the production costs of mAbs. Alternative production hosts such as yeast, *E. coli* and plants have been proposed, which may enable more rapid production *(12, 15)*. Nucleic acid delivery of mAbs (e.g. RNA, viral vectors) has also been suggested as a delivery platform, enabling rapid and high-volume production without the need for complex production or purification processes.

Innovations are being explored to improve the efficiency and reduce the costs of large-scale mAb production. These include integrated continuous biomanufacturing platforms and/or single-use automated operations. Single-use bioreactors can be used in tandem to produce at scale and require less capital investment to construct *(14, 16)*. Integrated continuous biomanufacturing may be faster and cheaper, offer more consistent processing and improved product quality, and reduce costs by 55% compared to conventional batch processing *(14, 16)*. Modular and transportable facility units are also being developed, as explored by manufacturers such as Serum Institute India, which could enable small-footprint in-country production in LMICs. However, most of these technologies have yet to be tested or used for quality-controlled local production in LMIC settings.

5. PPCS AND CLINICAL RESEARCH AND DEVELOPMENT CONSIDERATIONS

A series of detailed sessions were held over the course of two days, in which experts discussed key considerations for PPCs and the clinical development of malaria mAbs. A summary of the key topics for each discussion session is presented below.

5.1 Use case scenarios

- The most immediate use case is the reduction of morbidity and mortality in infants and children – the age group at highest risk of severe disease. mAbs able to maintain a high level of protection for the duration of a transmission season or high-risk period (e.g. 3–6 months) can be a potential alternative to seasonal malaria chemoprevention. For infants, mAbs could provide protection in the first year of life, particularly if increased drug resistance leads to reduced effectiveness of chemoprevention. However, it will first be necessary to understand the potential differences in efficacy and safety in young infants. Depending on the target age group and feasibility of administration in local health systems, mAbs could potentially be delivered either through the Expanded Programme on Immunization, routine health facility visits or mass immunization campaigns.

- Other use case scenarios may be of interest in the future as research and development of malaria mAbs evolves. These include the reduction of morbidity and mortality in adults, use in emergency situations to prevent malaria outbreaks or reduce the burden of febrile disease on the health system, or targeting of high-risk travellers or workers to prevent reintroduction in regions that have already cleared or eliminated malaria locally.

- For reduction of morbidity and mortality in adults, prevention of infection in pregnant women and/or women of childbearing age is of particular interest. Increased drug resistance in the future may reduce the effectiveness of chemoprevention during pregnancy. Furthermore, passive immunization during pregnancy may have a significant impact on both women and infants, particularly if delivered to primigravid women in the first trimester, a period of high malaria risk. Feasibility of delivery in adults will depend on the dose and volume required to achieve protective efficacy and whether it can be administered intramuscularly or subcutaneously. Given that the concentration of mAbs can range from 12 ug/mL to 200 mg/mL *(17)*, reducing the volume to enable intramuscular or subcutaneous administration in adults may require mAb formulations with higher concentrations or potency than those used in children.

5.2 PPCs

- **Efficacy and duration of protection:** Target efficacy and duration of protection should be defined and evaluated (e.g. 80% efficacy against clinical disease for three months), enabling better trial standardization and comparability across studies. While preferred duration is for a minimum of three months, duration of protection for up to six months would be highly desirable if needed to cover the period of malaria risk in a given setting.

  Trials conducted in perennial settings are better suited to assess duration of protection due to the longer transmission period available for follow-up, even for products initially indicated for seasonal administration.

  If repeat dosing is envisioned (annually or within a single transmission season), evidence should be provided to ensure that efficacy is not adversely impacted by ADAs.

- **Safety:** If repeat administration of mAbs per individual is expected, either during a single transmission season or annually, the impact of ADAs that may interfere with efficacy or lead to adverse reactions should be evaluated. ADA studies should have a follow-up period long enough to monitor repeat doses, which may vary according to the intended dose schedule. Studies may also want to consider the total number of repeat doses envisioned in the lifetime of an individual.

- **Co-administration:** Studies should demonstrate safe co-administration with routine interventions in children, including vaccines and malaria drugs used for treatment or chemoprevention, in the settings intended for use. Non-interference between malaria vaccines and mAbs that target the same antigen should also be considered. The risk of interaction with vaccines is expected to be low with passive immunization of mAbs, but early immunological studies may be needed to rule out potential safety concerns.

- **Dosing regimen:** Efficacy maintained after a single dose for the duration of the malaria risk period is preferred, but the need for more doses to cover the risk period can be evaluated based on additional evidence from clinical studies. Fixed dosing, based on age and weight categories, is typically used for mAb administration in LMICs.

- **Route of administration:** Aligned with WHO prequalification specifications, intramuscular or subcutaneous administration in children is preferred to ensure programmatic suitability in LMICs.

- **Product stability and storage:** Most mAbs are typically stable for several years when stored under refrigerated conditions (2 °C to 8 °C), and this should also be feasible for new malaria mAbs.

- **WHO prequalification:** WHO has published guidance documents on the regulatory considerations for biotherapeutics *(18)*. However, at the time of the meeting, additional guidance on the prequalification of preventive mAbs had not yet been issued. WHO is also in the process of drafting guidance on the manufacturing and quality control of mAbs and mAb fragments, as well as on regulatory considerations for the preclinical and clinical evaluation of mAbs specifically for infectious diseases. Developers are encouraged to seek advice from WHO early in the research and development process, such as through the WHO Coordinated Scientific Advice (CSA) procedure *(19)*.

- **Access and affordability:** The value proposition and cost-effectiveness of malaria mAbs for use in LMIC health systems should be defined by the local context and preferences of country-level end-users. Relevant evaluation frameworks include the WHO Evidence to Decision tables used for policy recommendations and the investment case frameworks of the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Gavi, the Vaccine Alliance.

5.3 Additional clinical development considerations

- **Primary and secondary end-points** to evaluate the efficacy of malaria mAbs to reduce clinical disease may include prevention of infection in CHMI studies or field trials under conditions of natural exposure; incidence of all episodes of clinical malaria in Phase 2b and Phase 3 trials, followed by evaluation of severe malaria, malaria-related hospitalizations and mortality; and all-cause mortality in post-licensure studies.

  While active case detection is useful for measuring infection end-points, particularly in Phase 2 studies, passive case detection of clinical malaria is preferred in Phase 3 trials to determine the public health impact of burden reduction in health facilities. Incidence of infection in Phase 3 can be measured in additional cohorts.

- **Comparator arms:** The choice of comparator arms and trial designs considered appropriate will depend on the context in which a candidate mAb is intended for use, the view of local ethical committees, the needs of regulators to support licensure and the opinions of public health stakeholders involved in decision-making for implementation.

  Interventions used in malaria control programmes are continually evolving. Seasonal malaria chemoprevention is the recommended standard of care in children under 5 years of age in highly seasonal transmission areas of the Sahel in Africa. Additionally, following the recommendation for widescale use of RTS,S/AS01, trial designs may need to consider licensure and use of malaria vaccines in the country where trials are planned.

- **Evaluation in younger, more vulnerable age groups:** Safety and efficacy in adults or older children should first be demonstrated in Phase 1 and 2 studies. Subsequent age de-escalation studies can be conducted to ensure that the product is equally safe and efficacious in younger children, followed by Phase 3 studies in the target age group.

- **Evaluation of mAbs during pregnancy and lactation:** Studies should follow similar staged evaluation designs as recommended for vaccines. Options may include first conducting studies in women of childbearing age with specific

follow-up in women who become pregnant in the months immediately following immunization with mAbs. For trials evaluating immunization during pregnancy, regulatory authorities may generally recommend starting trials in women in their third trimester *(20, 21)*.

- **Modelling to inform mAb product characteristics:** Data from early clinical development of candidate mAbs can be used to model pharmacokinetic and pharmacodynamic profiles, accounting for factors such as the initial efficacy, antibody half-life and efficacy decay shape. Combined with additional implementation considerations (e.g. target age range, population coverage, seasonal malaria patterns, and timing of deployment with the transmission season), this analysis can help to inform the likely dose range needed to achieve the level and duration of protection required to reduce clinical incidence and/or other outcomes of interest (i.e. incidence of infection, severe malaria, hospitalizations or deaths).

CONCLUSIONS

The development of mAbs for malaria prevention is a promising area of research and development, with the potential to produce new malaria control tools for use alongside vaccines, drugs for chemoprevention and vector control. mAbs may even overcome some of the limitations of these interventions. The potential use of multiple interventions or delivery strategies for malaria prevention can also help to maximize the public health impact of new and existing tools.

The most immediate public health priority for malaria mAbs is the reduction of malaria morbidity and mortality in children and infants. As research and development evolves, future priorities for malaria mAbs may include targeting adult populations, including the prevention of malaria in pregnancy. The feasibility of wide-scale implementation in these additional target groups will likely require improvements in potency, concentration and/or dosing.

For mAb candidates in the pipeline, clinical development will need to address several considerations and PPCs. These include safety considerations, such as the potential for ADAs that may lead to adverse reactions or reduced efficacy, especially if repeat dosing is needed to achieve sufficient duration of protection. Clinical trials should consider the use of age de-escalation studies, study designs that enable accurate measurement of duration of protection, and optimization of dosing regimens to cover the period of malaria risk in a range of epidemiological settings intended for use. Wide-scale use of any new mAb product will require a cost of goods sold that allows for affordable implementation in LMICs, given the potentially large target population. Innovations such as half-life extensions, engineering of biophysical properties to improve manufacturing efficiencies and new processing technologies can help to lower the cost of production.

As of January 2022, over 130 mAbs globally have been approved or are under regulatory review, but only 11 of these products are for infectious diseases *(14, 22)*. Updated guidelines for the clinical evaluation and manufacturing of infectious disease mAbs are under development. Pilot procedures for WHO prequalification have been developed for therapeutic mAbs, but specific guidelines for preventive mAbs have yet to be developed. Therefore, developers are encouraged to consult with relevant regulatory agencies and WHO departments on product-specific requirements for licensure or WHO prequalification and recommendation.

REFERENCES

1. Global Malaria Programme: Recommendation development process [website]. Geneva: World Health Organization (https://www.who.int/teams/global-malaria-programme/guideline-development-process/recommendation-pathway, accessed 23 November 2020).

2. Kratochvil S, Shen C-H, Lin Y-C, Xu K, Nair U, Pereira LDS, et al. Vaccination in a humanized mouse model elicits highly protective PfCSP-targeting anti-malarial antibodies. Immunity. 2021;54:2859–76. doi:10.1016/j.immuni.2021.10.017.

3. Seder RA, Chang L-J, Enama ME, Zephir KL, Sarwar UN, Gordon IJ, et al. Protection against malaria by intravenous immunization with a nonreplicating sporozoite vaccine. Science. 2013;341:1359–65. doi:10.1126/science.1241800.

4. Kisalu NK, Idris AH, Weidle C, Flore-Garcia Y, Flynn BJ, Sack BK, et al. A human monoclonal antibody prevents malaria infection by targeting a new site of vulnerability on the parasite. Nat Med. 2018;24:408–16. doi:10.1038/nm.4512.

5. Kisalu NK, Pereira LD, Ernste K, Flores-Garcia Y, Idris AH, Asokan M, et al. Enhancing durability of CIS43 monoclonal antibody by Fc mutation or AAV delivery for malaria prevention. JCI Insight. 2021;6:e143958. doi:10.1172/jci.insight.143958.

6. Gaudinski MR, Berkowitz NM, Idris AH, Coates EE, Holman LA, Mendoza F, et al. A monoclonal antibody for malaria prevention. N Engl J Med. 2021;385:803–14. doi:10.1056/NEJMoa2034031.

7. NCT04329104, Anti-malaria MAb in Mali. In: ClinicalTrials.gov. Bethesda: National Library of Medicine (US); 2022 (https://www.clinicaltrials.gov/ct2/show/NCT04329104, accessed 24 January 2022).

8. NCT05019729, VRC 614: A Phase 1, dose escalation, open-label clinical trial with experimental controlled human malaria infections (CHMI) to evaluate safety and protective efficacy of an anti-malaria human monoclonal antibody, VRC-MALMAB0114-00-AB (L9LS), in Healt... In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US); 2022 (https://clinicaltrials.gov/ct2/show/NCT05019729, accessed 24 January 2022).

9. NCT05400655, Anti-malaria MAb in Kenyan children. In: ClinicalTrials.gov [Internet]. Bethesda: National Library of Medicine (US); 2022 (https://clinicaltrials.gov/ct2/show/NCT05400655, accessed 3 June 2022).

10. NCT05304611, Anti-malaria MAb in Malian children. In: ClinicalTrials.gov. Bethesda: National Library of Medicine (US); 2022 (https://clinicaltrials.gov/ct2/show/NCT05304611, accessed 3 June 2022).

11. van der Boor SC, Smit MJ, Wu Y, Bousema T, Jore MM, Ockenhouse CF, et al. First-in-human evaluation of a Plasmodium falciparum trasmission blocking monoclonal antibody. Poster session presentation at the American Society of Tropical Medicine & Hygiene 2020 Annual Meeting, 15–19 November (virtual).

12. Kelley B. Developing therapeutic monoclonal antibodies at pandemic pace. Nat Biotechnol. 2020;38:540–5. doi:10.1038/s41587-020-0512-5.

13. Yang Y, Velayudhan A, Thornhill NF, Farid SS. Multi-criteria manufacturability indices for ranking high-concentration monoclonal antibody formulations. Biotechnol Bioeng. 2017;114:2043–56. doi:10.1002/bit.26329.

14. Expanding access to monoclonal antibody-based products: a global call to action. London: Wellcome Trust; 2020 (https://wellcome.org/reports/expanding-access-monoclonal-antibodies, accessed 28 January 2022).

15. Shukla AA, Wolfe LS, Mostafa SS, Norman C. Evolving trends in mAb production processes. Bioeng Transl Med. 2017;2:58–69. doi:10.1002/btm2.10061.

16. Walther J, Godawat R, Hwang C, Abe Y, Sinclair A, Konstantinov K. The business impact of an integrated continuous biomanufacturing platform for recombinant protein production. J Biotechnol. 2015;213:3–12. doi:10.1016/j.biotec.2015.05.010.

17. Strickley RG, Lambert WJ. A review of formulations of commercially available antibodies. J Pharm Sci. 2021;110:2590–608. doi:10.1016/j.xphs.2021.03.017.

18. Standardizing biotherapeutic products [website]. In: Activities. Geneva: World Health Organization (https://www.who.int/activities/standardizing-biotherapeutic-products, accessed 27 January 2022).

19. WHO coordinated scientific advice procedure for health product research and development. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/342560, accessed 28 July 2022).

20. Muñoz FM, Swamy GK, Hickman SP, Agrawal S, Piedra PA, Glenn GM, et al. Safety and immunogenicity of a respiratory syncytial virus fusion (F) protein nanoparticle vaccine in healthy third-trimester pregnant women and their infants. J Infect Dis. 2019;220:1802–15. doi:10.1093/infdis/jiz390.

21. Muñoz FM, Bond NH, Maccato M, Pinell P, Hammill HA, Swamy GK, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA. 2014;311:1760–9. doi:10.1001/jama.2014.3633.

22. Antibody therapeutics approved or in regulatory review in the EU or US [website]. Framingham: The Antibody Society; 2022 (https://www.antibodysociety.org/resources/approved-antibodies/, accessed 28 January 2022).

ANNEX 1. MEETING AGENDA

Day 1, 3 November 2021 **Malaria mAbs pipeline: challenges and opportunities**		
12:30–12:40	**Welcome and introductions** **Opening remarks**	David Schellenberg, Pedro Alonso Soumya Swaminathan
12:40–13:10	**Background on PPCs for malaria and mAbs** • Summary of malaria PPCs and WHO framework for PPC development • State of the art – mAbs for infectious diseases and WHO mAb PPC development Joint Q&A	Lindsey Wu Erin Sparrow
13:20–15:30	**Overview of malaria mAb development** • Discovery and target identification • Overview of malaria mAbs clinical development process and pipeline • *Pf*CSP mAb candidate CIS43 • Clinical evaluation and manufacturing Joint Q&A	Jean-Louis Ndiaye (Chair) Josh Tan Kayla Andrews Bob Seder Lisa Connell-Crowley
15:40–16:40	**Background on existing malaria mAb target product profiles (TPPs)** • Overview of Bill & Melinda Gates Foundation TPPs for mAbs • The use of modelling to inform PPCs • Technical criteria in Bill & Melinda Gates Foundation mAb TPPs Joint Q&A	Kevin Marsh (Chair) Jean-Luc Bodmer Narimane Nekkab Melissa Penny Jacqueline Kirchner
16:40–16:50	**Closing remarks**	David Schellenberg
Day 2, 11 November 2021 **Use case scenarios and PPC review (closed session with Scientific Development Committee members only)**		
12:30–12:40	**Plan for the day** Scientific Development Committee administration (DOIs), scene setting – epidemiological considerations	Lindsey Wu
12:40–13:50	**Discussion of use case scenarios** Discussion topics: development options that will affect PPC criteria, use in seasonal vs. perennial settings, prevention of infection vs. transmission, infants/children vs. older children/adults, malaria in pregnancy, emergency situations, mAbs used in combination with other malaria interventions	Francisco Saute (Chair)

14:00–16:15	**Review of PPC criteria for priority use cases** Discussion topics: detailed review of each PPC criteria description, need for additional use case scenarios and/or criteria	Kevin Marsh (Chair)
16:15–16:30	**Closing remarks**	David Schellenberg
Day 3, 29 November 2021 **Product development to implementation**		
13:30–13:50	**Welcome and introduction** Summary of Scientific Development Committee working session	Lindsey Wu (Chair)
13:50–14:50	**Session 1: Early clinical development** • Preclinical models • CHMI • Target life-cycle stages	Francisco Saute (Chair)
15:00–16:20	**Session 2: Late clinical development** • Standardizing efficacy end-points • ADAs, mAb–vaccine interactions • Age de-escalation, pregnancy studies	Kevin Marsh (Chair)
16:20–16:50	**Session 3: Phase 3 to implementation** • WHO prequalification and CSA • WHO Evidence to Decision policy process • Manufacturing to meet supply/demand	Kevin Marsh (Chair)
16:50–17:00	**Concluding remarks & next steps** **Closure**	Lindsey Wu

ANNEX 2. LIST OF PARTICIPANTS

Scientific Development Committee

Enrica ALTERI
Independent expert
Geneva, Switzerland

Subhash CHAND
National Institute of Biologicals
Indian Ministry of Health and Family Welfare
Noida, India

Alasanne DICKO
Malaria Research and Training Center
University of Bamako
Bamako, Mali

Kevin MARSH
University of Oxford
Oxford, United Kingdom of Great Britain and Northern Ireland

Jean Louis NDIAYE
Department of Parasitology, Faculty of Medicine
University of Thies / University of Cheikh Anta Diop
Dakar, Senegal

Melissa PENNY (Chemoprevention Guideline Development Group [GDG])
Swiss Tropical and Public Health Institute
Basel, Switzerland

Regina RABINOVICH (Malaria Vaccine Advisory Committee [MALVAC])
Barcelona Institute for Global Health (ISGlobal)
Barcelona, Spain

Francisco SAUTE (Chemoprevention GDG)
Malaria Elimination Initiative
Manhiça Health Research Center
Manhiça, Mozambique

Marian WENTWORTH (MALVAC)
Management Sciences for Health
Medford, United States of America

Observers

Kayla ANDREWS
Gates Medical Research Institute
Boston, United States

Ripley BALLOU
International AIDS Vaccine Initiative
New York, United States

Ashley BIRKETT
PATH Center for Vaccine Innovation and Access
Seattle, United States

Jean-Luc BODMER
Bill & Melinda Gates Foundation
Seattle, United States

Aurelio BONAVIA
Gates Medical Research Institute
Cambridge, United States

Lydia BRAUNACK-MAYER
Swiss Tropical and Public Health Institute
Basel, Switzerland

Lisa CONNELL-CROWLEY
Just-Evotec Biologics
Seattle, United States

Peter CROMPTON
NIH National Institute of Allergy and Infectious Diseases
Rockville, United States

Cristina DONINI
Medicines for Malaria Venture
Geneva, Switzerland

Patrick DUFFY
NIH National Institute of Allergy and Infectious Diseases
Rockville, United States

Shreetij DUTTA
Walter Reed Army Institute of Research
Silver Spring, United States

Daniel EMERLING
ATRECA
San Carlos, United States

Pete GARDNER
Wellcome Trust
London, United Kingdom of Great Britain and Northern Ireland

Lindsey KEIR
Wellcome Trust
London, United Kingdom

Randal R. KETCHEM
Just-Evotec Biologics
Washington (DC), United States

Jacqueline KIRCHNER
Bill & Melinda Gates Foundation
Seattle, United States

Lee HALL
NIH National Institute of Allergy and Infectious Diseases
Rockville, United States

Aurelia HALLER
Gates Medical Research Institute
Boston, United States

Josephine MALINGA
Swiss Tropical and Public Health Institute
Basel, Switzerland

Scott MILLER
Bill & Melinda Gates Foundation
Seattle, United States

Annie MO
NIH National Institute of Allergy and Infectious Diseases
Rockville, United States

Narimane NEKKAB
Swiss Tropical and Public Health Institute
Basel, Switzerland

Chris OCKENHOUSE
PATH Malaria Vaccine Initiative
Seattle, United States

Faith OSIER
International AIDS Vaccine Initiative
London, United Kingdom

Monicah OTIENO
Gates Medical Research Institute
Boston, United States

Jason REGULES
Walter Reed Army Institute of Research
Silver Spring, United States

Suzanne SCHEELE
PATH
Seattle, United States

Robert SEDER
NIH National Institute of Allergy and Infectious Diseases
Rockville, United States

Umesh SHALIGRAM
Serum Institute of India
Pune, India

Lorraine SOISSON
United States Agency for International Development
New York, United States

Joshua TAN
NIH National Institute of Allergy and Infectious Diseases
Rockville, United States

Eileen VILLASANTE
US Naval Medical Research Center
Walter Reed Army Institute of Research
Silver Spring, United States

Charles WELLS
Gates Medical Research Institute
Boston, United States

Timothy WELLS
Medicines for Malaria Venture
Geneva, Switzerland

Additional participants

Simon DRAPER
University of Oxford
Oxford, United Kingdom

Marion PEPPER
University of Washington
Seattle, United States

WHO Secretariat

Soumya SWAMINATHAN
WHO Science Division
Geneva, Switzerland

Pedro ALONSO
Global Malaria Programme
Geneva, Switzerland

David SCHELLENBERG
Global Malaria Programme
Geneva, Switzerland

Mary HAMEL
Immunization, Vaccines and Biologicals
Geneva, Switzerland

Peter OLUMESE
Global Malaria Programme
Geneva, Switzerland

Erin SPARROW
Immunization, Vaccines and Biologicals
Geneva, Switzerland

Ole OLSEN
Immunization, Vaccines and Biologicals
Geneva, Switzerland

Vasee SATHIYAMOORTHY
WHO Science Division
Geneva, Switzerland

Richard ISBRUCKER
Norms and Standards for Biological Products, Health Product Policy and Standards
Geneva, Switzerland

Ray CORRIN
WHO Prequalification
Geneva, Switzerland

Guido PANTE
WHO Prequalification
Geneva, Switzerland

Lindsey WU
Global Malaria Programme
Geneva, Switzerland

Glyn GARTHWAITE
Global Malaria Programme
Geneva, Switzerland

WHO meeting on preferred product characteristics for monoclonal antibodies for malaria prevention: meeting report, 3, 11 and 29 November 2021

ISBN 978-92-4-006040-1 (electronic version)
ISBN 978-92-4-006041-8 (print version)