Next-Generation Malaria Vaccines

Stakeholder Engagement Meeting

Meeting proceedings

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Introduction

This report captures the proceedings of a next-generation malaria vaccine stakeholder engagement meeting held in New Orleans on the 13th of November, 2024. The event was organized as a hybrid event by Simon Draper, Jean-Philippe Julien, Melissa Penny and Katharine Collins, and was attended by representatives from academia, industry, funding agencies, policy and implementation. A full list of participants can be found in Appendix 1: List of participants. The report provides a summary of the meeting intended for meeting participants, as well as the broader malaria vaccine community.

The purpose of the meeting was to bring together a diverse group of stakeholders to identify key barriers and challenges that need to be addressed to accelerate the development of next-generation malaria vaccines. As the malaria vaccine landscape continues to evolve, prioritizing and coordinating efforts across the community will be essential for achieving effective and efficient progress. Specifically, the meeting aimed to:

1. Identify opportunities to enhance community collaboration and strategic coordination, and
2. Establish a shared understanding of the community's needs while initiating discussions on potential solutions

The meeting included three main sessions:

- Session 1: Setting the scene with a series of panel discussions and Q&A
- Session 2: Working group discussions to identify ways to improve current practices for more efficient and impactful vaccine development
- Session 3: Working group discussions to refine barriers and challenges for next-generation vaccine development

Opening Remarks

The opening session of the event celebrated the progress that the malaria vaccine community has made in developing and beginning to roll out two vaccines (RTS,S/AS01 and R21/Matrix-M). While recognizing these milestones, the speakers also acknowledged that there is work yet to be done and that the future holds both opportunities and challenges. Questions remain, such as what next-generation vaccines should aim to achieve, how they should be evaluated, and how trade-offs can be managed in decision-making during both development and implementation.

Participants were encouraged to stay product- and approach-agnostic during the day's discussions, instead focusing on identifying challenges and solutions for the malaria community as a whole. Perspectives from all corners were invited. The speakers indicated that the views expressed during the day would be compiled into a report to guide the community's collaboration to achieve the goal of developing the most effective next-generation malaria vaccines as quickly and efficiently as possible.

Session 1: Setting The Scene With A Series Of Panel Discussions

The co-chairs led four panel discussions with experts from the community. The views expressed during the panel discussions are summarised below.

Optimizing vaccines for delivery and implementation

Panelists: Evelyn Ansah (University of Health and Allied Science in Ghana) and Mary Hamel (World Health Organization (WHO))

This session focused primarily on potential barriers to implementation, drawing from the rollout of RTS,S/AS01 and related implementation studies.

The panelists highlighted various challenges. Lack of funding was mentioned, particularly Gavi's restriction on the level of malaria vaccine support to 85% of need in high transmission areas only, and the uncertainties around the forthcoming Gavi and the Global Fund replenishments. The efficacy and duration of existing vaccines present challenges, while new schedules (for example, seasonal delivery) that could be more impactful may fail to be adopted by countries due to the lack of an established delivery model. With regards to community engagement, the RTS,S/AS01 pilots showed that implementation can be complicated by rumours and disinformation (for example, about why certain groups were targeted, or the limited efficacy of the vaccine) and concern from caregivers about children getting too many vaccines at once. Delivery logistics can be made more difficult if documentation is not prepared in advance of rollout, and cascade training can lead to frontline workers not fully understanding vaccine eligibility and schedules.

Some learnings from the RTS,S/AS01 rollout that could inform vaccine development and implementation were discussed. In Ghana, moving the timing of a fourth dose from two years to 18 months increased coverage. Given the distances that caregivers and children may travel to receive healthcare, integrating vaccine delivery with other platforms may also increase coverage. Considering these factors when determining the best vaccination schedule early in development could improve vaccine uptake and impact. The importance of community engagement was emphasized when introducing a new vaccine, and it was suggested that challenges may be reduced if any new vaccines re-use the RTS,S/AS01 delivery model to avoid retraining health providers.

Global health impact of malaria vaccines

Panelist: Lindsey Wu (WHO)

The panelist highlighted that although existing malaria vaccines show significant effects on hospitalizations and all-cause mortality, there is still space to innovate to address waning efficacy over time, establish operational models for seasonal delivery, and develop vaccines that target malaria cases as well as transmission.

The three major strategic goals for malaria vaccine research and development (R&D), which were published in 2022 alongside WHO's preferred product characteristics (PPCs), were highlighted: 1) prevent human blood stage infection at the individual level, 2) reduce morbidity and mortality in individuals at risk in malaria-endemic areas, and 3) reduce transmission of the parasite and thereby substantially reduce the incidence of human infection in the community.

It was emphasised that WHO's publication on Malaria vaccines: preferred product characteristics and clinical development considerations (2022) also includes information about possible clinical development pathways, and initial considerations for pregnant women, emergency situations, and vaccines targeting *Plasmodium vivax*. While the PPCs can currently be referenced for key information, going forward these could helpfully be updated with more discussion concerning two areas. First, to update understanding of the most impactful vaccine use cases in different target populations, including how use cases might vary between epidemiological settings, and how vaccine impact (both effectiveness and coverage) can be optimized by considering dosing schedules and delivery strategies (number of doses, timing, and method of administration) and local contexts. Second, to provide more guidance for the clinical development pathways for multi-stage or combination vaccines, such as how and when antigens should be tested alone or combined.

The malaria vaccine community was encouraged to provide feedback on WHO guidance, as this would allow the WHO to address the identified gaps early on through technical consultations and advice. This could help to accelerate R&D and policy processes, as the WHO could play a role in harmonising research and study designs, or facilitate the development of common reference materials and standards.

What are next-generation malaria vaccines?

Panelists: Ashley Birkett (PATH), Tom Richie (Sanaria Inc), Hedda Wardemann (Gates Foundation)

In response to being asked why there was a need to develop next-generation vaccines, panelists highlighted the unacceptable and persistent malaria burden, despite billions of dollars in spending each year on the existing malaria control tools. When asked what next-generation vaccines should aim to achieve, all panelists agreed that one ultimate goal was elimination, which could require vaccines that target all age groups; it was emphasised that elimination could also require a concerted effort in settings that might be operationally complex, with more limited opportunities to leverage existing delivery platforms like the Essential Programme on Immunization (EPI). Additionally, panelists expressed a need for improved vaccines that target burden reduction in children and are also suitable for women of childbearing age (including pregnant women), as well as vaccines with higher efficacy and longer durability than existing vaccines.

Two of the panelists shared thoughts on whether next-generation vaccines need to be multi-stage or need to include transmission-blocking components. They suggested that all possibilities should be considered, but urged that combinations should be designed to align with specific use cases and acknowledged that getting different components to work together may not be trivial. In the context of limited funding, there will be a need for prioritization. It was also noted the benefits of multiple funders with different goals.

A number of concerns regarding vaccine development plans were discussed. Panelists expressed a warning not to underestimate the malaria parasite, calling for more research to understand target populations (including host immune systems and impact on the host) and more consideration of other species of malaria. The need for funding mechanisms that provide longer-term support for big ideas, and are not deterred by negative results, was also mentioned.

Clinical trials for next-generation malaria vaccines

Panelists: Alassane Dicko (MRTC/USTTB), Simon Draper (University of Oxford), Sara Healy (NIH), Meta Roestenberg (Leiden University Medical Center)

In this session, panelists spoke about how the efficacy of next-generation vaccines could be evaluated. While acknowledging and appreciating that there is a good range of existing trial sites with experienced teams, the panel also recognised some challenges for future trials. As existing licensed malaria vaccines become the standard of care, trial designs may need to shift away from placebo-controlled studies, and there may be a need for more capacity at existing trial sites, or new trial sites, particularly in high transmission areas. Future developments - such as new components or vaccines used by adolescents and adults - may require infection endpoints or new trial designs. A panelist suggested that now is the time to develop guidelines for trials and endpoints, suggesting that while competition is healthy in a research ecosystem, consensus and alignment on how to evaluate different types of next-gen vaccines would likely save time and resources and improve comparability between studies.

Regulatory guidance and innovative regulatory approval pathways were also discussed. Multiple panelists suggested that regulatory agencies are open to innovative designs, and the malaria community should consider providing clear guidance to regulators on topics such as immunoequivalence, suitable assay readouts, and plausible biological surrogate endpoints, when required. Many aspects of how multi-stage vaccines will be evaluated remain uncertain; a panelist suggested that an approach that considers the additive effects of different components through an entire population may be appropriate to capture the full vaccine impact.

The need to facilitate more controlled human malaria infection (CHMI) in endemic sites was discussed. A persistent discrepancy in results between endemic and non-endemic sites was highlighted, with a suggestion that conducting simultaneous CHMI studies in both kinds of sites may lead to a better understanding of the underlying drivers.

One panelist called for clearer definitions and guidance on vaccine efficacy, durability, and feasible delivery schedules. Given that some trade-offs will be unavoidable, a sense of which aspects will be most important and impactful would help to guide the development of next-generation vaccines. More communication between early-phase research, and late-phase development and deployment, was noted as important in this regard.

Panel discussion: audience Q&A

Attendees asked questions anonymously via an online platform, Slido. A summary of the discussion of the most popular questions (as determined by attendee voting) is included below, and a list of all questions can be accessed on request.

Panelists discussed whether future vaccines need to demonstrate superior efficacy compared to current vaccines, or if similar (or even lower) efficacy would be acceptable if vaccines were improved in terms of scalability or dosing frequency. It was suggested that a non-inferior vaccine with an improved schedule would be a positive development. In addition, regarding optimising schedules for increased coverage, it was noted that vaccine developers may be able to consider schedules that do

not conform to existing EPI touchpoints, as these visits are becoming crowded. The community was encouraged to think about the overall impact of a vaccine, including the possibility that it may be worth considering earlier vaccinations that reduce child mortality sooner, even if an immune response is sub-optimal.

The prioritisation decisions regarding support for new technologies such as monoclonal antibodies versus vaccines for malaria at The Gates Foundation were discussed. It was noted that the Foundation is continuously exploring new tools, and vaccines remain a priority, especially since it is likely that multiple tools may be needed to reach the Foundation's goal of malaria eradication. It was also emphasised, that whilst monoclonal antibodies can be exciting new tools in themselves, they can also provide learnings to inform and improve vaccine development.

Regarding the development and regulatory process, experts discussed which regulators to engage with and when. It was acknowledged that important work is being done to strengthen the capacity of African regulators and that they should be engaged early in the vaccine development process, with support from the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) where necessary. Engaging early with the African Vaccine Regulatory Forum (AVAREF) in the Phase 2 process was cited as a positive experience; varying scientific advice across agencies, and difficulties maintaining engagement with African agencies over time, were cited as challenges with the regulatory process.

One expert described the role of modeling in informing and updating the PPCs: modeling can be helpful for some parameters (for example, target population, efficacy and duration) and has been employed to think about the use and impact of next-generation vaccines. It may, however, be difficult to use modeling where empirical studies are lacking, for example to inform choices about the schedule, timing and number of doses.

On the topic of how the community could reach a consensus on clinical trial designs going forward, one panelist highlighted a previous coordination success in the community, when an agreement was reached on a naming convention for "CHMI", and suggested that a similar approach could be followed: physically bringing people together to make these decisions.

Finally, experts discussed the prospects of vaccines for elimination. The challenges of developing and delivering such a vaccine were highlighted. Funders were encouraged to take a balanced approach to supporting both lower and higher probability of success candidates, appreciating that multiple next-generation vaccines are likely to be needed.

Session 2: Identifying Ways To Improve Current Practices For More Efficient And Impactful Vaccine Development

In the second session, participants were assigned to 11 groups (two online, and nine in-person). Each of these groups considered one of three worst-case scenarios provided by the organizers. They then discussed 1) theoretical activities that could lead to this scenario, 2) whether current practices resemble these activities, and 3) ways to improve current practices to prevent the worst-case scenarios.

Scenario 1: Difficulty prioritizing a candidate for Phase 3 evaluation

> “It’s 2034. Several next-gen malaria vaccines have completed their Phase 2 trials and show promising results, but we're stuck in a tricky spot—funders can only sponsor one Phase 3 trial and we do not know which one is truly the best!”

Current practices that contribute to achieving the worst-case scenario:

- "Best" is poorly defined, and may not always include all relevant factors such as cost of goods, accessibility and scalability of adjuvants, manufacturability, durability and deliverability.
- Comparing vaccine candidates in Phase 2 studies is slow, expensive and challenging to ensure comparability.
- Continued investment in new products without clear superior efficacy.
- Lack of cooperation between funding agencies.
- Research is often independent, non-collaborative, with many encountering limited access to methodologies, materials and data, preventing comparability and slowing progress.
- Low political will leads to reductions in available funding.
- Minimal investment in capacity in endemic countries.
- Public discussions about data that lack accuracy and nuance can contribute to vaccine hesitancy, hinder implementation efforts and polarise the community.
- Non-impartial influence over public perception and policy decision-makers.
- Lack of truly independent review of vaccines for global policy decisions.
- Vaccine aims/targets vary in ways that limit comparability (for example, a focus on different use cases or different measures of impact).
- No consensus in vaccine trial design limits comparability (setting, age groups, endpoints).

Proposed improvements to avoid the worst-case scenario:

- Ensure there is consensus on how to measure the full impact of a vaccine—the impact is likely multi-factorial (efficacy, durability, cost and uptake).
- Attempt to model or calculate the total cost of goods and delivery earlier in vaccine development.
- Consider the potential for immune escape when evaluating or estimating vaccine impact, and how combination vaccines could mitigate this.
- Focus on the importance of understanding manufacturability.

- Consider when vaccines can be compared and or licensed based only on immunogenicity endpoints or surrogate markers/assays to reduce time and costs.
- Provide funding for more collaborative projects.
- Prioritize using standardized reference assays to ensure consistency and comparability.
- Remove barriers to access to key reagents and materials.
- Build the business case to encourage more investment.
- Invest in African capacity for clinical trials, regulatory and manufacturing expertise.
- Collaborate and prioritise leading candidates for head-to-head comparisons during Phase 2
- Harmonize clinical trial designs and consider innovative alternatives.
- Agree on safety, immunogenicity and efficacy endpoints, which may differ by lifecycle stage and use case, and prioritize evaluating durability.
- Harmonise on when to use placebo control or standard of care in relevant endemic sites, or consistent comparator (i.e. R21/Matrix-M or RTS,S/AS01).

Scenario 2: A cost-prohibitive, highly effective vaccine completes Phase 3

> "A next-gen malaria vaccine just wrapped up Phase 3 trials. It's highly protective and durable but comes with a price tag that's out of reach for high-burden countries and GAVI support. Cheaper, less effective tools are more cost-effective and preferred by global funders, so the vaccine remains unused!"

Current practices that contribute to achieving the worst-case scenario:

- Cost of goods is not discussed, calculated and optimised early during development.
- Dose and schedule optimisation is not prioritised early in development, which could bring down the eventual costs.
- No guidance or framework for how to consider all factors related to vaccine impact (beyond efficacy), such as deliverability, number of doses, implementation costs etc.
- Many are focusing on novel technologies that are expensive and require complicated delivery logistics or mechanisms.
- Failure to engage early with regulators, funders, end users, and other stakeholders.
- Lack of investment and effort to tackle underlying cost drivers (for example, monopolies on certain technologies, inefficient or expensive manufacturing).
- There is no clear definition or analysis available to the community on the acceptable cost of goods and understanding of how this changes with potential impact (efficacy, durability, deliverability etc.).
- Vaccine affordability for countries not eligible for Gavi support is not considered.
- Affordable, effective adjuvants are not widely available.

Proposed improvements to avoid the worst-case scenario:

- Prioritize determining the optimal vaccine dose, number of doses, and delivery schedule to achieve impact.
- Optimise delivery schedules to integrate with EPI or occur alongside other new vaccines to improve the potential cost-effectiveness.
- Define how to evaluate and compare the costs of goods and delivery, and what is acceptable

to GAVI.
- Consider the cost requirements for countries that are not GAVI-eligible.
- Consider cost implications early in development, for example through modelling, and take action to address them.
- Estimate the cost of goods requirements for different settings, scenarios and age groups, and share findings.
- Improve data sharing and transparency so others can make informed decisions about optimal platforms, technologies, and schedules.
- Engage earlier with all stakeholders, and foster partnerships between academia and manufacturers.
- Collaborate more, especially on multi-stage and multi-species vaccines.
- Invest in optimising and scaling up manufacturing processes while clinical trials are ongoing, not after.
- When using new technologies, think about how the high production or delivery costs will be brought down in future.
- Lobby for Gavi replenishment.
- Encourage funding for early clinical evaluation of different doses, for example, multiple arms with varying doses that are powered for non-inferiority.

Scenario 3: Increasing malaria burden, without a licensed vaccine for all ages

> "Malaria burden is increasing both in new geographic areas and populations with little immunity, and also in older children. Everyone's clamouring for a vaccine that works for all ages, but there's no licensed product to be found!"

Current practices that contribute to achieving the worst-case scenario:

- Malaria elimination as a global health goal is not being prioritised.
- The perceived success of the existing malaria vaccines means funding support for improved malaria vaccines is being reduced.
- Vaccine hesitancy is increasing globally, resulting in less donor and country support for new vaccines.
- Lack of diversity in vaccine development efforts (for example, antigens and stages targeted), including limited support from funders for the more high-risk/high-reward research.
- Limited collaboration and shared learning within the community, which generally slows progress due to everyone working in silos without harmonised endpoints and metrics.
- No consensus on how to evaluate vaccines in all age groups.
- The bar in terms of target product profile (TPP) is set too high and is unreachable, meaning support for potentially impactful vaccines is limited.
- Trials not conducted in endemic areas give results that don't translate to pre-exposed populations, slowing progress.
- Lack of access to suitable adjuvants for research and development.

Proposed improvements to avoid the worst-case scenario:

- Support the goal of malaria elimination within the malaria community, unless strong data emerges to suggest this is not possible.
- Educate the public, for example, through outreach programs.
- Organize an initiative to improve engagement with stakeholders in malaria-endemic countries (a suggestion to follow examples from the tuberculosis field).
- Improve relationships between all stakeholders, and increase participation of malaria-affected groups in development and implementation discussions.
- Investigate where negative perceptions originate, and develop strategies to counter misinformation.
- Improve community coordination, data sharing and visibility through regular meetings and workshops involving all stakeholders, to identify areas where diversity is needed.
- Coordinate funding strategies so donors support diversification without diluting funding.
- Engage product developers earlier, and derisk and incentivise the development of new diverse products (for example, through mechanisms like priority review vouchers).
- Define and agree upon appropriate clinical trial endpoints for various use cases.
- Host regular, collaborative workshops with stakeholders and include local regulatory agencies.
- Fund local clinical trial centres in endemic areas.
- Invest in manufacturing in endemic countries.
- Work more collaboratively and also involve researchers from different fields.
- Share results openly and provide an opportunity for constructive dialogue within the malaria community.

Session 3: Refining Barriers And Challenges For Next-Generation Vaccine Development

In the last session of the day, participants were assigned to new groups (one online, and nine in-person). Two questions were posed to the room, and all groups were asked to discuss the related challenges, barriers and solutions. Throughout the day, participants also identified challenges and barriers in response to a Slido poll. The outputs of the discussions and poll are summarized below.

Round 1: What types of vaccines are we trying to develop and why?

Groups were encouraged to use the following prompts to guide their discussions:

- Is there clarity on the types of vaccines we are trying to make?
- What are vaccine developers doing right now?
- What use cases will have the greatest impact?
- Is there a clear understanding of how impactful different types of improved malaria vaccines would be?
- Should we be developing different vaccines for different use cases?
- Do we understand the tradeoffs between efficacy, durability, coverage and cost-effectiveness, and how these should inform vaccine design and use?

Challenges and Barriers:

1. Scientific and biological complexity

- *Plasmodium falciparum* is a highly complex pathogen with diverse and complex immune evasion strategies.
- Achieving high, durable efficacy may not be biologically feasible without substantial innovation.
- Developing multistage vaccines requires evaluating multiple components with potentially different target populations and endpoints.
- There is a limited understanding of how combination vaccines interact immunologically and the impact of any interference on efficacy.
- Co-administration with other vaccines (for example, via EPI) may lead to immune interference, reducing the efficacy of other vaccines.

2. Transmission dynamics and use cases

- Transmission intensity and seasonality vary by region, influencing optimal vaccine profiles.
- Malaria epidemiology is evolving due to other interventions and climate change, making future vaccine needs uncertain.
- Vaccine use cases differ: disease reduction, transmission interruption, and/or elimination. Each potentially requires different immune responses, endpoints, and delivery strategies.
- TPPs need to be tailored for different goals, but this is complicated as some vaccines may be useful for multiple use cases.
- There is limited focus on non-falciparum species, particularly *P. vivax*, and on underrepresented populations (for example, adults, pregnant women, older children).

3. Measurement, evaluation and trial design

- Lack of clear correlates or surrogate markers of protection.
- Tools like membrane-feeding assays are not yet reliable or widely accepted for regulatory use.
- Lack of standardized, validated assays.
- Difficulty linking CHMI trial results to field efficacy.
- Limited data on immune responses, especially in diverse populations like older children or pregnant women.
- No pre-clinical or clinical trial framework exists for combination, multi-component or multi-stage vaccines.
- Endpoints are unclear, especially for transmission-blocking or elimination-focused vaccines.

4. Data, knowledge gaps and modelling limitations

- There is limited methodology and insufficient data to systematically evaluate trade-offs between vaccine characteristics (for example, efficacy vs. regimen complexity vs. duration). This impedes the ability to make strategic development decisions.
- Modelling multi-stage vaccine impact requires a large parameter space to explore trade-offs, due to multiple parasite stages, schedules, efficacies and duration, and diverse use cases.
- There are gaps in data, making modelling and priority-setting difficult:
    - Age distribution of clinical burden in over 5-year-olds
    - Age distributions of the infectious reservoir
    - Impact of transmission-blocking vaccines
    - Efficacy in pregnant women and older children
    - *P. vivax* burden
    - Immune memory, co-administration, and antigen selection

5. Funding and investment barriers

- Limited, inconsistent funding with unclear criteria for what justifies the investment.
- Funders often change strategies, leadership, and interests rapidly.
- High bar for investment in vaccines (R&D and implementation) due to the cost-effectiveness of other interventions (for example, bed nets, SMC).
- Unviable candidates are sometimes pursued due to poor early cost-effectiveness evaluation.
- Complex or novel vaccines are perceived as too risky and costly.
- There is a lack of clarity on what efficacy or impact improvement over existing vaccines (RTS,S or R21) would justify investment.
- Funders and developers often struggle to weigh trade-offs between efficacy, durability, cost, availability and programmatic feasibility. These trade-offs are further complicated by limited data and modelling capacity, making it challenging to determine which candidates should be prioritized.
- Balancing funding for new product development with scaling existing effective tools remains a major strategic challenge.

6. Regulatory and policy uncertainty

- There is no clear regulatory pathway for multistage, transmission-blocking, or elimination vaccines.
- Existing WHO guidance and TPPs are not detailed enough and are not community-driven.
- Lack of standardized, validated assays that meet regulatory requirements.

- No coordinated roadmap for infection prevention or elimination-focused vaccine development.
- Trial designs for next-generation vaccines remain unclear, particularly regarding the inclusion of standard-of-care comparators or pre-treatment protocols.

7. Implementation and delivery gaps

- It is unclear whether vaccines that require delivery outside of standard immunization schedules (for example, EPI) are viable in existing health systems.
- Reaching adults, older children, and pregnant women remains a challenge.
- Different components of a combination vaccine may require different delivery schedules or age targets.
- Developers lack understanding of how to combine vaccines and other tools (for example, monoclonal antibodies) for maximum impact.
- The risk of genotype replacement post-rollout may affect long-term efficacy.

8. Coordination and transparency issues

- Vaccine development efforts are siloed, with limited visibility into others' work or data.
- Developers are often blind to other interventions or to what is happening in other parts of the ecosystem.
- There is no coordinated evaluation of progress across pipelines, and data are fragmented and not always shared.

Solutions and Opportunities

1. Targeted vaccine development

- Develop a portfolio of vaccines tailored to different use cases, age groups and species.
- Consider multistage and multi-antigen approaches, even with trade-offs, to increase impact.
- Advance vaccines by testing against the standard-of-care in head-to-head trials.

2. Improve data, surveillance and modelling

- Close knowledge gaps with better age-disaggregated data on burden, efficacy, transmission, and immunity.
- Improve surveillance systems to detect real-world impact and vaccine effectiveness.
- Improved modelling approaches are needed to explore trade-offs between vaccine attributes and delivery strategies, enabling more evidence-based prioritization and investment decisions.
- Use modelling and economic projections early to prioritize the most viable candidates.
- Expand CHMI studies to endemic settings and develop larger strain portfolios for testing.

3. Refine endpoints and evaluation methods

- Promote standardized assays and reference labs for comparability.
- Think beyond clinical endpoints—for example, infection or gametocyte carriage.
- Define and validate surrogate markers for field efficacy (eg, TRA, blood-stage density).
- Use membrane-feeding assays as a proxy for field efficacy, supported by community and regulatory engagement.
- Ensure vaccine antigens are conserved across parasite strains, and monitor potential genotype replacement during Phase 2 and 3 trials.
- Support trial designs that directly measure transmission-blocking effects—for example, using cluster-randomized controlled trials with readouts aligned to transmission endpoints.

4. Strengthen regulatory pathways

- Convene working groups to refine TPPs, PPCs, and develop regulatory guidance.
- Encourage community-driven early engagement with regulatory bodies.
- Clarify what data is needed for licensure and WHO policy recommendations.

5. Coordinate funding and investment

- Coordinate funding to support promising candidates through early-phase trials.
- Engage with manufacturers earlier for support from trials to licensure.
- Ensure funding decisions are aligned with use-case impact models, not just efficacy.

6. Improve transparency and collaboration

- Promote open data sharing, particularly from early-phase transmission-blocking vaccine and CHMI studies.
- Create a central pipeline or registry visible to funders and developers.
- Host bi-annual meetings organized around WHO strategic goals (for example, disease burden reduction, elimination, prevention of infection).

7. Focus on implementation feasibility

- Consider delivery strategies for hard-to-reach populations.
- Engage with communities early to understand perception and increase uptake.
- Consider lessons from primaquine and other interventions for delivering transmission-blocking tools.
- Recognize that delivery challenges are as important as biological ones in vaccine success.

Round 2: How are we going to evaluate each vaccine?

Groups were encouraged to use the following prompts to guide their discussions:

- Are there clearly defined pathways for how to evaluate the efficacy of future malaria vaccines?
- How are we going to ensure meaningful comparability between vaccines?
- When does coordination and comparability matter?
- How are we going to evaluate the full benefits of future malaria vaccines (including efficacy, durability, coverage and different mechanisms of action)
- Are there clearly defined requirements for regulatory pathways and policy decisions?
- How will we understand and manage trade-offs between efficacy, durability and different mechanisms of action in later stages of development?
- Is there a need for early community engagement with regulatory processes?

Challenges and Barriers

1. Coordination, harmonization and comparability difficulties

- Vaccine trials use different protocols, endpoints, and assays, limiting comparability.
- Even with strictly standardised assays, inherent variations across sites limit assay comparability.
- Coordination across countries and institutions is disjointed; regulatory processes differ significantly.

- Developers are often reluctant to engage in head-to-head comparisons due to the fear of downselection.
- No common framework exists for clinical trial design, endpoint definitions, or evaluation criteria across vaccine types or lifecycle stages.
- Epidemiological variation—even with protocol harmonization—limits cross-site comparison.
- Biorepositories and shared data (for example, serum samples) are underutilized due to access constraints.
- Coordination is mostly done by funders, limiting the broader alignment across the community.

2. Evaluation challenges

- We lack standardized, agreed-upon clinical endpoints and surrogate markers for various vaccine types.
- Different vaccines require different endpoints based on stage (for example, pre-erythrocytic, blood-stage, transmission-blocking), but there is no consensus on how to prioritize these.
- There is a limited understanding of how to evaluate immune interference, durability, and biophysical characteristics (for example, thermostability).
- The introduction of RTS,S/AS01 and R21/Matrix-M complicates the evaluation of new candidates as placebo-controlled trials may no longer be ethical.
- There are no validated biomarkers or correlates of protection; only one site (Seattle) has FDA validated infection endpoint via polymerase chain reaction (PCR).
- The FDA does not currently support infection-based endpoints as sufficient for licensure; clinical disease endpoints are required.
- A lack of best practices or precedents for biomarker qualification for regulatory approval.
- Vaccine delivery (regimen complexity, logistics, uptake) is not systematically incorporated into evaluation frameworks.
- There is no unified strategy for assessing broader benefits such as long-term protection, all-cause mortality, school attendance, or economic impact.
- CHMI data are not always predictive of field efficacy.
- We lack clinical endpoints tied to contextual factors such as prior exposure and existing interventions, which may influence how efficacy should be interpreted.
- We do not understand how to fully evaluate all components of a vaccine that will influence its efficacy (efficacy, durability, deliverability, cost, uptake, etc.) and how to manage trade-offs between different elements.

3. Regulatory, policy and operational complexity

- Regulatory and policy pathways are unclear, and guidance is lacking.
- There is a lack of early and consistent engagement with regulators (both national and WHO).
- Unnecessary/ill-informed regulatory requirements can substantially increase the time and cost of vaccine development, even prohibitively.
- Absence of shared documentation or public guidance on regulatory expectations (for example, for adjuvants or assay validation).
- Institutional legal barriers impede data and sample sharing.
- Trial capacity in Africa is limited; this slows evaluation and restricts where trials can be run.

Solutions and Opportunities

1. Standardization and harmonization

- Create standardized clinical trial design frameworks (Phase 1–3) with clearly defined endpoints for efficacy and durability by vaccine type.
- Develop shared protocols and common parameters (for example, parasitemia thresholds and duration metrics) to improve comparability.
- Promote harmonization of assays and validate them collectively to enable cross-study learning.
- Store and evaluate serum samples using centralized assays for comparability.
- Adopt non-inferiority trials using either RTS,S/AS01 or R21/Matrix-M as standard-of-care comparators.

2. Stronger collaboration and coordination

- Hold working groups and technical consultations across stakeholders to refine trial protocols, endpoint definitions, and evaluation approaches.
- Create more open communication channels and share early trial data and learnings—including failures—to prevent duplication and accelerate learning.
- Support coordination between African clinical trial sites with the capacity to evaluate vaccines and share lessons.
- Encourage safe spaces for open discussions about challenges.

3. Clear regulatory pathways and engagement

- Engage regulators (national, EMA, WHO) early and often to clarify expectations and co-design trials.
- Support the African Medicines Agency (AMA) as a regulatory convenor with alignment from WHO and national agencies.
- Advocate for public release of regulatory feedback and guidance (for example, acceptable endpoints, adjuvant use).
- Support validation studies to address FDA concerns and promote broader acceptance of novel endpoints.
- Develop guidance for data needed for regulatory approval and policy recommendation, similar to what exists for vector control tools.

4. Improve evaluation methods and metrics

- Develop a framework for evaluating the full impact of a vaccine considering all elements (efficacy, durability, deliverability, cost, etc.) and how to manage trade-offs.
- Invest in the identification and qualification of biomarkers for protection, durability, and transmission impact.
- Use CHMI models strategically (with an understanding of their limits) and explore new challenge models incorporating durability.
- Evaluate broader outcomes (for example, school attendance and productivity) and build frameworks to measure them.

5. Build capacity and infrastructure

- Strengthen local trial capacity, lab infrastructure, and manufacturing in Africa to reduce dependence on external actors.
- Invest in training for African regulators and trial designers to increase local ownership and speed.
- Increase investment in real-world data collection to complement trial data.

- Strengthen surveillance systems to better track vaccine impact post-implementation.
- Ensure capacity built for malaria vaccines can be leveraged for other pathogens.

Summary

The organizers expressed that they had been impressed and inspired by the discussions throughout the day and had found it valuable to hear different perspectives and opinions. Some key takeaways included the probable need for multiple vaccines for different use cases, and the need to think more about how we manage trade-offs with factors such as vaccine efficacy, durability, deliverability and cost. Participants identified a long and varied list of challenges and product-agnostic solutions. Many of these centred on the need for better coordination and integration on key topics, such as clinical trial designs and endpoints, regulatory pathways, and public health advocacy. It was anticipated that the outputs of the meeting would be helpful for informing planning and decision-making among funders and developers, and in increasing coordination going forward.

Attendee Feedback

Feedback was solicited from meeting attendees after the event, with 27 responses collected. The takeaways were broadly positive, as summarized below:

- **78% (21/27) said some form of structure, such as a Malaria Vaccine Alliance or Task Force, is needed** to help address the key challenges (such as the need for guidance on clinical trial design for improved comparability) to accelerate the development of impactful next-generation malaria vaccines.
- When asked what activities/challenges a Malaria Vaccine Alliance or Task Force should address or prioritise, 16/27 respondents highlighted the need to **develop better guidance for development pathways and clinical trial designs**, with a focus on comparability and inputs from African regulators. More suggestions can be found in Appendix 2.
- **70% (19/27) thought an annual meeting for data presentation would be beneficial** for community coordination, while **93% (25/27) said an annual meeting for continued discussions on barriers and solutions would be beneficial** for community coordination.
- Participants generally found the event useful: **82%** (22/27) thought the meeting was effective at facilitating meaningful dialogue between stakeholders, **82%** (22/27) thought the meeting effectively identified key challenges and opportunities in next-generation malaria vaccine development, and **85%** (23/27) thought the group discussions were a valuable format for engaging with all participants.
- Participants also emphasized the need for **greater transparency for the community into funders' strategies and plans**, as well as for improved coordination between funders. While improved transparency and coordination were identified as a priority, perspectives on how to achieve this were varied, with no clear consensus.

Appendix 1: List Of Participants

Chairs

Simon Draper	Melissa Penny	Jean-Philippe Julien

Organiser

Katharine Collins

Participants

Evelyn Anash	Michael Good	Sean Murphy
Marion Avril	Brian Greenwood	Irene Nkumama
Phillip Bejon	Jean Marie Habarugira	Lucy Okell
Caitlin Bever	Mary Hamel	Rafiq Okine
Ashley Birkett	Sara Healy	Ally Olotu
Montserrat Blazquez-Domingo	Adrian Hill	Jordan Plieskatt
Aurelio Bonavia	Steve Hoffman	Tom Richie
Teun Bousema	Azza Idris	Meta Roestenberg
Hannah Boycott	Matthijs Jore	Thierry Rolling
John Bradley	Holger Kanzler	Issaka Sagara
Joe Challenger	Stefan Kappe	Lorraine Soisson
Thomas Churcher	Melissa Kapulu	Danielle Stanisic
Nicolas Collin	Jacqueline Kirchner	Tara Tagmyer
Peter Crompton	Jim Kublin	Joshua Tan
Mehreen Datoo	Mirium Laufer	Florence Theberge
James Davie	Carole Long	Halidou Tinto
Alassane Dicko	Robin Miller	Alfred Tiono
Denise Doolan	Angela Minassian	Marcelle Van Mechelen
Chris Drakeley	Kazutoyo Miura	Ashley Vaughan
Patrice Dubois	Annie Mo	Hedda Wardemann
Patrick Duffy	Benjamin Mordemuller	Brandon Wilder
Katie Ewer	Jo Mulligan	Lindsey Wu
Jaline Gerardin		

Notetakers

Lydia Braunack-Mayer	Danton Ivanochko	Thiery Masserey
Daniella Figueroa-Downing	Annemieke Jansen	Tolu Okitika
Sophia Hailemariam	Hee Ryung Kim	Natasha Stretton
Julian Heng	Aisling Leow	Randy Yoo

Appendix 2: Activities/Challenges That A Malaria Vaccine Alliance/Task Force Should Address and Prioritise

The table below contains a summary of suggestions from the 27 responses to the post-event feedback survey.

Activity	Count
Act as an advisory board to coordinate multi-institution trials	1
Assist candidates after Phase 1 to improve efficiency	1
Clearly prioritize between strategic goals and research questions	2
Connecting partners for "head-to-head" studies, and "combo/multi-stage" studies	2
Coordinate support for shared resources, for example, CHMI	2
Create task forces for each goal	1
Develop better guidance for pathways and trials, with a focus on comparability and inputs from African regulators	16
Establish networks, for example, similar to the HIV Vaccine Trials Network (HVTN) or Collaboration for Aids Vaccine Discovery (CAVD), and between preclinical/translational researchers and regulatory agencies	3
Facilitate access to different vaccine platforms and adjuvants	2
Focus more attention on climate change	1
Give an indication of the price for next-generation vaccines	1
Incentivize and facilitate the sharing of data and learnings to speed progress, for example, via a prize grant	4
Incentivize innovation	2
Inform and advocate for more regulatory harmonization in endemic countries	1
Provide clarity on other vaccines that could be combined with malaria to add value and ease crowding in EPI schedule	1
Provide guidance for the development of benchmarks and go/no-go criteria	1
Reduce duplication of work	2
Review and discuss evidence generated in trials and post-deployment surveillance, and recommend a way forward	1
Review progress toward WHO strategic goals	1
Standardize assays	2
Support reference center(s) in Africa to evaluate vaccine candidates	1