Report of an Expert Consultation on the Clinical Development Plan for a Multistage Malaria Vaccine Targeting the Circumsporozoite (CS) and Blood Stage (BS) Antigens

May 3 to 4, 2023
A hybrid meeting at PATH Washington, DC
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Contents

ABBREVIATIONS ........................................................................................................................................ II

INTRODUCTION ........................................................................................................................................... 1
  Technical rationale ................................................................................................................................. 1
  Historical perspectives .......................................................................................................................... 2

OBJECTIVE OF THE CONSULTATION ...................................................................................................... 4

MEETING SUMMARY .................................................................................................................................. 5
  The current state of CS- and BS-based vaccines and CHMI models .................................................... 5
  Limitations of current preclinical models for application to combination CS+BS vaccines ............... 6
  Potential for and limitations of CHMI in malaria-naïve and malaria-endemic populations ............... 7
  Status of efforts for multistage malaria interventions ........................................................................ 7
  Clinical development pathway discussion ............................................................................................ 8

KEY RECOMMENDATIONS ...................................................................................................................... 12
  Clinical development plan for CS and BS antigens with clinical experience ........................................ 12
  Clinical development plan for CS and BS antigens without clinical experience ................................. 13
  Proposed clinical development plan after initial adult study(ies) .......................................................... 13
  Clinical testing first in malaria-naïve or malaria-exposed African populations versus malaria-naïve US-based or European populations and related regulatory requirements ........................................ 14
  Requirements for advancement from Phase 2b to Phase 3 ................................................................ 14
  Cost of goods and co-formulation considerations .............................................................................. 14
  Summary of key recommendations .................................................................................................... 15

CONCLUSIONS AND NEXT STEPS ......................................................................................................... 17

REFERENCES ............................................................................................................................................ 18

APPENDIX 1. CONSULTATION AGENDA ............................................................................................... 20

APPENDIX 2. CONSULTATION ATTENDEES ......................................................................................... 21
  Names and affiliations of experts ......................................................................................................... 21
  Names and affiliations of participants ................................................................................................... 21

APPENDIX 3. CONSULTATION PRE-READ DOCUMENTS .................................................................... 23
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad</td>
<td>adenovirus</td>
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<tr>
<td>AMA1</td>
<td>apical membrane antigen 1</td>
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<tr>
<td>AR</td>
<td>attack rate</td>
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<td>BS</td>
<td>blood stage</td>
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<td>CHMI</td>
<td>controlled human malaria infection</td>
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<td>CS/CSP</td>
<td>circumsporozoite protein</td>
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<tr>
<td>GIA</td>
<td>growth inhibition assay</td>
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<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
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<td>IMV</td>
<td>Innovations in Malaria Vaccine Development</td>
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<td>KEMRI</td>
<td>Kenya Medical Research Center</td>
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<tr>
<td>MSP1</td>
<td>merozoite surface protein 1</td>
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<tr>
<td>P. falciparum/Pf</td>
<td><em>Plasmodium falciparum</em></td>
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<tr>
<td>PMR</td>
<td>parasite multiplication rate</td>
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<tr>
<td>PPC</td>
<td>preferred product characteristic</td>
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<td>P. vivax</td>
<td><em>Plasmodium vivax</em></td>
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<td>SPZ</td>
<td>sporozoite</td>
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<tr>
<td>USAID</td>
<td>US Agency for International Development</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Introduction

In 2021, nearly 500,000 young African children died from malaria and tens of millions more experienced significant morbidity. These numbers highlight the urgent need for new interventions to reverse this unacceptable burden of disease. Two malaria vaccines (RTS,S/AS01 and R21/Matrix-M) are now prequalified and recommended by the World Health Organization (WHO) for use in African children living in malaria-endemic areas. Both vaccines are being introduced in African countries starting this year. While these two vaccines are safe and efficacious, there remains a need for additional malaria vaccines that are more efficacious, durable, and cost-effective, and that require fewer doses.

In 2022, WHO updated their preferred product characteristics (PPCs) to serve as key tools in guiding the development of next-generation malaria vaccines. One of the WHO’s strategic goals is the development and introduction of “malaria vaccines that reduce morbidity and mortality in individuals at risk in malaria-endemic areas.” Driven by the PPCs, PATH is researching a range of malaria vaccine approaches that focus on different stages of the Plasmodium parasite’s complex lifecycle. Part of this portfolio is funded by the US Agency for International Development (USAID) Malaria Vaccine Development Program* under the Innovations in Malaria Vaccine Development (IMV) contract. The goal of the USAID IMV contract is to develop a next-generation Plasmodium falciparum (P. falciparum) malaria vaccine that prevents clinical malaria in young African children and is superior to RTS,S and R21 from a public health impact perspective, based on standard measures of cost-effectiveness.

One promising approach for next-generation malaria vaccines is the development of multistage vaccines targeting the pre-erythrocytic and asexual blood stages of the parasite’s lifecycle. While circumsporozoite protein (CS or CSP) and blood stage (BS) vaccine approaches are generally being advanced independently, the potential for additive and/or synergistic efficacy when CS and BS vaccine candidates are combined is both compelling and firmly aligned with the IMV goal. For this reason, USAID and PATH convened a panel of experts in malaria, vaccine development, regulatory affairs, and the conduct of clinical trials in Africa, Europe, and the United States to consider and inform the development of a comprehensive clinical development plan for a multistage (CS+BS) malaria vaccine.

Technical rationale

The central hypothesis for this vaccine approach is that a combination CS+BS vaccine will provide additive and/or synergistic efficacy by targeting two sequential parasite lifecycle stages, thereby reducing the potential for progression to clinical disease in individuals not completely protected by the anti-infection (CS) component. Both RTS,S and R21 are CS-based vaccines. Individuals not protected by partially efficacious CS-based vaccines following controlled human malaria infection (CHMI) frequently exhibit significant delays in progression to patent parasitemia. This reduction in the number of merozoites emerging from the liver (as the result of reduced liver stage infection due to CS immunity) is expected to lower the force of infection of the first cycle of asexual BS parasite growth. Therefore, a BS vaccine might help improve the efficacy of a partially efficacious CS vaccine by providing a “safety net” in the event of incomplete neutralization of sporozoites (SPZs), and/or clearance in the liver, and benefit itself from a relatively lower initial force of infection contributed by CS immunity. Further, induction of BS immunity

*The goal of the USAID Malaria Vaccine Development Program is to develop efficacious, durable, and cost-effective malaria vaccines aimed at mitigating morbidity and mortality due to Plasmodium falciparum malaria for implementation as components of malaria control efforts in malaria-endemic regions of the world.
could be important within the context of waning natural exposure, due to reduced levels of local transmission and/or reduced infection including due to CS vaccination, by helping to substitute for lower levels of naturally acquired BS immunity that is known to protect from clinical disease.

Ongoing early clinical evaluation of both CS and BS vaccine candidates involves distinct, well-established CHMI models using SPZ or BS challenge, respectively. To date, SPZ CHMI using mosquito delivery, routinely used in Europe and the United States, has not proven feasible for implementation in Africa. A main reason for this is lack of access to insectaries for housing infected mosquitoes. Alternatively, the use of purified and cryopreserved SPZs for CHMI in Africa, which bypasses the need for such insectaries, has been proven feasible, including via a study at the KEMRI-Wellcome Trust Research Programme of 161 Kenyan adults within the context of better understanding naturally acquired immunity. In addition to the traditional assessment of CS vaccines via SPZ challenge by bites from infected mosquitoes, a study comparing the direct venous versus intradermal inoculation of cryopreserved SPZs in African volunteers, previously immunized with R21, is currently underway in Kenyan adults. Preliminary findings from this study demonstrate the potential for using this CHMI model to assess the efficacy of CS-based vaccines functioning primarily via circulating antibodies. An SPZ CHMI model suitable for use in Africans could be a valuable tool for consideration of a CS+BS vaccine clinical development plan, so the progress of this study should be closely monitored.

**Historical perspectives**

The concept of multistage vaccines, particularly a CS+BS combination vaccine to prevent clinical malaria, is not novel. Various approaches, including protein-adjuvant, vectored, and heterologous prime/boost, have been evaluated preclinically and clinically, including for CSP and apical membrane antigen 1 (AMA1) or merozoite surface protein 1 (MSP1) combinations. Clinical evaluation of early CS+BS combinations failed to yield additivity or synergy based on CHMI using infectious mosquito bites. It has since been determined that the BS components in early combinations were associated with relatively low functional immunogenicity and significant allelic diversity. Further, the development of the BS CHMI for vaccine testing at the University of Oxford has enabled early clinical “de-risking” of BS approaches prior to advancing to pediatric studies in young African children and/or studies of CS+BS combinations. There are plans to utilize BS CHMI in adult African populations as well.

Advancements over the past decade have clearly demonstrated that the RH5 antigen has distinct advantages over prior BS antigens; specifically, it is highly conserved across diverse strains and is associated with more functionally potent antibody responses. Indeed, RH5 is the first BS antigen to demonstrate a measurable reduction in parasite multiplication rate (PMR; i.e., biological activity) in human volunteers. Available data from Phase 1a/b trials suggest it is highly immunogenic for antibodies in African and European adults, and even more immunogenic in 5- to 17-month-old African children (submitted). These data have elevated interest in considering RH5 for evaluation in combination with RTS,S and R21, as well as potentially with earlier stage, next-generation CS-based vaccine candidates. An R21+RH5/Matrix-M combination vaccine candidate is currently undergoing initial clinical testing in a small study in young African children (NCT05357560).

Further, efforts to evaluate novel vaccine approaches, such as mRNA, may also benefit from a CS+BS vaccine clinical development plan. BioNTech initiated a Phase 1 safety, tolerability, and immunogenicity study of an mRNA candidate vaccine expressing part of PfCSP (BNT165b1) in US volunteers in December 2022. Three dosage levels, delivered in a three-dose schedule, are being evaluated. The primary endpoint completion target date is March 2024, and the study completion target date is
September 2024 (NCT05581641). In the apparent absence of a CHMI phase, additional studies will be needed to determine initial protective efficacy, and, perhaps more importantly, durability of protection.
Objective of the consultation

The objective of this expert consultation was to critically and constructively review several possible clinical pathways for the development of a combination CS+BS multistage malaria vaccine, discuss pros and cons of each, and identify a preferred pathway(s) for consideration by all malaria vaccine stakeholders.

The desired outcome of the meeting was a set of key recommendations to inform the development of a comprehensive clinical development plan for a CS+BS combination \textit{P. falciparum} malaria vaccine for young African children in alignment with strategic goal 2 of the 2022 WHO PPC document.\textsuperscript{2} This report summarizes the expert discussions held during the consultation and includes the preferred options for an early clinical development plan (through Phase 2), supported by a comprehensive list of opportunities and challenges associated with each.

In order to focus the discussion during the consultation, the group of experts agreed to certain topic areas that should be considered “out of scope.” As a result, the following topics were not covered during the meeting’s discussions:

- Specific vaccine constructs, antigens, and/or platforms.
- Sample size calculations and budget projections beyond “macro considerations.”
- Vaccine approaches not aligned with WHO PPC strategic goal 2 of “malaria vaccines that reduce morbidity and mortality in individuals at risk in malaria-endemic areas.”
- Vaccines primarily intended for use in adult populations and/or non-endemic populations.
- Cost for the purposes of pathway prioritization.
Meeting summary

The expert consultation was held in a hybrid format (virtual and in-person) on May 3 to 4, 2023, at PATH’s Washington, DC office (see Appendix 1 for the full agenda). Matt Laurens, MD, moderated the meeting, which was attended by 7 experts and 31 stakeholder participants from academia, industry, public health agencies, funding bodies, and regulatory authorities (see Appendix 2 for list of participants and Appendix 3 for list of pre-read documents). The experts were the main discussants at the meeting and developed the recommendations outlined in this report. The other participants served as resources to the experts and were engaged in the meeting discussions as needed.

The current state of CS- and BS-based vaccines and CHMI models

Chris Ockenhouse, MD, presented a review of the state of the art of CS-based vaccines and candidates. This included vaccine candidates using platforms such as virus-like particle, soluble recombinant proteins/conjugates/synthetic peptides, viral/bacterial vector, nucleic acid (DNA/mRNA), and prime-boost strategies. Key malaria vaccine data and considerations for advancement in clinical development were highlighted, including timelines and important data from RTS,S and R21. The experts also discussed potential biomarkers of an effective anti-CS immune response. The discussion concluded with an overview of opportunities and risks for next-generation CS-based vaccines.

Meta Roestenberg, MD, summarized a discussion of current SPZ challenge models in malaria-naïve adults, including mosquito bite administration and intravenous inoculation of \( P. falciparum \) SPZs, routinely the NF54 strain or its clone, 3D7. In addition, heterologous \( P. falciparum \) strain challenge and \( Plasmodium vivax \) (\( P. vivax \)) models were reviewed, as was the predictability of CHMI models for assessing the performance of RTS,S and other candidate malaria vaccines in malaria-endemic areas. CHMI is viewed as a means to move the risk of failed clinical efficacy in studies in malaria-endemic areas further along in the clinical development pathway to maximize resources, which is especially useful where markers of protection are nonexistent. Advances in scientific knowledge of vaccine mechanism and immune correlates are also valuable benefits of CHMI. Finally, it was noted that inclusion of CHMI as a critical pathway activity for malaria vaccine development depends on a multitude of factors, including the availability of vaccine-specific correlates of protection, projected risks, and development timelines/costs.

Melissa Kapulu, DPhil, presented the topic of SPZ challenge models in malaria-experienced adults using injectable SPZs thawed from their cryopreserved state. She reviewed \( P. falciparum \) CHMI studies either conducted or ongoing in six countries in sub-Saharan Africa: Equatorial Guinea, Gabon, The Gambia, Kenya, Mali, and Tanzania. These studies have helped to illuminate naturally acquired antimalarial immunity for vaccine antigen discovery, accelerate vaccine development, and test vaccine efficacy. An ongoing study of \( P. vivax \) CHMI in Thailand is being used to identify candidate vaccine antigens. Persons with previous \( P. falciparum \) exposure who undergo CHMI can be studied using different endpoints for treatment compared to non-immunes, including a higher-threshold parasitemia. Samples collected for immunology testing in this controlled setting can provide significant insight into antibody and effector functions, including putative correlates of protection/immunity. Participating scientists from malaria-endemic and non-endemic countries alike applauded this work and enthusiastically recommended the continuation of CHMI in malaria-experienced adults due to the knowledge gained, known safety of the approach, and community support for malaria research.
Angela Minassian, MBBS, presented an overview of BS CHMI in malaria-naïve adults. Following this method, relatively small numbers of parasitized red blood cells are intravenously infused in challenged individuals. To measure biological activity of antibodies induced by a BS vaccine candidate, BS CHMI measures parasitemia post-injection to derive a PMR. This PMR, when compared in vaccinees versus controls, provides an indication of the potential for induced antibodies to slow, or ideally abort, growth of asexual stage parasites in the blood. The ability to control a BS infection may translate to clinical benefit via a decreased risk for complicated malaria and severe outcomes following natural exposure. BS CHMI studies using the standard Pf3D7 clone parasites from a malaria-infected blood type O Rh(d)-negative donor have been successfully conducted in malaria-naïve and malaria-experienced adults in Mali and Tanzania. Similar BS CHMI strains of P. falciparum, P. vivax, and P. malariae have also been developed.

Finally, Simon Draper, DPhil, presented an update on the state of the art of BS vaccine candidates, which target proteins found in the blood stages of the parasite to prevent red blood cell invasion. The value of BS CHMI was first demonstrated using an AMA1 vaccine candidate that failed to demonstrate significant efficacy in a Phase 2 pediatric study in Mali; it similarly failed to slow PMR following homologous CHMI in adults in the United Kingdom. RH5 is a highly promising BS candidate antigen, with data supporting use of threshold growth inhibition assay (GIA) results in Aotus monkeys and humans as a correlate of protection against cumulative and peak parasitemia in BS CHMI, increased potency of vaccine-induced anti-RH5 immunoglobulin G compared to historical BS targets, and significantly reduced PMR in RH5-vaccinated adults after BS CHMI. To date (studies are ongoing), antibody responses in 5- to 17-month-old African infants have been significantly higher than in malaria-naïve adults and have exceeded the GIA target threshold. The BS candidate antigen P. vivax Duffy binding protein adjuvanted with Matrix-M recently demonstrated reduction in PMR after BS CHMI and is advancing in clinical trials.

Limitations of current preclinical models for application to combination CS+BS vaccines

It was acknowledged that preclinical models that support testing of combination CS+BS vaccine candidates are not readily available. However, the experts reviewed the positive contribution of the Aotus monkey model to BS vaccine development. Briefly, a study of PIRH5-based vaccine candidates with heterologous BS challenge was conducted to compare an RH5 protein-in-adjuvant vaccine to a viral-vectored RH5 vaccine and to controls. The Aotus model with BS challenge demonstrated efficacy of both vaccine products against cumulative and peak parasitemia, with superior efficacy of the RH5 protein-adjuvant vaccine. In addition, GIA testing in protected animals demonstrated a threshold effect such that animals with 60% GIA using 2.5 mg/mL purified total immunoglobulin G correlated with protection against BS challenge. Similarly, testing of an MSP1-based vaccine in the Aotus model showed that a threshold anti-MSP1 antibody titer and the same threshold of GIA activity correlated with protection against BS challenge. A study of an AMA1-based vaccine in Aotus monkeys found a threshold GIA that would have predicted no impact on PMR in malaria-naïve humans. In summary, the Aotus model may be able to predict BS challenge outcome in malaria-naïve adults. This could offer efficiency in clinical development of BS vaccines or vaccine components.
Potential for and limitations of CHMI in malaria-naïve and malaria-endemic populations

CHMI is highly advantageous, as it provides a portfolio of different tools that each provide utility for scientific advancement. Within the context of vaccine development, CHMI can help identify candidates early in development that are unlikely to succeed in studies in malaria-endemic areas. If a candidate vaccine shows promise in CHMI, the antigen, adjuvant, and/or dose can be further optimized toward maximizing the protective effects in large studies in malaria-endemic areas. In addition, CHMI facilitates investigation into mechanisms/correlates of vaccine-induced immunity, which can subsequently be prioritized for testing in malaria-endemic areas. This is particularly important for pediatric studies, in which sample volumes are severely limited. Development risks, timelines, and costs must be taken into consideration when determining if and how CHMI will be used for a candidate vaccine.

When specifically deciding on BS versus SPZ CHMI for testing BS vaccine candidate efficacy, the amplifying role of the liver stage contributes an important “force of infection” consideration. A single infected hepatocyte releases approximately 30,000 merozoites into the blood, and the current BS CHMI delivers only a few hundred infected red cells; therefore, while BS CHMI can reveal biological activity against asexual parasites, it is not yet able to predict clinical benefit in the target population following natural exposure. Further, in considering CS+BS vaccine combinations, by limiting progression to BS merozoites, a partially efficacious CS vaccine component could impair the ability of a BS vaccine to demonstrate efficacy against CHMI. While a relatively large effect size of an efficacious BS vaccine should be shown by both models, the combined effect of a CS+BS vaccine would likely be best demonstrated by an SPZ CHMI. However, measuring other specific efficacy endpoints, including the BS component’s effect on gametocytemia, may require BS CHMI.

In terms of the role of CHMI in vaccine product development, adults who undergo CHMI may not accurately mimic the target population for malaria vaccines. For instance, the pediatric population achieves a higher level of anti-RH5 antibody than adults in response to vaccination, and adult CHMI could underestimate vaccine efficacy in the pediatric population. However, CHMI can help to demonstrate a functional biological effect generated by a candidate vaccine, supporting further clinical evaluation in an endemic setting.

Overall, CHMI can provide a significant advantage by giving an early signal if a vaccine could be clinically efficacious and testing heterologous protection. For BS CHMI in particular, while PMR typically has been used as a primary outcome, vaccine candidates with improved efficacy might benefit from a different efficacy endpoint, including area-under-the-curve parasitemia, time to diagnosis, or even sterile protection. Finally, CHMI in malaria-experienced adults would facilitate vaccine testing in those with a background of naturally acquired immune responses and would reflect the reality that next-generation malaria vaccines are prioritized for areas where individuals are seasonally and/or perennially exposed to malaria.

Status of efforts for multistage malaria interventions

There are ongoing, concerted efforts by vaccine developers and funding institutions to advance multistage vaccines. This is aligned with the goal of USAID’s Malaria Vaccine Development Program for CS+BS vaccine development. The Bill & Melinda Gates Foundation previously convened a meeting of multiple stakeholders, including some USAID IMV partners, to inform their investment strategy for next-generation medical interventions (i.e., long-acting injectable malaria prevention, vaccines for elimination).
As portions of this earlier convening aligned with the objectives of this expert consultation, Jean-Luc Bodmer, PhD, presented highlights from the Gates Foundation meeting, held March 13 to 14, 2023, in London, United Kingdom, which are summarized below.

The foundation’s three strategies defining a pathway to malaria eradication by 2040 are to drive down burden using short-acting interventions, shorten the endgame with long-acting interventions, and get ahead of resistance by supporting a pipeline of alternative interventions. They are accelerating both next-generation malaria vaccines and monoclonal antibodies that achieve proof of principle and are optimized using the CHMI model. These and other malaria elimination tools can be combined to augment effect, similar to studies of seasonal malaria chemoprevention administered alongside RTS,S. A multistage, effective elimination vaccine with at least two years of durability could provide cost-benefit efficiency to malaria elimination efforts, recognizing the need for broader deployment strategies for an elimination use case.

The current research and development landscape for next-generation malaria vaccines targets children and adults, but with a low probability of technical and regulatory success. A malaria vaccine that protects for at least two years in all age groups could fill an important gap for long-term prophylaxis needed to ensure malaria elimination success. Other use cases for a next-generation vaccine include in infants 0 to 6 months of age to maximize pregnancy and birth outcomes, in children 6 months to 18 years to minimize burden, and in adults to reduce the parasite reservoir. Important characteristics of a next-generation malaria vaccine include a product that combines no more than two active components, targets all at-risk populations in endemic areas, prevents at least 80% of infection, has a favorable risk/benefit profile, can be administered using three or fewer doses, and can be safely administered with antimalarial drugs or other interventions. Improvements in level and duration of protection could be achieved by decreasing the rate of antibody decay and/or increasing antibody potency. A multistage malaria vaccine development plan could employ novel platforms (mRNA, nanoparticles, adjuvants, etc.), preclinical models that are reverse engineered from current clinical tools, and CHMI, with the caveat that such combinations may cloud efficacy data, depending on the endpoint.

The USAID IMV strategy complements several overall outcomes of the Gates Foundation convening, including the strategies to identify a novel vaccine target to complement CS-based antigen vaccines with priority for an anti-merozoite component; however, the IMV focus is on prevention of disease in young African children and does not include deployment in adult populations.

**Clinical development pathway discussion**

Three potential high-level clinical development pathways (Phases 1 through 3) for a combined CS+BS *P. falciparum* vaccine candidate were presented to facilitate discussion among the experts, as shown in Figures 1 through 3 below. The arrows indicate go/no-go criteria for advancement.
Figure 1. Proposed development pathway 1: Initial proof of concept in the target population.

Abbreviations: BS, blood stage; CHMI, controlled human malaria infection; CS, circumsporozoite protein; SPZ, sporozoite; US, United States.

Figure 2. Proposed development pathway 2: Initial proof of concept in the controlled human malaria infection model.

Abbreviations: BS, blood stage; CHMI, controlled human malaria infection; CS, circumsporozoite protein; SPZ, sporozoite; US, United States.
The experts were asked to consider the three proposed development pathways and to prioritize one (or propose an alternative) that represents the best pathway going forward, as well as provide a comprehensive list of advantages and disadvantages of the selected pathway in a ranked order. They were also encouraged to flesh out opportunities, challenges, and potential solutions for a given clinical pathway. Assumptions made for planning were reviewed, including that the CS+BS vaccine would be superior to RTS,S and R21, and that mosquito-based SPZ CHMI studies would not be available in Africa in the near future. The experts also discussed some challenges, including an unclear regulatory pathway for product use in school-age and adult populations. They reviewed potential solutions and opportunities to assess immune interference, including use of preclinical tools such as transgenic parasite mouse challenge models and GIA testing in preclinical and clinical studies. Such strategies were viewed as important considerations for informing and de-risking a pivotal Phase 3 efficacy study.

In terms of regulatory considerations, a new paradigm was introduced—evaluation of new medicinal products by the African Medicines Agency, especially vaccines considered priority for the continent when planning for approvals, including marketing authorization. The experts also considered an accelerated approval pathway that could expedite the time to initial approval, though a novel concept for a malaria vaccine would require significant thought and planning, may be worth considering if it would reduce the time required to advance to a critical Phase 3 efficacy study.

Additionally, the experts discussed multiple components of a successful clinical development plan. Target product profile elements that influence the clinical development pathway, including target population and durability of protection, will guide strategy. Clinical studies in adults, including CHMI, that generate evidence to support advancing to testing in children were also seen as critical. This includes considerations for whether to conduct such adult studies in Africa or in Europe/the United States, and which level of type I and type II would be acceptable for these adult CHMI studies. However, some experts suggested that CHMI studies could only provide a broad signal and not a precise estimate of efficacy due to the limited population studied using CHMI models. In addition, studies in children living in malaria-endemic areas may provide different immunogenicity results when compared to adults (as has been seen with RTS,S, R21, and RH5, for example). Others suggested setting a relatively low bar for
success for CHMI studies of CS and BS components tested separately, to avoid the potential for type II errors.

Discussion to constructively evaluate the three proposed clinical development pathways followed, and the experts felt it likely that a further improved plan could be generated. Important aspects of the development pathway highlighted by the group include immunogenicity studies, which in the absence of a defined correlate of protection are needed to assess for possible interference of the CS and/or BS component, such as functional antibody titers. Preclinical models in rodents and rabbits could also inform the question of non-interference. Generating the clinical development plan in a stepwise manner starting with the very first Phase 1 studies could also help guide the planning of subsequent studies, including Phase 2 clinical trials.

The experts considered the example of RTS,S combined with adenovirus 35 encoding CS (Ad35), a CS-based vaccine candidate, where superiority (defined as 80% power to demonstrate a 50% increase in efficacy) using CHMI was not met during an interim analysis. Futility criteria were established such that vaccination of cohorts B and C could only proceed if the calculated point estimate of increased vaccine efficacy in the Ad35/RTS,S group over the RTS,S alone group was more than 0%, providing a 4% risk of stopping the trial if the true increase in vaccine efficacy is 50%, assuming an attack rate (AR) of 50% in the RTS,S alone group. The increase in vaccine efficacy of the Ad35/RTS,S group over the RTS,S alone group was defined as 100*(1-AR Ad35 / AR RTS,S). Given that such a positive outcome was unlikely, the experts were doubtful that such a study and approach would be repeated in the future. Potential outcomes of CHMI after a combined R21 or RTS,S and BS vaccine were debated, including whether a compelling efficacy readout would be attainable. Some felt that the combined product could provide measurable increased protection against CHMI using a parasitemia endpoint compared to the CS component alone (as was the approach with RTS,S +/- Ad35). They also discussed the impact study population for CHMI; specifically, if CHMI studies in semi-immune African adults allow for higher treatment thresholds for parasitemia (due to natural immunity), they could provide additional insights into BS protection conferred by a CS+BS vaccine.

The concept of clinical development velocity was also introduced, in terms of how limitations of time and resources could be overcome by employing CHMI studies to advance clinical development. CHMI studies could efficiently provide both efficacy and immunogenicity/interference readouts. Another consideration for a combination vaccine is that a BS component may only work effectively against SPZ challenge when it is combined with CS and the force of infection is reduced. The experts agreed that from an ethical standpoint, combining BS with CS would need to have some proven advantage over the CS component alone. For the purposes of this discussion, it was assumed that both components would have individually met the first bar of promising clinical and/or biological effects before being combined.
Key recommendations

Based on the discussions at the expert consultation described above, the following outlines key recommendations to inform a clinical development plan for a CS+BS combination *P. falciparum* malaria vaccine.

**Clinical development plan for CS and BS antigens with clinical experience**

If the individual antigens already have clinical experience, the proposed first step for a CS+BS combination is a Phase 1 study to test for safety, immunogenicity, and non-interference, compared to the individual components. The target population for this study could be non-immune or low-immune adults in Africa, possibly including CHMI. Requirements for this first step include that preclinical testing has informed variables such as dose level and adjuvant-to-antigen ratio, and that preclinical toxicology studies conducted under Good Laboratory Practice (GLP) have confirmed a maximum dose for clinical testing. Possible challenges to this approach include the need to mix the two antigens with adjuvant at bedside and to determine the vaccination schedule. Different adjuvant-to-antigen ratios could also be evaluated. This initial study could include testing administration of each component separately (concomitant) for non-interference; and then when delivered together (admixed), if acceptable levels of interference are detected. Non-interference would serve as an early signal of potential for clinical success. An example of a similar Phase 1 trial of R21 combined with RH5 in Gambian children employed bedside mixing of the two vaccines and adjuvant Matrix-M in a single syringe, following initial testing in mice for immunogenicity and non-interference. This was supported by preclinical toxicology studies of the combination. The immunogenicity endpoints for this first-in-human combination vaccine study included GIA and anti-CS immunology. Considerations for this approach include:

- **Obtaining a rapid safety and immunogenicity readout in the target population using concomitant administration may represent a more attractive first step prior to embarking on significant investment in co-formulation.** An admixed product requires time-consuming animal toxicity and stability and potency studies of the mixture, whereas concomitant likely does not. A key advantage of an admixed approach is that it more closely mimics the anticipated product presentation; however, it requires more “up-front” development work to mitigate compatibility risks, including precipitation, hence the risk of concomitant administration may be relatively lower. One potential solution is a four-arm study testing admixed versus concomitant administration. Chemistry, manufacturing, and controls work is a prerequisite to ensure product integrity.

- **Prespecified fractional doses of established vaccines could be employed as a “disaster check” to assess for the potential that adding a second antigen interferes with the immune response to the first antigen.** A predefined threshold for interference (e.g., a 50% reduction in the immune response when the antigen is given alone) could be employed to model an acceptable reduction in immunogenic response to the co-administered antigen.

- **For initial clinical testing of a CS+BS combination product, individual components could be administered concomitantly and at separate injection sites to measure initial safety and immunogenicity, while also assessing for immunodominance and/or immune interference.** This administration approach would bypass the need for co-formulation of a single product and the
additional need for preclinical toxicity studies of a new, combined product before first-in-human studies. If concomitant administration of separate CS and BS products demonstrates safety and immunogenicity without immunodominance, co-formulation and preclinical studies could be prioritized to develop a single CS+BS investigational product for injection.

- The target population for initial studies should prioritize African non-immune or low-immune adults over European or US-based naïve adults.

**Clinical development plan for CS and BS antigens without clinical experience**

For CS and BS components not previously evaluated in clinical studies and targeted for initial testing as a multistage combination vaccine, the proposed first step includes administration of each component individually and combined. This approach would support limited dose-finding, immunogenicity, and non-interference readouts. CHMI testing could be employed as a disaster check go/no-go decision point. The BS component could be evaluated with a BS CHMI and using a threshold PMR reduction or other in vivo effect. The CS component could be assessed using SPZ CHMI and a minimum threshold for efficacy such as 60%, or a confidence interval that includes 60% efficacy. For the combined new CS + new BS, sequential SPZ CHMI followed by BS CHMI in protected individuals could be used. This Phase 1/2a trial could be conducted in malaria-naïve or low-immune adults in Africa. Considerations for this approach include:

- A potential advantage of this approach is that immunogenicity could be assessed and then CHMI could follow in a single clinical trial if an immunogenicity readout is quickly obtained. However, a drawback to this approach is that correlates of protection as measured in peripheral blood specimens may be better defined for BS than CS, so immunogenicity thresholds may be difficult to establish before CHMI.

- This initial study should be conducted in malaria-experienced African adults to look at BS-induced protection if they are not drug-cured after SPZ CHMI. Alternatively, an SPZ CHMI could be conducted in the BS-only arm to look at BS protection from that component, following a more biologically relevant challenge and force-of-infection. This may require a larger sample size depending on the expected BS component effect. If looking for small effect size, then BS CHMI (with its very precise force of infection) could be used, though SPZ CHMI could detect a larger effect size.

- It may be helpful to test baseline antimalarial immunity status to refine the study population in malaria-experienced African adults and provide a more homogeneous study population. Alternatively, an SPZ CHMI followed by BS CHMI could sequentially evaluate for efficacy in African adults who are malaria exposed.

**Proposed clinical development plan after initial adult study(ies)**

After initial testing of a CS+BS combination vaccine in adults, if predesignated safety, immunogenicity, and efficacy thresholds are met, the next studies could be initiated in the pediatric population. The overall goals of these clinical trials would include dose- and regimen-finding, as well as age de-escalation to target pediatric populations in endemic areas. These studies could be completed in two phases, with the first to establish safety and immunogenicity and the second to demonstrate safety, immunogenicity, and efficacy. In parallel, preclinical and chemistry, manufacturing, and controls development of the co-formulation could be conducted for efficiency. Considerations for this approach include:
• Interference should initially be assessed in adults.
• It is important to conduct dose ratio refinements in the target pediatric population, as regimen refinements may help to overcome issues with dose ratio.
• The ratio of antigen to adjuvant should be maintained to not exceed the established safe adjuvant dose.
• Incorporating engineering models/bioinformatics can support the optimization of dose ratio.

Clinical testing first in malaria-naïve or malaria-exposed African populations versus malaria-naïve US-based or European populations and related regulatory requirements

Both the African scientists and the researchers who work in endemic areas who were at the consultation strongly supported the idea of first-in-human testing in African malaria-naive or malaria-exposed populations. Multiple countries in Africa have conducted first-in-human studies as well as CHMI studies using cryopreserved SPZs, and the local ethics committees supported these studies. The KEMRI-Wellcome Trust Research Programme in Kenya has conducted first-in-human studies for malaria and Ebola vaccine candidates. In Mali, the Malaria Research and Training Center in Bamako is actively advocating for Phase 1 testing of malaria vaccine candidates and therapeutics in endemic populations. The rationale is that it may not be ethically appropriate to wait for Phase 1 vaccine studies with CHMI in the European Union/United Kingdom/United States and subsequent regulatory reviews before testing in target populations, particularly given the capacity to conduct rigorous clinical trials of candidate malaria vaccines in endemic areas. The consultation experts support initial testing in endemic countries as a first step and for subsequent steps in clinical development. This would help fuel a much-needed increase in velocity to advance next-generation malaria vaccines.

Requirements for advancement from Phase 2b to Phase 3

Overall, any product that advances from Phase 2b to Phase 3 would need to be data driven and informed by planned and ongoing studies. A Phase 2b candidate should be worthy of substantial investment before advancing to Phase 3 testing. A possible threshold for determining advancement might include threshold efficacy at or above current efficacy of R21 and/or RTS,S.

Cost of goods and co-formulation considerations

Development costs for a new BS (or CS) vaccine antigen would be helpful to estimate the investment requirement for Phase 3 testing. It would also inform risk and facilitate a decision about whether to pursue new products versus existing antigens.
## Summary of key recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Prerequisite(s)</th>
<th>Challenge(s)</th>
<th>Advantage(s)</th>
<th>Output(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. First step for CS+BS clinical testing for established antigen-adjuvant testing: Phase 1 testing of safety, immunogenicity, and non-interference in non-immune or low-immune African adults, +/- CHMI.</td>
<td>• Preclinical testing to inform antigen and adjuvant dosing. • Preclinical toxicology under GLP to confirm maximum dose for clinical testing.</td>
<td>• Possible need to mix two antigens with adjuvant at bedside. • Determining vaccination schedule. • Determining antigen-to-adjuvant ratios.</td>
<td>• Concomitant administration avoids need for investment in co-formulation (animal toxicity, stability, potency studies).</td>
<td>• Rapid safety and immunogenicity +/- efficacy readouts in malaria-endemic population.</td>
</tr>
<tr>
<td>2. First step for CS+BS clinical testing for novel antigen-adjuvant testing: Phase 1 testing of safety, immunogenicity, and non-interference in malaria-experienced African adults with CHMI. Testing of a BS component with BS CHMI and separately testing a CS component with SPZ CHMI before combining CS+BS, and testing of sequential SPZ CHMI followed by BS CHMI in protected individuals.</td>
<td>• Preclinical testing to inform antigen and adjuvant dosing. • Preclinical toxicology under GLP to confirm maximum dose for clinical testing.</td>
<td>• Correlates of protection in peripheral blood may be better defined for BS than CS.</td>
<td>• Would confirm immunogenicity before CHMI. • BS CHMI with threshold PMR reduction could serve as go/no-go criterion for new BS component. • SPZ CHMI with requirement for 60% efficacy could serve as go/no-go criterion for new CS component. • Baseline antimalarial immunity status could provide homogeneous study population of malaria-experienced African adults.</td>
<td>• Safety, immunogenicity, and preliminary efficacy readouts in malaria-endemic population.</td>
</tr>
<tr>
<td>Recommendation</td>
<td>Prerequisite(s)</td>
<td>Challenge(s)</td>
<td>Advantage(s)</td>
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</table>
| 3. Next steps for clinical development after initial studies in recommendations 1 and 2:  
  a. Phase 1: Safety and immunogenicity in pediatric population.  
  b. Phase 2: Safety, immunogenicity, and efficacy in pediatric population. | - Non-interference demonstrated in adult studies.  
- Dose ratio and regimen refinements in target pediatric population.  
- Incorporation of models/bioinformatics to optimize dose ratio. | | | - Safety, immunogenicity, and preliminary efficacy readouts in target population. |
| 4. First-in-human testing of malaria vaccines should be done in African malaria-naïve or malaria-exposed populations. | | | | - Multiple African countries have conducted first-in-human studies and CHMI studies.  
- African ethics committees have supported first-in-human and CHMI studies.  
- Avoids time required for Phase 1 studies in European Union/United Kingdom/United States and subsequent regulatory reviews before testing in endemic countries. |
| 5. Decisions to advance a vaccine from Phase 2b to Phase 3 testing should be data driven. | - Possible threshold at or above the current efficacy of RTS,S/AS01 and R21/Matrix-M vaccines. | | | |
| 6. Estimate development costs for a new BS (or CS) vaccine antigen to inform risk and facilitate the decision to use existing candidates versus new candidates. | | | | |
Conclusions and next steps

Overall, this expert consultation achieved the objective to critically and constructively review potential clinical pathways for the development of a combination CS+BS multistage malaria vaccine, discuss the pros and cons of each, and identify a preferred pathway(s) for consideration by all malaria vaccine stakeholders. Based on these discussions and decisions made during the consultation, this report shares the experts’ key recommendations to inform the development of a comprehensive clinical development plan for a CS+BS combination *P. falciparum* malaria vaccine for young African children.

The consultation experts identified several next steps that would help put these recommendations into action in the malaria vaccine development community. Specifically:

- Critical decisions must be made regarding supporting advancement of existing versus new CS+BS vaccine antigens or both.
- A transparent review of data (when available) from the CS+BS vaccine trial using R21 and RH5 with Matrix-M in The Gambia will be helpful to determine the prospect for this type of combination.
- Further discussions are needed to “work backward” to outline the preclinical studies needed to support a Phase 1 clinical trial of a CS+BS combination vaccine.
References


### Appendix 1. Consultation agenda

#### Wednesday, May 3

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic(s)</th>
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<tbody>
<tr>
<td>12:00-1:00 p.m.</td>
<td><strong>Lunch</strong></td>
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<tr>
<td>1:00-1:15 p.m.</td>
<td>Introductions (All)</td>
</tr>
<tr>
<td>1:15-1:45 p.m.</td>
<td>Consultation problem statement, objectives, &amp; intended outcomes (Ashley Birkett, Matt Laurens)</td>
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</tbody>
</table>
| 1:45-3:00 p.m.  | Setting the Stage 1: Review of the state of the art of CS- and BS-based vaccines and available challenge models  
                    • State of the art: CS vaccines (Chris Ockenhouse)  
                    • Sporozoite challenge models in malaria-naïve adults (Meta Roestenberg)  
                    • Sporozoite challenge models in malaria-experienced adults (Melissa Kapulu)  
                    • State of the art: BS vaccines (Simon Draper)  
                    • BS challenge in malaria-naïve adults (Angela Minassian) |
| 3:00-3:15 p.m.  | **Break**                                                                |
| 3:15-3:45 p.m.  | Setting the Stage 2: Update from recent Convening on Multistage Malaria Interventions (Jean-Luc Bodmer) |
| 3:45-4:15 p.m.  | Consultation assumptions, including expected preclinical data (Ashley Birkett, Matt Laurens) |
| 4:15-5:00 p.m.  | Introduction of proposed priority pathways (Matt Laurens)                |
| 5:30 p.m.       | **Dinner**                                                               |

#### Thursday, May 4

<table>
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<th>Time</th>
<th>Topic(s)</th>
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<tr>
<td>8:00-8:30 a.m.</td>
<td><strong>Breakfast</strong></td>
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| 8:30-9:00 a.m.   | Introduction to Day 2 (Matt Laurens)  
                    Review of consultation intended outcomes |
| 9:00-10:30 a.m.  | Clinical Development Pathway 1 Discussion (Melissa Kapulu, Kent Kester)  
                    • Pros/Cons  
                    • Data required to inform decision to progress to this pathway  
                    • Proposed modifications  
                    • Milestone criteria for advancement within pathway  
                    • Priority consideration |
| 10:30-10:45 a.m. | **Break**                                                                |
| 10:45 a.m.-12:15 p.m. | Clinical Development Pathway 2 Discussion (Meta Roestenberg, Alex Juma Ismail)  
                        • Pros/Cons  
                        • Data required to inform decision to progress to this pathway  
                        • Proposed modifications  
                        • Milestone criteria for advancement within pathway  
                        • Priority consideration |
| 12:15-12:45 p.m. | **Lunch**                                                                |
| 12:45-2:15 p.m.  | Clinical Development Pathway 3 Discussion (Mahamadou Thera, Thierry Rolling)  
                    • Pros/Cons  
                    • Data required to inform decision to progress to this pathway  
                    • Proposed modifications  
                    • Milestone criteria for advancement within pathway  
                    • Priority consideration |
| 2:15-2:30 p.m.   | **Break**                                                                |
| 2:30-3:40 p.m.   | Prioritization of Clinical Development Pathways and final recommendation(s) (Matt Laurens) |
| 3:40-4:00 p.m.   | Next Steps/Concluding Remarks (Ashley Birkett, Matt Laurens)             |
Appendix 2. Consultation attendees

Names and affiliations of experts

- Alex Juma Ismail, MSc, DRA, Programme Officer, Regulatory Systems Strengthening, African Medicines Regulatory Harmonization Initiative of the African Union Development Agency-New Partnership for African Development, Johannesburg, South Africa
- Melissa C. Kapulu, DPhil, MSc, Post-Doctoral Research Assistant, KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya
- David C. Kaslow, MD, Director, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA
- Kent E. Kester, MD, Vice President, Translational Medicine, International AIDS Vaccine Initiative, New York, New York, USA
- Meta Roestenberg, MD, PhD, Professor, Leiden University Medical Center, Leiden, The Netherlands
- Thierry Rolling, MD, MSc, Director, Clinical Development Infectious Diseases, BioNTech SE, Mainz, Germany
- Mahamadou A. Thera, MD, PhD, Malaria Research and Training Center, University of Sciences, Techniques, and Technologies of Bamako, Bamako, Mali

Names and affiliations of participants

- Evelina Angov, PhD, Center for Infectious Disease Research, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA
- Ashley Birkett, PhD, Global Head, Malaria, Center for Vaccine Innovation and Access, PATH, Washington, DC, USA
- Jean-Luc Bodmer, PhD, MBA, Senior Program Officer, Bill & Melinda Gates Foundation, Seattle, Washington, USA
- Graham Brown, DPhil, MBBS, MPH, Professor, University of Melbourne, Melbourne, Australia
- Danilo R. Casimiro, PhD, Chief Science Officer & Global Head, External Scientific Affairs, Vaccines Research and Development, Sanofi, Swiftwater, Pennsylvania, USA
- Camila H. Coelho, PhD, MBA, Assistant Professor, Icahn School of Medicine at Mount Sinai, New York, New York, USA
- Katharine A. Collins, PhD, Program Officer, Global Health Research and Development, Open Philanthropy, San Francisco, California, USA
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- Mary J. Hamel, MD, Senior Technical Officer and Lead, Malaria Vaccine Implementation Programme, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland
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• Jason A. Regules, MD, Director, Foundational Sciences, US Army Medical Research Institute of Infectious Diseases, Frederick, Maryland, USA
• Eleanor M. Riley, PhD, Professor, University of Edinburgh, Edinburgh, United Kingdom
• Paul M. Robben, MD, PhD, Deputy Director, Division of Infectious Diseases; Director, Biologics Research & Development Branch, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA
• Lorraine A. Soisson, PhD, Senior Technical Advisor, Malaria Vaccine Development Program, US Agency for International Development, Washington, DC, USA
• V. Ann Stewart, DVM, PhD, Professor, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA
• Eileen Villasante, PhD, Head, Malaria Research Program, US Naval Medical Research Center, Walter Reed Army Institute of Research, Silver Spring, Maryland, United States
• Lindsey Wu, Technical Officer, Global Malaria Programme, World Health Organization, Geneva, Switzerland
• Yimin Wu, PhD, Scientific Advisor, Center for Vaccine Innovation and Access, PATH, Washington, DC, USA
• Susan Youll, MPH, Malaria Prevention Branch Chief, US Agency for International Development, Washington, DC, USA
Appendix 3. Consultation pre-read documents

The following documents were provided to all experts and participants as pre-reads to inform the discussion:

- **World Health Organization (WHO).** *Malaria Vaccines: Preferred Product Characteristics and Clinical Development Considerations.* WHO; 2022. [https://www.who.int/publications/i/item/9789240057463](https://www.who.int/publications/i/item/9789240057463)

- **Reviews of human challenge models:**
  - Sauerwein RW, Roestenberg M, Moorthy VS. Experimental human challenge infections can accelerate clinical malaria vaccine development. *Nature Reviews Immunology.* 2011;11(1):57–64. [https://doi.org/10.1038/nri2902](https://doi.org/10.1038/nri2902)

- **Combination malaria vaccines:**
  - Sklar MJ, Maiolatesi S, Patterson N, et al. A three-antigen *Plasmodium falciparum* DNA prime-adenovirus boost malaria vaccine regimen is superior to a two-antigen regimen and protects against controlled human malaria infection in healthy malaria-naïve adults. *PLOS ONE.* 2021;16(9):e0256980. [https://doi.org/10.1371/journal.pone.0256980](https://doi.org/10.1371/journal.pone.0256980)