Building an effective malaria vaccine pipeline to address global needs

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ABSTRACT

Despite impressive gains over the last 15 years in reducing the mortality associated with malaria, it remains a public health emergency. New interventions, such as vaccines, are needed to ensure that previous gains serve as a foundation for future progress. Vaccines have the potential to prevent severe disease and death in those most vulnerable, and to accelerate elimination and eradication by breaking the cycle of parasite transmission. The pipeline is as healthy as it has ever been, with approaches targeting different stages of the parasite lifecycle using an array of technologies. This article reviews recent progress and reviews key considerations in the quest to develop products that are aligned with the unmet medical need.

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1. Introduction

Significant progress in reducing malaria morbidity and mortality has been achieved via coordinated scale-up of a range of interventions. Between 2000 and 2013, estimated malaria mortality rates decreased by 47% worldwide and by 54% in Africa. Further, while a total of 97 countries remain endemic for malaria, the number is steadily falling with an estimated 34 countries targeting elimination over the next 10–20 years [1]. In view of the fact that these impressive gains have been achieved in the absence of an available vaccine, it is critical that vaccine development efforts be targeted to address the residual, unmet medical need.

The current unmet medical need for vaccines to reduce morbidity and mortality remains most urgent in populations associated with the highest burden of disease. This burden remains greatest in sub-Saharan Africa, where an estimated 90% of all malaria deaths occur, and particularly in children aged less than 5 years of age, who account for approximately 80% of all deaths. In 2013, an estimated 437,000 African children died before their fifth birthday due to malaria [1]. Therefore, a vaccine capable of preventing disease and death in this population has the potential for significant public health impact.

In addition to the development of vaccines to address the immediate unmet medical need associated with malaria morbidity and mortality, there has been, in recent years, an increased focus on the development of vaccines to break the cycle of Plasmodium (P.) falciparum and Plasmodium vivax parasite transmission to accelerate future elimination and eradication efforts [2]. Existing interventions have proven to be highly effective in eliminating malaria in certain settings and reducing malaria transmission to extremely low levels in many more. Sustaining those gains, however, particularly once control programs have ended, has proven challenging. A recent review of 75 resurgence events in 61 countries, occurring from the 1930s through the 2000s, concluded that almost all resurgence events (68/75 = 91%) were attributed at least in part to the weakening of malaria control measures [3]. In short, the impressive gains could not be maintained in the absence of labor intensive and costly programs. New tools, with longer durability, are needed to interrupt the cycle of malaria (parasite) transmission, prevent parasite reintroduction, and accelerate elimination. A leading strategy is to develop vaccines that interrupt malaria transmission (VIMT) to provide an ‘immunological bed net’ that prevents parasite transmission [2]. By virtue of the inherent properties of vaccines, this impact would be achieved in a manner that is independent of user behavior and the temporal and spatial constraints associated with other interventions, preventing reintroduction of parasites into humans and thereby re-establish the human parasite reservoir, even in the most challenging environments. Importantly, in the event of malaria resurgence, vaccines conferring direct clinical benefit would provide a ‘safety net’ to protect populations rendered vulnerable to severe malaria and death by the lack or loss of accumulated natural immunity that would accompany elimination efforts [4].

This article will review the progress toward development of a malaria vaccine pipeline, sufficient to address global needs associated with preventing clinical disease (i.e., averting cases, thereby preventing disease and saving lives) and interrupting the cycle of transmission (thereby supporting control and elimination). There is a particular emphasis on development progress in the context...
of the Malaria Vaccine Technology Roadmap (Roadmap) [5], and a focus on key factors that are expected to influence the environment in which the malaria vaccine development community is expected to operate over the coming years.

2. Clear community goals: Malaria Vaccine Technology Roadmap

To ensure alignment of vaccine development efforts with the unmet public health need, the first Roadmap was published in 2006, following an extensive consultation with scientists and public health experts from non-endemic and malaria-endemic countries, industry, non-governmental organizations, and funding agencies. This first iteration of the Roadmap focused exclusively on the need to develop vaccines to prevent P. falciparum malaria disease in young African children. In 2013, the Roadmap was updated, again based on extensive consultations with key stakeholders [5], to include two strategic goals to be met by 2030; namely, vaccines that are highly efficacious in preventing clinical malaria and vaccines that prevent transmission to accelerate malaria parasite elimination. The Roadmap also includes an updated set of priority areas in research, vaccine development, key capacities, policy, and commercialization, where further funding and activities are likely to be crucial for success [5].

A landmark goal, established by the first Roadmap in 2006, to develop and license a first-generation malaria vaccine by 2015 that has a protective efficacy of more than 50% against severe disease and death and lasts longer than one year, remained in effect following the 2013 revisions. The RTS,S vaccine candidate, developed by GSK in partnership with the PATH Malaria Vaccine Initiative with financial support from the Gates Foundation, has the potential to fulfill the landmark goal. Recent progress and next steps in the development of this vaccine candidate are described in the accompanying article (see, ‘RTS,S: a first landmark on the Malaria Vaccine Technology Roadmap’). In June 2014, GSK submitted an application for a scientific opinion by the Committee for Medicinal Products for Human Use (CHMP) on RTS,S through the European Medicine Agency’s (EMA) Article 58 procedure. The EMA is evaluating data on the quality, safety, and efficacy of the RTS,S/AS01 vaccine candidate. On Thursday, July 23, 2015, CHMP adopted a positive opinion. This is not licensure, but will be helpful to African regulatory authorities as they receive submissions, knowing that a stringent regulatory authority has provided a positive assessment of quality and risk/benefit. The WHO will issue policy recommendations regarding the RTS,S malaria vaccine candidate as early as the fourth quarter of 2015. The EMA assessment does not include aspects such as feasibility of implementation, cost-effectiveness, and the role of RTS,S in the context of available malaria control measures, all of which will be important parts of the WHO policy recommendation process.

The relatively modest vaccine efficacy (VE) criteria for the 2006 landmark Roadmap goal was justified based on the potential for high public health impact. Indeed, several examples of how VE, the traditional barometer of vaccine performance, often imperfectly predicts the public health impact of a vaccine on disease burden, including for the most advanced malaria vaccine candidate (RTS,S/AS01), have been reported [7]. It has been proposed that VPD1 (Vaccine Preventable Disease Incidence), which assesses the amount of disease prevented when considering both VE and baseline disease incidence, is a superior measure of public health impact against severe clinical disease/syndromes. This measure provides a direct assessment of the preventable incidence of the most relevant public health outcome for policymakers. Over the coming years, these measurements could be influenced, toward a potential for greater public health impact, in view of the emerging resistance to malaria interventions that have been temporally associated with the gains of the last 10–15 years. Specifically, the spread of resistance across Africa to insecticides in Anopheline mosquitoes, and the ever closer threat of resistance to leading Artemisinin Combination Therapies (ACT) reaching the African continent [8–11], without the near term prospect of alternative molecules, may cause the value of other available interventions, imperfect as they may be, to be viewed in a different light.

While the Roadmap goals provide high-level targets for malaria vaccine development efforts, additional specificity is needed to describe the preferred characteristics of vaccines to ensure that they are ‘fit-for-purpose’ to achieve the desired impact. In recognition of this need, a series of preferred product characteristics (PPCs) were recently published by the WHO [12]. The PPCs describe preferences for parameters of vaccines, in particular their indications, target groups, and possible immunization strategies, as well as the clinical data desired related to safety and efficacy. PPCs are meant to provide early guidance for the development of new products or the improvement of existing ones. Each PPC addresses early-stage vaccine R&D generally at least 5–10 years from the vaccine’s availability, and will be reviewed and updated if necessary, at least every 5 years. PPCs are not static exit criteria, but are structured in such a way so as to drive innovation towards meeting public health needs [12].

A critical gap in the current profile of elimination vaccines is the target protective efficacy and coverage levels required to confer sufficient community immunity to prevent reintroduction, under a given transmission setting. This will need to be estimated, over the coming years, to support investment decisions associated with advanced clinical development where accelerating elimination and eradication is the primary investment driver. Initial mathematical modeling studies have suggested that very high levels of efficacy (and coverage) will be needed, particularly in high transmission settings [13,14]; however, new population-based preclinical models have suggested that elimination could be achieved by transmission-interrupting interventions exhibiting relatively modest efficacy at low transmission settings [15]. Therefore, a cautious approach is warranted in using mathematical models to inform product development decisions with integration of biological data and realistic assumptions critical to their optimal use.

3. Financing the malaria vaccine development pipeline

The absence of a significant developed world market for malaria vaccines has led to a heavy reliance on public and philanthropic funding to support development efforts. From 2007 to 2011, public funders contributed 44% ($327 million) of malaria vaccine R&D funding, whilst philanthropic organizations accounted for 36% ($267 million) and industry for 20% ($148 million) [16]. While different funding agencies generally favor one or other of the Roadmap goals, they are generally aligned with one of the two goals associated with P. falciparum. However, there continues to be a chronic lack of support for the development of P. vivax vaccines to prevent clinical disease and to prevent transmission. A major contributor to this deficiency is continued prioritization of P. falciparum, over P. vivax, for the limited available resources. A major risk of this approach is that vaccines to interrupt P. vivax transmission, which is recognized as being a significantly greater challenge than for P. falciparum, will not be available in a timely manner to support the eradication agenda [17].

An opportunity associated with this challenging environment, particularly in the context of clear community goals and preferred product characteristics (also discussed above), is the application of a portfolio-based investment strategy to ensure optimal use
of limited resources. This investment strategy is most appropriate in the pre-proof-of-concept development phase to enable maximal flexibility in resource allocation. This is achieved by facilitating ‘real-time’ responses to new data to increase or decrease investment in specific projects, in the context of the performance of a broader portfolio of projects. Retaining an ability to reallocate resources across a portfolio of projects during early-stage development supports the focus on achieving the product development goal as opposed to a specific vaccine approach that may or may not specifically achieve the desired outcome.

However, once proof-of-concept has been successfully achieved in the target population, and the vaccine is considered ‘fit-for-purpose’ based on alignment with preferred product characteristics, a strong case can be made for an alternative funding strategy; namely, a product-specific investment. The highly defined and more substantial financial requirements associated with late-stage development are preferably isolated from pre-proof-of-concept investments, in large part to protect the relatively modest budget associated with them.

4. Commercial considerations for different classes of vaccines under development

Malaria vaccines are being developed to benefit individuals living in some of the poorest communities on earth, and therefore considered to be of limited commercial value. The different classes of vaccine under development, whether to prevent clinical malaria in at risk populations (Roadmap Goal 1) or to reduce transmission to accelerate elimination (Roadmap Goal 2), are associated with defined ‘use case’ scenarios that make the two vaccine classes quite distinct. These distinctions, which are summarized in Table 1, will need to be considered early in development and are likely to be of key strategic interest to vaccine developers/manufacturers. In addition to the obvious differential in ‘benefit’ (i.e., individual/disease versus community/elimination), the target population and associated implementation strategies are expected to be distinct. Vaccines intended to prevent clinical disease are most likely to be delivered via established immunization program mechanisms, which are expected to ensure coverage for those enduring the greatest burden of disease; this, in turn, is likely to provide a consistent and predictable demand that is favorable to the manufacture. Conversely, vaccines being deployed for elimination will need to target all individuals at risk of becoming infected and/or transmitting the parasite, a level of coverage only likely to be achievable via mass campaigns; in turn, this is likely to lead to an uncertain demand dependent on the timing and size of elimination campaigns.

The product lifecycle for each type of vaccine is similarly expected to be distinct, with vaccines targeting standard immunization programs associated with a more favorable business model, which can be likened to a multi-decade annuity with favorable capital amortization and high barrier to biosimilar entry. Vaccines for elimination can be likened more to patented drugs, with rapid market growth and a demand cliff once eradication has been achieved; this is likely to lead to the developer/manufacturer retaining significant stranded assets.

Additional commercial considerations include definition of metrics to assess public health impact and return on investment for elimination vaccines. For vaccines preventing clinical disease, cost-effectiveness can be determined using well-defined metrics. However, the ‘value for money’ of elimination products that, particularly late in elimination campaigns, will be associated with minimal reduction in clinical cases, will need to be determined.

5. Regulatory considerations for next-generation vaccines

Identification of a regulatory acceptable correlate of protection for RTS,S will significantly accelerate development of next-generation vaccines targeting the circumsporozoite protein (CSP), in large part by avoiding the need for costly Phase 3 efficacy trials. In the absence of a regulatory acceptable correlate of protection, vaccines intended to prevent clinical malaria by targeting at-risk populations (Roadmap Goal 1) are associated with a traditional development pathway that is likely to be similar to the one followed by RTS,S [18]. In view of the absence of an approved malaria vaccine, RTS,S was evaluated in a series of trials in which the comparator (control) vaccine was not targeting malaria. However, in the event that RTS,S is recommended for use, novel vaccines targeting a similar indication (i.e., prevention of *P. falciparum* malaria disease in young African children) will require consideration of the inclusion of RTS,S as a comparator vaccine, which could present technical and financial challenges due to the size of trial needed to effectively demonstrate non-inferiority, or superiority, to RTS,S. Alternatively, there are ethical issues associated with vaccine trials assessing vaccine efficacy and/or effectiveness, where a placebo is being considered in the study design despite the existence of an efficacious vaccine. This challenge is not unique to malaria, having been faced by other vaccine development efforts where first-generation products failed to fully address the unmet medical need associated with a disease, particularly in resource-limited settings. Examples include development of novel rotavirus vaccines in India and novel pneumococcal vaccines in Bangladesh.

A 2013 expert consultation led by the WHO identified five situations in which placebos may be ethically acceptable even in the presence of an efficacious vaccine [19]. One of the situations pertains to resource constraints associated with access to the existing vaccine that could be overcome by the next-generation product. The other four situations relate to scientific constraints, one or more of which may be relevant; however, this would need to be considered in the context of the profile of the next-generation vaccines under consideration.

In recent years, there has been an increased focus on development of vaccines that interrupt malaria (parasite) transmission (VIMT) to support malaria elimination [5]. The two primary vaccine development strategies are to induce pre-erythrocytic (PE) immunity that prevents infection of humans or to induce sexual, sporogonic, or mosquito-stage (SSM) immunity to prevent transmission to mosquitoes [20]. While the focus of these vaccines is to prevent infections (as opposed to clinical disease), it is important to note that infection endpoints have historically not been sufficient to support vaccine licensure. Furthermore, SSM-VIMT would not confer immediate, direct clinical benefit to the recipient, unless paired with an intervention that provides such a benefit. In the absence of such pairing, cluster-randomized trials have been considered the default pathway to regulatory approval and expert consultations have recently presided over potential study designs for pivotal Phase 3 cluster-randomized trials for an SSM-VIMT [21]. In addition, exploration of innovative regulatory pathways for next-generation malaria vaccines that interrupt transmission to encourage the development of this important class of interventions—while at the same time safeguarding the health and well-being of the population that SSM-VIMT are intended to benefit—is urgently needed. One consideration under active discussion is the potential eligibility of SSM-VIMT for an Accelerated Approval (AA) method of licensure by the US Food and Drug Administration, based on a proposed surrogate endpoint with confirmatory trials performed post-licensure [22]. Resolving this important dilemma will require vaccine developers and other key stakeholders to work closely with regulatory authorities, including those in endemic counties, and with the WHO. An important step
forward in this regard was achieved at the inaugural convening of the WHO Product Development for Vaccines Advisory Committee meeting held in Geneva, September 8–10, 2014, where a specific recommendation was that identification of a feasible regulatory pathway for TBVs be a priority area of work for the WHO [23].

6. Controlled human malaria infection (CHMI) models: Accelerating and de-risking future vaccine development efforts

Controlled human malaria infection (CHMI) models have served as important stage gates in the early clinical development of malaria vaccine candidates and are likely to continue to serve a similar role going forward [24]. The use of CHMI models has facilitated rapid and cost-effective assessment of vaccine candidates for their efficacy against infection, informing the decision to advance to field efficacy studies. The most widely used malaria CHMI model employed to date involves experimental infection of volunteers via the bites of infectious mosquitoes [25,26]. While the endpoint for this model is infection, as determined by axenic blood-stage parasitemia measured by microscopy or polymerase chain reaction (PCR), parasitemia has proven to be a valuable proxy for the development of vaccines, such as RTS,S, with a target indication of prevention of clinical malaria [27].

In recent years, two groups have reported successful sporozoite challenge studies in human volunteers using P. vivax strains derived from human donors [28,29]. Further, the development of infectious, purified, and vialized sporozoites now offers the potential to perform CHMI studies in the absence of insectary requirements, with studies ongoing to optimize dose and route to ensure reliable infectivity in non-endemic [30,31] and endemic populations [32,33]. In view of the unnatural challenge route for purified vialized sporozoites (direct intravenous inoculation), its value as a stage gate to inform advancement to efficacy studies in endemic regions has yet to be proven. Specifically, concerns have been raised that direct venous inoculation (DVI) of vialized sporozoites could bypass immune-mediated protection in the skin, which is known to interfere with sporozoite motility [34]. It will therefore be important to assess the DVI model, with mosquito challenge serving as the gold standard, for testing pre-erythrocytic vaccines with presumed antibody-mediated mechanisms of protection.

Significant innovation in the use of CHMI models has occurred over the past several years, which has the potential to further enhance the tools available to accelerate vaccine development efforts and reduce risk of failure during operationally complex and expensive field studies. This need is most urgent in the assessment of vaccines targeting asexual blood-stage and sexual-stage antigens, where there has historically been a strong reliance on readouts from functional assays that have not been conclusively shown to correlate with clinical outcomes. Such CHMI models will also strengthen the ability to test existing assumptions and new hypotheses associated with functional assays, as well as to investigate more rigorously immune correlates of protection. Sexual blood-stage challenge models, first developed in the 1990s, have emerged as a potential tool to better inform the development of these two classes of vaccine [35]. The blood-stage model involves direct intravenous infection with low numbers of asexual blood-stage parasites, which replicate in vivo in a reproducible manner [35–37]. Bypassing the liver stage results in a more consistent blood-stage infection, which can be effectively monitored (using PCR) over a longer period of time. This ability to induce a consistent, low-grade asexual blood-stage parasitemia offers the potential to support the assessment of the impact of vaccine-induced immunity, and possibly passively-transferred immunity, on the parasite multiplication rate (PMR) of asexual-stage parasites [36,37]. The first test of concept to assess a vaccine candidate using the blood-stage CHMI model was with AMA1-C1/Alyhydrog + CPG 7909; however, it failed to induce immune responses that reduced the overall mean PMR in the vaccine group in comparison to the controls [38]. More recently, another AMA1 vaccine candidate vaccine candidate (FMP2.1/AS02B), derived from D7-strain parasites, was assessed in the same model. When formulated with AS02 adjuvant, this vaccine candidate was shown to induce a low level of vaccine efficacy against clinical malaria in Malian children (VE 17.4%—hazard ratio for the primary end point, 0.83; 95% confidence interval [CI], 0.63–1.09; P=0.18). Efficacy against clinical malaria caused by parasites with AMA1 corresponding to that of the vaccine strain was 64.3% (hazard ratio, 0.36; 95% CI, 0.20–0.80; P=0.03) [39]. To determine whether these findings could be ‘back validated’ to the blood-stage CHMI model, 15 healthy, malaria-naive volunteers were immunized with 3 doses of FMP2.1 in AS01B using the same schedule as used in the field [40]. Despite being immunogenic, eliciting functional IgG-mediated growth inhibition assay (GIA) in vitro against D7 clone parasites, there was no delay to diagnosis seen in the vaccinees compared with controls. The mean PMR in vaccinees, modeled from the quantitative PCR (qPCR) data by protocol pre-specified methodology, was 10.32 (95% CI, 8.97–11.67) and in controls was 10.31 (95% CI, 9.00–11.62), demonstrating no significant difference [40]. These observations suggest that the blood-stage CHMI model could serve as an important stage-gate in the early clinical assessment of asexual blood-stage vaccines by determining whether induced immunity has a biological effect on parasite replication in vivo, and supporting the identification of immune correlates. The development of banks of parasites that are antigenically distinct, at key vaccine target alleles, offers the potential for CHMI studies to estimate the capacity of novel immune interventions to function against a diverse parasite repertoire in advance of advancing to endemic field studies.

A second potential use of the blood-stage CHMI model is in the evaluation of human-to-mosquito transmission for transmission-blocking vaccines. For P. vivax, this may be achievable following
asexual blood-stage challenge, as evidenced from the recent observations from McCarthy and colleagues, where gametocytes where identified in the blood as early as two days after the onset of PCR-confirmed parasitemia and more than two days before the onset of symptoms or slide positivity [41]. While infectivity to mosquitoes of these sexual stages was not confirmed in this study, the authors highlighted the consistency of their findings with previous reports documenting the infectiousness of patients with early P. vivax infection. Records of volunteers with induced P. vivax infection for malariatherapy for syphilis showed that 39.3% of mosquitoes that fed on patients with similar sub-microscopic gametocytemia became infected [42]. For P. falciparum, where gametocytes are produced later following human infection, it is likely that manipulation of the model, using anti-malaria drugs to differentially suppress asexual-stage parasites but not sexual-stage parasites, will be needed. In addition to testing immune interventions for their capacity to block human-to-mosquito transmission following direct skin feeding, this model has the potential to enable a better understanding of the association of the standard membrane feeding assay and direct membrane feeding assay with direct skin feeding [22,43].

7. Malaria vaccine portfolio

The global malaria vaccine portfolio is actively monitored via a WHO-led initiative known as the ‘Rainbow Tables’, which was most recently reviewed in a 2012 manuscript [44]. Projects in the database are organized based on the parasite target (i.e., P. falciparum or P. vivax), the stage of the parasite lifecycle being targeted (i.e., pre-erythrocytic, asexual blood-stage, sexual stage, or multistage), and the current development stage (i.e., pre-clinical or clinical). According to the most recent online version of the Rainbow Tables, updated in January 2015, there are a total of 33 active clinical-stage vaccine projects. The overwhelming majority of these are targeting P. falciparum (32/33), with only one targeting P. vivax. The dominant lifecycle-stages being target are pre-erythrocytic and asexual blood-stage (15/33 each), with sexual stage (2/33) and multistage (1/33) continuing to be the minorities.

Subunit pre-erythrocytic vaccine approaches are generally dominated by three antigens: CSP, TRAP, and CFTOS, with four of the CSP projects aiming to build directly on the RTS,S/AS01 vaccine candidate that recently completed Phase 3 testing. Irradiated sporozoites (PSPZ), delivered intravenously, have been shown to protect six subjects receiving five doses and three of nine subjects receiving four doses of 1.35 × 10^7 (Note: only five of six non-vaccinated controls were infected following controlled human malaria infection; P = 0.015 in the five-dose group and P = 0.028 overall, both versus controls) [45]. Initial clinical testing of a genetically attenuated sporozoite vaccine approach, delivered via mosquito bites, led to breakthrough infection associated with incomplete attenuation [46]; however, next-generation parasites are expected to be tested over the coming years [47,48].

The portfolio of clinical-stage asexual blood-stage vaccine approaches is the most diverse with a total of nine antigens under investigation (AMA1, EBA175, GLURP, MSP1, MSP3, Pf11.1, PFF0165c, R5, and SERAS). Over the coming years, one or more VAR2CSA-based vaccines approaches are expected to transition to initial clinical-stage testing, with the long-term goal of preventing pregnancy-associated malaria [49].

The only two sexual-stage clinical projects target a single antigen (F525), highlighting the need for new target antigens to transition to clinical testing. F5230 is expected to be only the second sexual-stage antigen to progress to human clinical testing over the next one to two years.

8. Concluding remarks

Since the first iteration of the Malaria Vaccine Technology Roadmap was published almost 10 years ago, significant progress has been made toward achieving the 2015 landmark goal of a first-generation P. falciparum vaccine to protect those at greatest risk from severe disease and death: young African children. As a result of the 2013 revision to the Roadmap, and availability of PPs and TPs, the community now has greater clarity on the required attributes of next-generation vaccines, including those that will be essential to ensure effective implementation.

While the pipeline is impressive, with diverse approaches targeting different parasite development stages, it would benefit from a broader list of promising target antigens on which to draw. There has been a movement in this direction in recent years, with targets such as CeTOS, R5, and VAR2CSA at or nearing initial clinical assessment, but more are needed [49–51]. Novel approaches to validating vaccine target antigens, such as via passive transfer of monoclonal antibodies, followed by CHMI, are advancing with the potential to accelerate development efforts; however, they remain as yet unproven.

A significant opportunity is associated with understanding of the protective mechanism of the remarkable finding that volunteers immunized under chloroquine chemoprophylaxis with P. falciparum sporozoites (CPS) exhibit durable protection from homologous challenge following bites from just 45 infected mosquitoes [52,53]. Such knowledge has the potential to be translated into novel vaccine development strategies, founded on strong biological rationale, and thereby further diversify and strengthen the global malaria vaccine development portfolio.

Of significant importance is the recent progress toward the expanded use of CHMI models to include the assessment of asexual blood-stage and transmission-blocking vaccines to support stage-gate decisions for many vaccines in the current pipeline. If used effectively, these models have the potential to increase the probability of success for vaccine approaches that advance to endemic field-testing and thereby ensure optimal use of precious resources. In view of the fact that developing vaccines inducing durable protection is likely to prove more challenging than conferring a high level of efficacy over a short period, the manner in which CHMI models are used and interpreted will be critical. Therefore, we will need to not only ‘raise the bar’ with respect to target efficacy, but also with respect to durability of protection by placing greater emphasis on challenge results obtained at more distant time points following immunization.

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