Perspective

Development of a transmission-blocking malaria vaccine: Progress, challenges, and the path forward

Julia K. Nunes a,1, Colleen Woods a, b, Terrell Carter a,2, Theresa Raphael a, Merribeth J. Morin a, Diadier Diallo c, Didier Leboulleux d, Sanjay Jain a,3, Christian Loucq a,4, David C. Kaslow a,e, Ashley J. Birkett a,*

a PATH Malaria Vaccine Initiative, Washington, DC, USA
b PATH Malaria Vaccine Initiative, Seattle, WA, USA
c PATH Malaria Vaccine Initiative, Dakar, Senegal
d PATH Malaria Vaccine Initiative, Ferney, France
e PATH, Seattle, WA, USA

A R T I C L E   I N F O

Article history:
Received 25 April 2014
Received in revised form 12 June 2014
Accepted 8 July 2014
Available online 29 July 2014

Keywords:
Malaria vaccine
Transmission blocking
Elimination
Eradication

A B S T R A C T

New interventions are needed to reduce morbidity and mortality associated with malaria, as well as to accelerate elimination and eventual eradication. Interventions that can break the cycle of parasite transmission, and prevent its reintroduction, will be of particular importance in achieving the eradication goal. In this regard, vaccines that interrupt malaria transmission (VIMT) have been highlighted as an important intervention, including transmission-blocking vaccines that prevent human-to-mosquito transmission by targeting the sexual, sporogenic, or mosquito stages of the parasite (SSM-VIMT). While the significant potential of this vaccine approach has been appreciated for decades, the development and licensure pathways for vaccines that target transmission and the incidence of infection, as opposed to prevention of clinical malaria disease, remain ill-defined. This article describes the progress made in critical areas since 2010, highlights key challenges that remain, and outlines important next steps to maximize the potential for SSM-VIMTs to contribute to the broader malaria elimination and eradication objectives.

© 2014 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

1. Introduction

The 2013 update to the Malaria Vaccine Technology Roadmap (Roadmap) expanded the vision to develop “safe and effective vaccines against Plasmodium (P.) falciparum and P. vivax that prevent disease and death and prevent transmission to enable malaria eradication” and introduced an important new strategic goal: “The development of malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria (parasite) infection” [1]. This complemented the original 2006 Roadmap strategic goal of developing a highly efficacious vaccine to prevent clinical disease [2] and highlighted the definitive shift of the broader malaria community to a focus on the development of tools to accelerate elimination and eventual eradication of malaria. The leadership of the Bill & Melinda Gates Foundation (Gates Foundation), along with the World Health Organization (WHO), the Roll Back Malaria Partnership, and other key stakeholders, have challenged the malaria community to renew its efforts to eradicate malaria [3], therefore leading to a significant refocusing of associated product development efforts [4].

Over the last several years, as the malaria community began to embrace the challenge of eradication, questions arose about the
feasibility of such an endeavor, the tools and strategies that would enable it, and the gaps that would need to be addressed in order to support eradication as a long-term goal. A number of meetings and consultations took place in and around 2010 to define the research agenda for malaria eradication, including those associated with the development of a malaria vaccine to interrupt malaria (parasite) transmission (VIMT) [5–16]. Initially *P. falciparum* and *P. vivax* were prioritized, with the recognition that to truly eradicate malaria, all species that infect humans must eventually be addressed. This article describes the progress that has since been made in critical focus areas identified during those meetings (Clinical development pathway and regulatory strategy; Assays; Transmission measurements and epidemiology; Communications and ethics; Policy and access; Process development and manufacturing; specific challenges associated with targeting *P. vivax*), and highlights the next steps that will be critical to developing the classes of vaccines needed to support the community’s malaria-eradication goals, as laid out in the revised Roadmap.

While vaccines have the potential to interrupt malaria transmission at multiple points in the parasite lifecycle, this paper will focus on strategies targeting the sexual, sporogonic, and mosquito (SSM) stages of the parasite (hereafter referred to as an SSM-VIMT), which are involved in the transmission of malaria parasites from an infected person to a female mosquito, rather than those involved in parasite infection of the human host or causing malaria disease. While not a novel concept, as evidenced by the 2000 meeting report on transmission-blocking vaccines (TBVs), “an ideal public good” [17], the product development resources now available to apply to the development of such products have created significant new opportunities. Unique development challenges associated with this class of VIMT, most notably the delayed as opposed to immediate benefit conferred to immunized individuals, require special consideration.

2. Ideal characteristics of an SSM-VIMT

The availability of a target product profile (TPP), in which key preferred and minimally acceptable characteristics of the vaccine have been defined, at an early stage in development helps ensure alignment between the product developed and the developing-country context in which its use is intended [18,19]. The PATH Malaria Vaccine Initiative (MVI) presented a draft TPP for a stand-alone SSM-TBV against both *P. falciparum* and *P. vivax* that was used as the basis for discussion at the MVI-sponsored TBV workshop in 2010 and the malaria vaccine advisory committee (MALVAC) meeting the same year [15]. There was consensus among participants on a number of key elements, including that the vaccine would need to be amenable to campaign administration, and therefore safe for administration to all who may transmit malaria parasites, effective in as few doses as possible for as long as possible, and low cost [18]. The WHO is currently leading an effort to develop consensus preferred product characteristics to guide the community’s progress toward developing a VIMT that meets the updated Roadmap goals; the characteristics with outstanding questions are described below.

A critical gap in the TPP is the required vaccine effect (a combination of factors including efficacy and coverage) [20] needed to support elimination efforts. Preliminary modeling data indicate that efficacy and coverage are equally important in the impact of a TBV [21]. Although the implications of this relationship on the required level of vaccine efficacy are not yet known, it is of critical importance to identify the minimally required efficacy (and coverage) to support defining stage-gate criteria that will inform early clinical decision-making. In addition to mathematical models (reviewed in the Malaria Eradication Research Agenda [malERA] Consultative Group on Modeling, 2011 [8]), biological and population models may also help to inform these criteria [20].

There is general agreement that a vaccine designed to contribute to elimination would need to be suitable for use in campaigns; however, it is still too early to have consensus on its exact formulation. In addition to the development of a stand-alone SSM-VIMT, which would not confer an immediate, direct benefit to the vaccine recipient, a vaccine targeting both SSM and other stage malaria antigens, a vaccine co-formulated with one targeting a different disease, and/or co-administration with another health intervention that targets the same population have been proposed. Strategies of combining antigens from different stages of the parasite lifecycle (such as RTS.S [22]) or co-administering the vaccine with a transmission-blocking drug are some of those currently being explored and could prove to be synergistic, while leveraging the successes in product development to date.

There has been significant debate on the merits of targeting antigens that are expressed while the parasite resides in the human, thus creating opportunity for an anamnestic immune response upon subsequent infection. As elimination is approached, fewer and fewer infections will occur, perhaps making natural boosting of a protective immune response a less impactful attribute of a product’s TPP. Furthermore, expression in the human increases the possibility that immune selection will lead to the proliferation of escape mutants. Additional data are therefore needed to support whether endemic boosting should be a critical attribute of an ideal SSM-VIMT.

3. Clinical development plan and regulatory pathway

The clinical development plan (CDP) and the basis of regulatory approval for an SSM-VIMT will likely be different from those applied to pre-erythrocytic and blood-stage malaria vaccines due to the methods in which vaccine effect will be established at the level of the community rather than the individual. In 2010, the major points of discussion on CDP/regulatory pathway were on the acceptability to regulatory authorities of a vaccine acting via delayed clinical benefit, the appropriate CDP and regulatory pathway, including the potential need for a cluster randomized trial (CRT), and the required level of efficacy.

A critical outcome of the 2010 MVI TBV workshop was that the US Food and Drug Administration (FDA) indicated that there is no legal bar to prevent a vaccine such as an SSM-TBV from being considered for licensure in the context of their review process. The FDA has the authority to license biological products that are demonstrated to be “safe, pure, and potent” (Section 351 of the Public Health Service Act & Section 505(b) of the Food, Drug, and Cosmetic Act), regardless of whether the disease occurs in the United States [23]. This feedback has encouraged the malaria vaccine development community to consider product development pathways for vaccine approaches exclusively targeting parasite transmission from human to mosquito. In 2012, moreover, the report on the MALVAC meeting states, “great progress has been made in recent years with a general acceptance in malaria vaccine circles that the issue of community benefits for TBV is not a major hurdle for clinical or regulatory pathways” [24]. The challenge moving forward will be to further define both the CDP and regulatory pathways and seek specific feedback from regulators, such as the FDA, European Medicines Agency, or another stringent regulatory authority.

Another important outcome of the VIMT research agenda-setting meetings and consultations was the preliminary definition of two potential clinical development pathways for an SSM-VIMT (Fig. 1). One involves a large-scale, Phase 3 efficacy trial, which, in the case of an SSM-VIMT, has been proposed by regulators to be a CRT to demonstrate vaccine impact on incidence of infection
in the community. An accelerated approval pathway, such as the one used by the FDA [25], was also discussed in which the vaccine would receive approval for use based on an analytically and biologically, but not clinically, validated surrogate of efficacy (which does not yet exist), with impact on transmission at the community level confirmed during post-approval studies. In the latter approach, the success of the work described under Assays and Correlates will be critical for this regulatory pathway to be considered acceptable. For the approval pathway based on a single CRT, the feasibility of conducting such a study, the statistical power to conclusively demonstrate the efficacy of the vaccine, and the translation of those results to the variety of settings contemplated for introduction of an SSM-VIMT, are important questions that need to be answered.

Toward identification of the preferred regulatory strategy, MVI has convened a series of technical consulting groups composed of independent experts to elucidate both of these potential CDP and regulatory pathways, considering overall feasibility, specific endpoints, requisite baseline data, malaria transmission levels, scale, and cost. The reports generated by these technical groups will be used to prepare a briefing document for consultation with regulatory authorities on the preferred approach, which will impact other areas of vaccine development, from ethics to policy to assays (see Table 1). Finalizing a CDP/regulatory pathway will require coordination with those assessing the measures of transmission and epidemiological data needs of SSM-VIMT trials. Alongside the efforts to finalize a regulatory pathway and CDP, progress must continue in the strengthening of clinical and regulatory capacity of endemic countries, where clinical trial sites will be selected in accordance with the CDP.

The level of efficacy required for an SSM-VIMT to have an impact on transmission and contribute to achieving elimination has not yet been determined. In 2010, the draft TPP presented at the MVI TBV workshop targeted ≥85% transmission-blocking efficacy, defined as the percent reduction in infection in mosquitoes [26]. However, there were not yet robust data to support a specific target efficacy. Furthermore, as the ultimate goal is to prevent incidence in the human population, a measure of efficacy that reflects vaccine effect on a human endpoint must be utilized. Initial evidence was recently reported using a population-based, non-clinical model of malaria transmission indicating that interventions with lower efficacy levels may contribute to elimination [20]. Just as targeting antigens from multiple parasite stages may create synergies, the use of a vaccine and drug together could maximize the impact on transmission. For example, a drug could be used to clear the parasites from an infected individual at the same time as administration of a SSM-VIMT, which would prevent transmission for a longer period than a drug could. Coordination of development strategies between the drug and vaccine communities through the alignment of TPPs will ensure the most efficient progress toward common goals.

4. Assays and Correlates

To determine whether an SSM-VIMT candidate is able to block transmission, reliable assays are required that measure the ability of an immunized, infected individual’s serum to prevent sporogony in and subsequent invasion of the mosquito mid-gut after a blood meal, as the traditional endpoints used to evaluate efficacy against future episodes of clinical disease are not informative (see Box 1). The decision to pursue a CDP in which licensure is based on a single CRT or to pursue a CDP relying on analytical endpoints (described above) to secure accelerated approval will significantly impact the level of development needed for such functional assays. As of 2010, the two major areas of focus for feeding assays were their reproducibility (in relation to their ability to be qualified), and the correlation between lab and field assays (outcomes of the 2010 MALVAC meeting and mafERA consultations have been detailed elsewhere in the literature [13,15,16]).

The prospect of qualifying the standard membrane feeding assay (SMFA) had been questioned due to a lack of reproducibility. The SMFA had demonstrated a low sensitivity in addition to the questions about its utility in the middle ranges of transmission-blocking activity [15]. Since 2010, significant progress has been made and the SMFA assay has been qualified for the characteristics of precision, linearity, range, and specificity. The range of the assay was limited to results of 80% or greater reduction in oocyst density, though modifications could potentially expand this range [27]. Future efforts continue toward full qualification of the assay, which, along with conclusive evidence that it predicts outcomes from more
Table 1
Impact of choice of clinical regulatory pathway on SSM-VIMT development.

<table>
<thead>
<tr>
<th>Ideal characteristics</th>
<th>Approval based on CRT</th>
<th>Accelerated approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process development and manufacture</td>
<td>No impact.</td>
<td>No impact.</td>
</tr>
<tr>
<td>Assays and correlates</td>
<td>Assays required to move development forward, but surrogate not required.</td>
<td>Surrogate approved by regulatory authority required.</td>
</tr>
<tr>
<td>Transmission measures and epidemiology</td>
<td>Specific baseline data would be required to appropriately and accurately design the CRT.</td>
<td>Specific baseline data may be required to measure the surrogate.</td>
</tr>
<tr>
<td>Communication and ethics</td>
<td>Ethical issues associated with CRTs would need to be addressed (e.g., randomization of communities to receive intervention). Communication of results would require distinct messaging.</td>
<td>Sites for clinical trials may not be the same as those targeted for first deployment presenting ethical challenges.</td>
</tr>
<tr>
<td>Policy and access</td>
<td>Analysis required to determine which pathway would allow vaccine use sooner in areas where most impact will be made.</td>
<td>Design of post-approval efficacy studies would be more informed by modeling, which would also require regulatory support.</td>
</tr>
<tr>
<td>Clinical trial site selection</td>
<td>Sites capable of conducting CRT would be needed in areas with very specific transmission levels: sufficient to limit sample size and make conclusive results likely, yet low enough to measure vaccine effect.</td>
<td>Data generated at clinical trial sites in areas that still have moderate transmission would be used for regulatory approval. These may not be the first regions to implement an SSM-VIMT, and the ethical implications would need to be addressed.</td>
</tr>
</tbody>
</table>

Box 1: Membrane feeding assays.
Definitions
Standard membrane feeding assay (SMFA): Laboratory-based assay where lab-reared mosquitoes feed on cultured P. falciparum gametocytes through a membrane, as depicted below. Direct membrane feeding assay (DMFA): Field-based assays (carried out in endemic areas) where progeny of wild-caught mosquitoes feed on a blood meal from a malaria-infected host through a membrane. Direct feeding assay (DFA): Field-based assays (carried out in endemic areas) where progeny of wild-caught mosquitoes feed directly through the skin of a malaria-infected host.

Assay readouts
For a week following a feed, all mosquitoes are kept alive to allow ingested parasites to develop into oocysts. Mosquitoes are then dissected and the number of oocysts counted in the mid-guts. (MVI is supporting efforts to develop higher throughput, less labor-intensive methods for determining the number of oocysts in the mosquito mid-gut.) For the SMFA, the results are reported as a percent reduction in the number of oocysts compared to a pre-immune control. The SMFA readout, reduction in oocyst intensity, can be understood as oocyst reducing/inhibiting activity. For the field assays, results can be reported in a binary fashion, where mosquitoes are scored as having oocysts or not (oocyst prevalence). This readout can be referred to as transmission-blocking activity, and indicates whether or not the mosquito was infected and had the potential to transmit disease. In the context of a malaria program reaching elimination, this is the most relevant readout.

Bridging lab- and field-based assays
How the lab- and field-based assays relate to one another, and how a vaccine candidate that performs well (strong oocyst reducing activity) in the SMFA will perform in a field-based feeding assay (DMFA or DFA), is not well understood. Following the review described under “Assays and Correlates,” MVI-funded efforts on bridging the assays are underway with the hope to have clearer understanding of the relationship between the lab and field assays in the coming year or two. How robust the feeding assays need to be will depend on the clinical development path chosen (see Fig. 1), as an assay that can serve as a surrogate for transmission reduction in humans will be required for the shorter path to licensure.

To address the identified knowledge gap with respect to the correlation between the SMFA and transmission reduction in the field, MVI coordinated a review to compare results from the DMFA and DFA [28] in terms of efficiency of parasite infection and to better understand variability within the DMFA. In summary, the group found that the DFA is a more efficient means of infecting mosquitoes than the DMFA, though the mosquito infection rates in the DFA strongly correlated with those in the DMFA. Their work also highlighted some differences in the feeding assay methodology, which might have contributed to assay variability and identified some gaps in our knowledge of the performance of the assays. As our understanding of the utility of each feeding assay in the different stages of vaccine development matures, the interpretation of assay readouts is also evolving (see Box 1).

To progress toward the Roadmap strategic goal of a vaccine that reduces transmission, MVI released a Call for Proposals to improve the existing assays and to address the gaps in the knowledge of how the assays relate to each other. The following priority areas were targeted: quantification of variability in feeding assays;
assay improvements or surrogates; and factors intrinsic to the parasite, mosquito vector, or human host that influence transmission. Projects currently supported by MVI include those that address optimizing the SMFA, correlating results of SMFA to DMFA, optimizing the DMFA and DFA, alternative methodology and readouts for the assays, reagent development, and developing a lab-based model to evaluate transmission dynamics.

5. Transmission measures and epidemiology

Transmission measures and epidemiology (TM&E) is a broad area in which large gaps in data had been identified, from a basic understanding of the parasite reservoir and the dynamics of transmission to the development of new, and further characterization of existing, methods to measure transmission. These issues are common across all efforts to eliminate malaria and not specific to vaccine development. Therefore, the field of TM&E may stand to gain the most from increased collaboration and data sharing. Specific to vaccine development, the projects described below will help to inform TPP development, clinical trial site selection, and clinical trial endpoint identification, as well as provide information on the appropriate use and evaluation of the impact of an SSM-VIMT in different transmission settings and in combination with different interventions. All of the work in these areas could not be covered in this article, which highlights projects supported by MVI [29] and the Malaria Eradication Scientific Alliance (MESA) [30], the Gates Foundation-funded continuation of the malERA project.

To address the need for a comprehensive assessment of current P. falciparum transmission measures, MVI sponsored an evaluation, which would also evaluate the correlations between measures\(^5\) and their appropriateness for use in the field. Conducted at the London School of Hygiene and Tropical Medicine and the Johns Hopkins University, the evaluation included: (1) describing their methodology, precision, accuracy, and cost; (2) evaluating which measures work best in each setting; (3) defining the mathematical relationship between measures; and (4) recommending the most appropriate measures for monitoring changes in transmission to evaluate malaria interventions. The results were described in Tusting et al. [31]. With respect to the mathematical relationship between some of the entomological measures, it was found that insufficient data were available and a collaborative project was begun [32,\(^6\)] which relies on the generous sharing of data between researchers. A MESA-sponsored investigation will compare the performance of a number of current epidemiological, molecular, and serological transmission measures in a variety of settings, including very low transmission, for both P. falciparum and P. vivax [33].

The development of novel methods for measuring infection, disease, and transmission, in particular identifying people carrying infectious gametocytes, including asymptomatic individuals, for both P. vivax and P. falciparum infection could be important tools for the broader effort to eliminate malaria, as well as the development of VIMTs. Such methods would need to be not only standardized, rapid, sensitive, and capable of high throughput, but should also be low cost and appropriate for use in low-transmission settings [10].

To target specific populations and gametocyte carriers, the ability to quickly generate higher-resolution maps that show human risk and disease in a spatial and temporal manner, track migrant populations, link with surveillance systems, and contain more detail on ecological factors, mosquito breeding sites, and quantified vector capacity will be critical to the entire field of malaria elimination [10]. A MESA-supported project will map transmission potential in countries targeting elimination and determine whether new cases have been imported using parasite genetics [33]. Data sharing between those researching transmission measures and those collecting ecological and epidemiological data would further facilitate progress.

Ongoing basic research to support the gaps identified above include the relationship between infectivity of humans to mosquitoes (including the role of asymptomatic individuals), the infectious reservoir [32,\(^3\)] and transmission [35,36], the extent and importance of naturally acquired transmission-blocking activity [37], and the nature and importance of changes in parasite genetic diversity that might occur as transmission declines [38].

6. Communications and ethics

Effective public health communications and consideration of ethical concerns are critical for the design, development, and use of any vaccine, but are particularly important for an SSM-VIMT given that benefit is experienced as a community, with delayed individual benefit. The priority needs for communications related to TBVs that had been highlighted at the MVI TBV workshop, MALVAC meeting, and in the malERA publications, were a re-framing of the benefits of TBVs to individuals and communities, research on the best way to engage communities, the development of strategies to ensure the continued use of other malaria control interventions, and establishment of the acceptability of a vaccine that would provide protection at the community level.

The concept of a vaccine that does not provide immediate, direct clinical protection to the recipient, while novel to the field of malaria, is not unprecedented in vaccinology; accordingly, ethicists made a strong recommendation to refrain from referring to SSM-VIMTs as vaccines that do not provide individual benefit. Rather, the message that individual benefit will be derived from community benefit over time should be communicated [16]. There is now greater awareness of the other examples of vaccines and drugs that aim to limit disease in one population by treating another (although in the case of an SSM-VIMT, given the local and focal nature of malaria transmission, many of the recipients would likely also be the beneficiaries). In addition to the examples of vaccines given to one population to protect another, such as those against rubella [39] and cytomegalovirus [40,41], primaquine is administered in some countries to P. falciparum-infected patients [42] to kill the sexual stage parasites and prevent disease transmission, despite the fact that it does not alleviate their symptoms [43,44]. Countries may require a particular vaccine, such as yellow fever, to prevent disease importation [45], and an SSM-VIMT against malaria could be used similarly to prevent reintroduction of the parasite into malaria-free zones.

MVI has conducted a series of community perception studies on malaria and pre-erythrocytic vaccines that address the call for research on community engagement and maintaining the use of other interventions following introduction of any malaria vaccine [46–48]. Attitudes were positive toward vaccines overall, and there was concern about malaria and its impact on a family’s economic stability. People were aware of the importance of and need for malaria interventions. An important consideration highlighted by the studies, and that will also be applicable to an SSM-VIMT, was the need to obtain the endorsement of local community leaders.

---

\(^5\) The analysis included the following measures of transmission: net infectiousness of humans (the proportion of mosquitoes that become infected after feeding on humans), parasite prevalence in humans, entomological inoculation rate, force of infection and molecular force of infection, multiplicity of infection, seroconversion rate, slide or clinical positivity rate, incidence of clinical malaria or annual parasite index, proportion of fevers with P. falciparum parasitaemia, vectorial capacity, and basic reproduction number.

\(^6\) Conjugation to Pseudomonas aeruginosa exoprotein A (EPA), diphtheria toxin (CRM197), E. coli outer membrane protein C precursor (OMPC), and tetanus toxoid (TT) are being considered.
and to ensure their involvement in the developing and spreading of communication messages [46–48].

More work will need to be done to assess communities’ understanding and acceptance of a vaccine that provides delayed benefit at the level of the community, but these initial studies suggested that the proposed ideal target population for an SSM-VIMT is aligned with the communities’ needs; indeed, people expressed concern that the most advanced malaria vaccine candidates are currently targeted only to infants and young children [46–48]. To achieve elimination, it would be ideal to define the target population as all those who are likely to transmit malaria. Such a target may include groups that are not accustomed to receiving vaccines, such as children above three years of age, women of childbearing age, and adult men. MVI plans to conduct a customer survey that will address this and other questions of SSM-VIMT acceptability at the community level. A working group of experts has also been convened, which could serve as a forum to coordinate the overall communications and ethics efforts in the malaria community.

7. Policy and access

Adequate consideration of policy and access issues will be critical to ensure that a vaccine most appropriate for the community’s goals is developed, and that it becomes available and accessible to the intended audience. Two of the three main points of discussion regarding policy and access have been covered above: whether a vaccine that did not provide immediate, direct clinical protection would be accepted by communities (see Section 6), and how to define the preferred characteristics of the product (see Section 2). Other important topics with respect to enabling access to a vaccine are the delivery strategy (including its health economic impact) and modeling.

In 2010, the discussion of modeling focused on its potential contribution to developing an SSM-VIMT, and an elucidation of the data needed to improve models [15]. Models can play a role in understanding the potential effect of new malaria vaccines, particularly in the context of other malaria interventions simultaneously in use and when field data may be difficult to obtain. Modeling groups have committed to articulating the main drivers of their models, as well as the limitations of the models and the available data used to parameterize them [24,49,50]. WHO, MVI, and the Gates Foundation have each encouraged and facilitated data sharing between modeling groups, with the intention of helping the broader community understand the models, their outputs, and the significance of any differences between them [51]. In the context of an SSM-VIMT, it is anticipated that modeling results will help define the target efficacy early in the development process, as well as provide insight into the potential public health impact of a vaccine in different transmission settings. Once the vaccine is approved for use across entire communities, introduction studies will be required, and they will facilitate validation and refinement of the models. Although the current models only apply to P. falciparum, research is underway to support the development of models specific to P. vivax.

A vaccine that delivers benefit at the community level and is administered in campaigns as part of an elimination effort would require very large numbers of doses (unless technological advances allow for rapid, reliable, and inexpensive means of identification of ideal recipients, thereby reducing the necessary volume) and may also require an innovative delivery and access strategy [24], with particular attention paid to the economic considerations of implementation. A growing body of work (based on modeling) has explored the cost-effectiveness of a pre-erythrocytic malaria vaccine [49,52] and, while economic evaluation of an SSM-VIMT may require distinct analyses, the lessons learned thus far have laid the groundwork for the research that will need to be conducted into the economic impact of implementation. A vaccine candidate that does not provide direct clinical protection to the recipient (as a vaccine for travelers or the military must), and does not have a large market in high-income settings, will not be considered a valuable addition to the portfolios of Western pharmaceutical companies. Therefore, cost-reducing strategies should be given high priority, and it is critical to begin consideration early in development of a model in which partners are engaged that can contribute to the significant financial requirements of product development. In the context of novel development partnerships that deliver vaccines at extremely low cost, a major milestone was achieved for meningitis with the approval and introduction of MenAfriVac®, a vaccine developed in a partnership between PATH, a developing world vaccine manufacturer, and WHO costing less than USD $0.50 per dose [53]; such a development partnership between a product development partnership and WHO has been identified as one potential model for an SSM-VIMT. It was recently reported that this vaccine can be removed from constant refrigeration for mass campaign administration, which is the first such example in Africa and could extend vaccination coverage to the most remote regions of sub-Saharan Africa; such an attribute would be ideal for a vaccine for malaria elimination [54].

8. Process development and manufacture

The implications of campaign delivery for product design are that the vaccine must have an appropriate risk/benefit ratio, ideally a single product (versus heterologous prime boost) that would induce sufficient and lasting antibody titers in as few doses as possible, exhibit a product profile that is “fit-for-purpose” to support mass administration, and be cost-effective [15,16]. To identify SSM-VIMT candidates most likely to meet the preferred characteristics, the community must focus on developing high-quality immunogens with structure that effectively mimics the native (target) antigen, toward minimizing the need for potent adjuvants. A variety of expression systems (Escherichia coli, including cell-free systems, Lactococcus lactis, Drosophila S2 cells, or Baculovirus insect cells, plant-based systems [55], and algae [56]) are being explored for their capacity to produce correctly folded proteins. Through industry/academic collaborations, all of the leading SSM-VIMT target antigens (Pfs25, Pfs48/45, Pf230, AnAPN1) are being considered for conjugation [57,58], in an attempt to enhance their immunogenicity, with particular focus on carriers with robust safety data from use in other vaccines. Another avenue that researchers are pursuing is evaluation of particle-delivery technologies, such as virus-like particles [55] (one Pfs25 candidate has entered Phase 1 clinical trials [59]) and nanoparticles [60]. In assessing the merits of different vaccine strategies, direct comparison of them in relevant preclinical models will be critical to ensure forward momentum is maintained with regard to continuous improvement of clinical-stage candidates.

9. P. vivax

It has become increasingly apparent that P. vivax transmission will need to be tackled alongside P. falciparum given the recently recognized disease severity [61–63], the large population at risk, and the low endemicity in many countries (which prevents the development of immunity) [64,65]. The updated Roadmap goals call for vaccines against P. vivax [1], yet the overall strategy,

---

1 Conjugation to P. aeruginosa exoprotein A (EPA), diphtheria toxin (CRM197), E. coli outer membrane protein C precursor (OMPC), and tetanus toxoid (TT) are being considered.
including development of a TPP, lags behind that for *P. falciparum* vaccines. *P. vivax* projects also face additional hurdles. Preventing the transmission of *P. vivax* is made more complicated by the presence of the hypnozoite stage of the parasite, which remains dormant in the liver and often causes relapse disease over the course of the two years following initial infection [66,67], a consideration that must be accounted for when setting the target for vaccine duration in the TPP. The lack of standardized reagents for *P. vivax* and the inability to routinely conduct a SMFA add to the challenges in developing a TBV against this species [4]. Progress is being made in the use of non-human primate models, and increasing the availability of the *P. vivax* controlled human malaria infection (CHMI) model would further accelerate vaccine development. With respect to the latter, the early emergence of gametocytes in *P. vivax* infection (reviewed in [68]), make possible a transmission-blocking model for clinically evaluating SSM-VIMTs in early clinical development.

### 10. Conclusion

New tools are needed to accelerate elimination efforts and support eventual malaria eradication [5–9,13,14]. A survey of dozens of previous control/elimination efforts revealed that a rapid resurgence of parasite transmission was associated with an inability to sustain control programs [69]. Therefore, based on our experiences of the past 70 years, an intervention that could prevent transmission of malaria parasites between humans and mosquitoes, over a sustained period of time and with minimal human intervention, and therefore maintain effectiveness in the most difficult of environments, would be a valuable asset in achieving and sustaining elimination. Vaccines that induce immune responses to interrupt transmission have the potential to fill this critical gap in our current interventions [13]. Indeed, VIMTs are now considered a development priority, as evidenced by their inclusion in the 2013 revision of the Roadmap.

One class of VIMTs under consideration is the SSM-VIMT, a number of which are being developed to induce long-lived antibodies that block parasite transmission from infected humans to mosquitoes, thereby breaking the cycle of transmission. Since this class of vaccines would confer a delayed benefit to vaccine recipients (i.e., a community effect), the development pathway for such a vaccine is complex and has not been defined. However, in 2010, the FDA indicated that there is no legal bar to considering an SSM-VIMT for licensure and it would be eligible for its review process, given that specific criteria are met. Subsequently, two development pathways have been prioritized for consideration to support the regulatory approval and eventual implementation of SSM-VIMTs. The first is to seek regulatory approval based on a single, large CRT that attempts to demonstrate vaccine efficacy against incidence of infection/disease, while the second proposes to secure accelerated approval, based on analytically and biologically validated endpoints, enabling a more thorough investigation of true efficacy in Phase 4 studies. Work is ongoing to fully explore the merits and limitations of each approach in preparation for consultation with regulatory authorities. The regulatory pathway selected will have important implications on a host of associated activities, including the criticality of identifying an analytically and biologically validated correlate of transmission-blocking activity. Further, development and optimal implementation of VIMTs will benefit from the effective use of modeling and an ability to reliably detect gametocyte carriers. The generation of real-time tracking systems of infection will also be an important tool beyond vaccine development to achieve the ultimate goal of eradication.

The ability to communicate the delayed benefit of an SSM-VIMT to communities and recipients, and the acceptability of such an intervention is one that needs to be confirmed to ensure that the vaccine is well received, as coverage will be key to achieving transmission reduction. In addition, economics will be an important driver, and an SSM-VIMT must be low cost, cost-effective, and fit within the budget of a country’s malaria elimination program.

Significant progress has been made since the malaria community first considered transmission-blocking vaccines: multiple conferences and consultations have been devoted to the topic, and the inclusion of transmission reduction as a target in the updated Roadmap in 2013 provides both the framework and the impetus for those in the field to continue striving toward development of an SSM-VIMT. While much work still needs to be done, measurable progress has been made in recent years toward identification of a preferred regulatory approval pathway to inform vaccine development efforts.

### Authors’ contributions

JN and AB drafted the manuscript. All authors participated in the conception, development, oversight, or operation of MVI’s Transmission Blocking Vaccine Program, whose work forms the basis of this manuscript. All authors contributed to, reviewed, and approved the manuscript.

### Competing interests

All authors have declared that no competing interests exist.

### Funding

The funders had no role in the decision to publish or the preparation of the manuscript.

### Acknowledgments

The authors would like to thank Carla Botting and Brian Childress for their contributions to this manuscript, as well as Cynthia Lee, Alexander Golden, and Corinne Warren for their contribution to the Transmission Blocking Vaccine Program at MVI. This work was supported by grants from the Bill and Melinda Gates Foundation to the PATH Malaria Vaccine Initiative.

### References


53. PATH. Deadly epidemic gives rise to groundbreaking partnership. PATH Meningitis Vaccine Project. Available at: http://www.path.org/topics/about-path/meningitis-vaccine-project.php [accessed 30.01.14].


