Background

Since the introduction in 2006 of the Malaria Vaccine Technology Roadmap, intended to align and guide the malaria vaccine community, the primary goal of the PATH Malaria Vaccine Initiative (MVI) has been the development of a vaccine for *Plasmodium falciparum* with at least 80 percent efficacy against clinical malaria in children through age five. Hence, a key component of MVI’s research and development strategy is to build on the success of GlaxoSmithKline Vaccines’ RTS,S malaria vaccine candidate, now in Phase 3 clinical trial at 11 sites throughout Africa, the first and only malaria vaccine candidate to reach this stage.

However, driven primarily by the shift in the global agenda toward control, elimination, and eventual eradication of malaria, the focus during recent years has expanded to include increased consideration and support for development of transmission-blocking vaccines (TBVs).

In June of 2010, MVI hosted a workshop that provided leading voices in the malaria vaccine field an opportunity to explore how TBVs can be incorporated into overall strategies toward malaria elimination and eradication, and to prepare for the licensure, design, and delivery of TBVs. The focus of the workshop was on the feasibility of developing a stand-alone TBV vaccine that targets sexual, sporogonic, and/or mosquito antigens (SSM-TBV). Use of the acronym SSM-TBV adds specificity to the term TBV, while recognizing that vaccines targeting the pre-erythrocytic antigens could also function to interrupt transmission. The specific objectives of the meeting are listed below.

1. Develop a consensus on whether the development of a vaccine that targets only *P. falciparum* and/or *P. vivax* sexual-stage or mosquito antigens is biologically and technically feasible, and if such a vaccine could have a policy and regulatory pathway defined for recommendation for use as a public health intervention in conjunction with other malaria interventions to eliminate transmission of malaria.

2. Establish consensus on appropriate assays to use in each phase of clinical testing, and whether decisions for advancing candidates can be made using surrogate measures.

3. Understand the designs of clinical trials and data required to demonstrate safety, immunogenicity, and efficacy in healthy adults, children, and vulnerable populations in endemic areas.

4. Discuss specific ethical and strategic challenges associated with implementing a TBV with the goal of progressive transmission interruption toward elimination.

5. Identify the critical next steps to be taken to accelerate the process toward a TBV, or a vaccine that contains a transmission-blocking component, if a TBV is deemed too difficult to develop and implement at this time.
Descriptions and highlights of the workshop sessions

SSM-TBV target product profile

Focus: A draft target product profile (TPP) served as a platform for discussion over the course of the workshop. The two characteristics in the TPP that drive the targets for many of the other characteristics are the target population and efficacy. Ideally, the vaccine would be delivered to all who are exposed to *P. falciparum* and/or *P. vivax* parasites, and therefore amenable to campaign delivery. One implication of such a broad target population is that a TBV must be safe for use in all populations (including pregnant women) in combination with other vaccines they routinely receive, in as few doses as possible, in a presentation that is fit for purpose and very low in cost. In the case of an SSM-TBV, both high efficacy and coverage are important to achieve the desired impact on transmission. Vaccine developers cannot guarantee coverage, but do need a defined minimally acceptable target for efficacy; the draft TPP proposed a preliminary target of 85 percent, as measured by the reduction in proportion of infected mosquitoes.

Feedback: Resolution was not reached, but discussion of the following issues highlighted the challenges that remain in defining the TPP:

- **The best way to define and measure efficacy:** whether efficacy can be measured in a mosquito endpoint versus a clinical endpoint.
- **The appropriate minimally acceptable target for efficacy,** duration of response, and frequency of booster doses.
- **The use of modern adjuvants and delivery platforms,** how to balance increased immunogenicity, clinical acceptability, cost, and access concerns.
- **Whether both *P. falciparum* and *P. vivax* can be tackled simultaneously.**

Regulatory considerations

Focus: It was unclear whether the US Food and Drug Administration (FDA) Center for Biologics Evaluation and Research could authorize a vaccine that does not confer immediate, direct clinical benefit to the vaccinee. Discussion focused on relevant policies and regulations.

- Section 351 of the Public Health Service Act and Section 505(b) of the Food, Drug, and Cosmetic Act do not limit their approvals to products that prevent conditions or diseases that occur in the United States; the FDA encouraged vaccine developers to submit an Investigational New Drug (IND) application for products whose primary use would be in the developing world.
- The [FDA Guidance for Industry document](#) on the development of vaccines against infectious diseases or conditions that are endemic to areas outside the United States specifies:
  - The FDA has the authority to license vaccines that protect against infectious diseases or conditions not endemic to the United States.
  - The regulations that govern these licensures are the same as for vaccines licensed for use in the United States.
Clinical data generated in trials conducted outside the United States can be used in support of licensure by the FDA. Clinical studies can be performed either under an IND, or they can be foreign studies that meet certain conditions, including compliance with Good Clinical Practice and independent institutional review board (IRB) approval.

Feedback/outcome: The FDA indicated that there is no legal bar to the development of an SSM-TBV, even though it does not confer immediate, direct clinical benefit to the recipient. As regulatory agencies around the world often look to the FDA as an example, this indication enables the community to consider the development of a stand-alone SSM-TBV.

Assays

Focus: What are the most appropriate ways to measure the efficacy of an SSM-TBV at each stage of development? While pre-erythrocytic vaccines, such as RTS,S, benefit from well-established methods and standards for evaluation, an SSM-TBV will require different tools, including assays to determine the reduction in transmission to mosquitoes. A number of tools exist (listed below), but there is great variability in results and the relationship between them is not well understood:

- The **ELISA** measures the antibodies produced in the human vaccinee, and is a standard tool in vaccine development.
- Feeding assays measure the impact of vaccine-induced antibody on infection rates in mosquitoes that feed directly on immunized individuals or on their blood through a membrane. The readout from all of these feeding assays is the reduction in infected mosquitoes (either reduction in oocyst density or the proportion of mosquitoes infected).
  - Standard membrane feeding assay (SMFA): uses laboratory-reared mosquitoes and a controlled, high number of cultured gametocytes from a single parasite strain.
  - Direct membrane feeding assay (DMFA): local mosquitoes (with precautions to prevent disease transmission) feed on gametocytes collected from individuals infected with parasites of various strains.
  - Direct feeding assay (DFA): local mosquitoes (with precautions to prevent disease transmission) directly bite immunized, infected individuals. It is the closest to reality in terms of biting mechanism and genetically diverse parasites, yet results in an unknown number of gametocytes being tested.

Feedback:
- Efforts should be made to standardize the membrane feeding assays, including agreement on reagents and controls. A review summarizing the sources of variability in the assays and identifying opportunities to standardize the protocol for each would facilitate this process.
- While it may not be possible to validate the SMFA, assay qualification may be possible.
- Additional data would help enumerate the correlation between the ELISA, SMFA, DMFA, and DFA. This would help resolve questions about the stringency of the assays, since lower densities of gametocytes are found in infected individuals than typically are used.
in the SMFA, and a greater proportion of mosquitoes are infected when feeding through a membrane.

- The DFA should be used to measure the primary endpoint in the first Phase 2 field trial, which would ideally be conducted in a high-endemicity setting to test the feasibility of the assay in a trial. The DFA will offer the most realistic assessment of the vaccine, given the genetic diversity represented by gametocytes collected directly from patients.

- The FDA views the membrane feeding assay as a proof-of-concept assay to determine biologic activity, but without a demonstrated correlate, not to provide a link to the prevention of human infection. Data on whether antibodies to the vaccine antigens correlate with the transmission-blocking assay results are welcome.

**Clinical development**

**Focus:** Beyond the Phase 1a studies of safety and immunogenicity, the clinical development plan (CDP) for an SSM-TBV will have a distinct pathway from previous vaccine candidates targeting the pre-erythrocytic and blood stages of the parasite. Vaccines are generally approved based on their demonstrated impact on clinical disease, yet the most proximal effect of an SSM-TBV will be on the transmission of sexual-stage parasites from infected humans to mosquitoes. It is unknown whether a regulatory agency will accept such an endpoint for vaccine approval; therefore, this session focused on the potential clinical development and regulatory approval pathways for an SSM-TBV. Two potential regulatory/clinical development pathways were discussed:

1. **Approval of the vaccine (potentially for limited use) based on demonstrated reduction of transmission to mosquitoes via the feeding assays described above.** Such a pathway would require a much better understanding of the relationship between the assays described above, and how they link to clinical disease. In this case, vaccine impact on human disease and transmission would be evaluated during post-approval or Phase 4 studies.

2. **Approval of the vaccine only after demonstration of impact on human disease.** The FDA indicated that they would likely require a clinical efficacy endpoint [as a Phase 3 study]. A cluster-randomized trial (CRT), in which an entire village receives the vaccine and other villages serve as controls, might be necessary to demonstrate such impact, and the steps required to prepare for a CRT were highlighted.
   - The specific endpoints (e.g., disease incidence, parasite prevalence within a particular age range) must be defined.
   - Multiple, reliable estimates of the selected primary endpoint(s) are required prior to the trial in order to properly power a CRT; power comes from the number of clusters rather than the number of individuals enrolled.
   - Estimates of the pair-wise correlation among members of clusters (intraclass correlation) are also needed to design a CRT.

**Feedback:**

- It will be important to discuss the feasibility of these potential pathways with regulatory agencies from other countries early in the process and to maintain that communication.
• The target population includes pregnant women, children, and elderly persons; these groups will need to be adequately represented for the collection of safety data. Developmental toxicology studies will be a prerequisite for testing in these groups, and communication with the regulators will be imperative. The group recommended that the appropriate time to include these groups in studies would be once the product has been fully characterized with respect to dose, formulation, schedule, etc., and would most likely be after a first Phase 2b trial has been completed.

Measuring transmission

Focus: When the goal is to interrupt transmission in a community, the ability to detect a change in transmission and to target the intervention to the right places is critical.\(^1\) Both entomological and clinical measures will need to be used in parallel.

• Methods to assess the number of infectious bites a person receives per year (entomological inoculation rate/EIR) remain very crude, and do not allow for detection of modest reductions in EIR or accurate estimates in settings with low levels of transmission. More needs to be understood about the precision and accuracy of entomological measures.

• The challenges will be distinct in areas of low and high transmission, and trials may need to be conducted in both (potentially via factorial study design). During a TBV trial in areas of high transmission, particularly where the population is semi-immune, transmission may decline without a corresponding decrease in disease incidence. Plans must be in place to adequately detect such an impact.

• In low-transmission areas, significant resources may be necessary to perform the surveillance needed to accurately monitor cases of disease. As transmission declines, parasite prevalence, incidence, and seroconversion rate are appropriate measures.

• A vaccine must be used in coordination with other malaria control interventions. Used together, transmission can be lowered to the point where elimination is possible. Trials will necessarily be conducted within the context of these other interventions, and potential implications need to be considered in the trial design.

• Recent work by Bejon, Bousema, and others has identified hotspots of transmission in regions of Kenya and Tanzania (Bejon 2010 PLoS Med, Bousema 2010 JID, and Bousema 2012 PLoS Med). Such hotspots of malaria may offer an opportunity to target the vaccine to the appropriate locale (and to gametocyte carriers), leading to a large impact on transmission throughout the community. More research on the dynamics of transmission in these hotspots is warranted, including exploring the difference between hotspots of transmission, disease, and asymptomatic infection.

Feedback: After reviewing the status of current transmission measures and identifying the challenges that need to be addressed to facilitate the development of an SSM-TBV, the group concluded that it would be worth the investment to improve transmission measures.

1 This is in contrast to a pre-erythrocytic vaccine like RTS,S—the goal of which is to reduce morbidity and mortality in infants and young children—in which case, it is not necessary to monitor disease transmission in the community in order to demonstrate vaccine efficacy and plan for appropriate delivery.
Product design

Focus: The advantages and disadvantages of four potential product design approaches:

1. **Stand-alone SSM-TBV**: This approach is likely to have a complicated CDP with respect to demonstrating vaccine impact on disease, and ensuring that an appropriate balance of safety and benefit is afforded to the trial participants. There will also be economic barriers to this approach since such a vaccine would not be suitable for travelers or the military. Ensuring access to affordable quantities of the vaccine for deployment at the levels of coverage required for elimination may be a significant challenge.

2. **SSM-TBV antigens formulated with other Plasmodia pre-erythrocytic or asexual-stage antigens** (e.g., RTS,S): This approach may have fewer ethical considerations, given the immediate, direct individual benefit it would provide. However, formulation challenges may result in a complex and expensive manufacturing process. In addition to the added value in terms of efficacy, tolerability, and immune response, non-inferiority would have to be demonstrated.

3. **SSM-TBV antigens formulated (in the same vial) with a vaccine against another disease**: One strategy is to formulate the SSM-TBV with an approved vaccine (e.g., group A meningococcal conjugate vaccine for use in Africa, or typhoid Vi conjugate for use in Asia). Another would be to combine it with a new vaccine. Either approach has the advantage of attacking two significant public health problems in a single inoculation and may also have a more simple clinical development process than an SSM-TBV alone. However, transmission-blocking efficacy, safety, and serological non-inferiority for the combination would need to be demonstrated.

4. **SSM-TBV antigens administered concomitantly with a second vaccine also intended for the target population**: Under this scenario, the two vaccine antigens would not be formulated in the same vial, and would thus require two inoculations. This option may be more economically feasible if manufacturing costs are a concern, but the same challenges would apply as for the SSM-TBV alone approach.

Feedback: While a stand-alone SSM-TBV would be more straightforward from a process development and manufacturing perspective, the potential synergy from adding additional target antigens to increase transmission blocking should be explored.

Acceptability

Focus: An important challenge facing the clinical testing and implementation of an SSM-TBV is how to communicate the individual benefits of vaccination. Historically, however, the malaria community has described an SSM-TBV as an altruistic vaccine, with no direct clinical benefit. The ethicists present at the workshop urged that this description be revised to explain the delayed individual benefit.

Feedback:

- There are precedents, such as the rubella vaccine and the mass administration of ivermectin against onchocerciasis, where individuals accepted the risk of an

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2 Acceptability of a TBV was not a scheduled session during the workshop, but discussion of this topic took place throughout the event. Hence, we have included a summary of those discussions.
intervention in order to benefit another target population. Other vaccines, such as polio, continue to be used in areas where immunized individuals are unlikely to be exposed, and their immunization contributes to community benefit via herd protection.

- Early education of prospective clinical trial volunteers, IRBs, ministries of health, national regulatory agencies, Expanded Programmes on Immunization, and national malaria control program managers and community members will be critical to establish the acceptability of an SSM-TBV for use as a public health tool against malaria in the push toward elimination. Additionally, community perceptions studies will play a central role in gauging and responding to public perception.

- Go/no-go criteria must be set such that maximally safe and immunogenic candidates are retained for further development, while ensuring that potentially promising candidates are not rejected due to overly stringent evaluation criteria.

- The generally accepted paradigm in vaccine development that human subjects agree to accept risk for the sake of generating knowledge that will benefit others also applies to an SSM-TBV. Important ethical considerations of developing an SSM-TBV include:
  - The social value of malaria elimination.
  - The scientific validity of trials, ensuring that data they yield can inform decisions.
  - The fair selection of subjects, understanding the vulnerability of particular groups.
  - Risk/benefit ratio: communicating the differences associated with an SSM-TBV.

### Next steps

At the end of the workshop, six areas (listed below) were defined as being essential to furthering development plans for an SSM-TBV. MVI convened internal working groups to address these issues raised during the workshop, drawing upon external expertise as appropriate.

- Clinical development plan and regulatory strategy.
- Assays and correlates.
- Baseline transmission measures and epidemiology.
- Product development and manufacture.
- Communications and ethics.
- Policy and implementation.