MALARIA VACCINE INITIATIVE

ISSUE BRIEF

Transmission-blocking vaccines (TBVs) against malaria

The need: Eradicating malaria

Meaningful gains against malaria have been made with interventions such as bed nets, indoor residual spraying, anti-malarial drugs, and diagnostic tools. Even as these efforts to control and eliminate malaria in some settings continue, the international community has set its sights on the long-term goal of eradicating the disease altogether. Key to eradication will be the ability to break the cycle of transmission of the malaria parasite between its human and mosquito hosts—a challenge faced by developers working on drugs, insecticides, and vaccines for malaria. A vaccine with the ability to prevent transmission of the parasite that causes malaria would be a critical tool for achieving the long-term goal of malaria eradication.

The PATH Malaria Vaccine Initiative (MVI) is leading the way to accelerate the development of promising malaria vaccines, including an innovative approach—a transmission-blocking vaccine (TBV)—that is designed to prevent mosquitoes carrying malaria parasites from spreading them. When used in conjunction with other malaria control tools, a TBV could help push a geographic region past the threshold of control to elimination, ultimately contributing to global eradication. Blocking transmission of malaria parasites is viewed as particularly important to malaria elimination and eradication efforts, including prevention of reintroduction of the disease.

TBVs are also referred to as vaccines that interrupt malaria parasite transmission (VIMTs). There are two types of VIMTs. A malaria vaccine that interrupts transmission from infected humans to mosquitoes is called a sexual, sporogonic or mosquito-stage VIMT (SSM-VIMT). This is in contrast to a pre-erythrocytic-VIMT (PE-VIMT), which interrupts transmission from mosquitoes to humans. A PE-VIMT targets infection when the parasite first enters a person.

The concept: Get rid of the parasite to provide "community immunity"

The survival of the malaria parasite depends on mosquitoes carrying it from one human to another—and on its ability to survive in humans. The cycle of transmission begins when a mosquito bites a person who has malaria. This infected mosquito transmits the malaria parasite when it bites another person. A TBV would break the cycle of parasite transmission by preventing the mosquito from transmitting the malaria parasite—even after the mosquito has fed on an infected person.

While a TBV, by itself, would not provide a direct and immediate benefit to the immunized individual against infection and illness, the vaccine would reduce the chances that other

individuals in the community get malaria. Over time, this approach would lower the probability that an immunized individual would contract malaria again.

In addition, a TBV given to an entire community—especially at one point in time—could drastically reduce the number of parasites traveling through the mosquito and back into another person. Over time, the numbers of mosquitoes and people carrying the parasite in a given community would decline. This, in turn, would steadily reduce the number of new malaria infections in that community and lead to "community immunity."

A TBV could become part of a comprehensive elimination and eradication effort by helping to drive parasite transmission to zero—especially in settings where other interventions have already had an impact. The immunity induced by a TBV would also be independent of user behavior even in the most challenging environments and no matter where the immunized person went. Such a vaccine could serve as a kind of "safety net," protecting populations whose natural immunity may have waned as exposure to parasites fell.

Why it would work: Mosquito behavior

A TBV would take advantage of the limited nature of malaria transmission patterns. Since mosquitoes usually stay within a mile of where they breed and hatch, transmission tends to be "focal," or specific to a limited area. Every person immunized with a TBV within a particular malaria hotspot would have the potential to decrease the number of parasites being transmitted by a mosquito to the next person. Simply put, a TBV would seek to drain what malaria experts call the "parasite reservoir" in a community and help prevent reintroduction.

The way forward: MVI's TBV strategy

MVI's goals for its TBV program focus on three critical product development areas: (1) conducting clinical studies to test whether targeting certain proteins or antigens in the parasite can prevent parasite transmission; (2) developing evaluation tools to support development of TBVs; and (3) working with regulatory authorities to identify the appropriate clinical development pathway for a vaccine of this type.

Clinical studies

In recent years, MVI has formed development partnerships to test several leading TBV antigens. Initial efforts centered on the effective transfer of these antigens from academic to product development partners and on establishing robust production processes. Today, MVI uses both preclinical and clinical studies to identify and evaluate those TBV approaches found to be promising and to apply the lessons learned across the portfolio.

New regulatory pathways

MVI and partners have consulted with the US Food and Drug Administration (FDA) to explore the development of a regulatory pathway for a proposed novel vaccine that does not confer immediate personal protection against malaria parasite infection.

Specifically, MVI and partners are exploring potential regulatory and policy approaches with the FDA and World Health Organization, respectively, for a stand-alone TBV that confers community immunity and for one that also protects the person immunized against the bite of a mosquito infected with the malaria parasite.[1] Since 2010, the FDA has consistently indicated that there is no legal barrier to the development of a TBV, even if it does not confer immediate, direct clinical benefit to the recipient.[2]

Tools to evaluate TBV performance

In an effort to demonstrate the potential efficacy and benefit of TBV candidates, MVI is also working with partners to develop evaluation tools, including assays and a human challenge model, specific to TBVs.

Feeding assays: Feeding assays are important evaluation tools that measure the impact of vaccine-induced antibodies on infection rates in mosquitoes that feed on blood containing infectious parasites. Criteria used to measure success would include a reduction in the number of parasites in the mosquitoes or a reduction in the number of infected mosquitoes—with the latter representing a more meaningful measure when looking at the impact on malaria elimination. Three assays have been identified as key in evaluating the ability of a TBV to block parasite transmission:

- Standard membrane-feeding assay: This assay uses laboratory-reared mosquitoes and a controlled, high number of cultured gametocytes—the lifecycle stage of the parasite responsible for transmission to mosquitoes—from a single parasite strain.
- Direct membrane-feeding assay: Mosquitoes feed on gametocytes collected from individuals infected with the malaria parasite.
- Direct-feeding assay: Mosquitoes directly feed on individuals infected with the malaria parasite. This assay is the closest to nature in terms of biting mechanism.

Challenge model: MVI is pursuing development of a novel human "challenge model"[3] for evaluating the efficacy of TBVs to prevent transmission of the malaria parasite from humans to mosquitoes. The adaptation and use of established controlled human malaria infection models will be instrumental in achieving MVI's development goals for TBVs. In the adapted challenge model, mosquitoes would be allowed to feed on blood from immunized and infected volunteers, either directly (skin feeding) or through a membrane, and then evaluated for the presence or absence of infection by parasites. The goal is to make determinations about feasibility and efficacy of antibodies against TBV antigens under controlled challenge conditions and therefore earlier in the clinical development process. This would enable vaccine developers to proceed to large field studies with a greater likelihood of success.

Looking ahead

Research and development for vaccines is a long and painstaking process that requires many rounds of testing to ensure safety and efficacy in specific populations. It is therefore difficult

to predict when a TBV would be available for use. At the same time, achieving the goal of malaria eradication requires a long-term vision, and MVI is actively pursuing partnerships to accelerate development of this novel intervention. A vaccine that can work in tandem with other interventions to break the cycle of malaria parasite transmission would be a critical tool in the battle against malaria.

1 Product Development for Vaccines Advisory Committee (established April 2014). World Health Organization Immunization, Vaccines, Biologicals Programme. Available at: www.who.int/immunization/research/meetings_workshops/pdvac/en/.

2 Nunes Julia K, et al., Development of a transmission-blocking malaria vaccine: Progress, challenges, and the path forward. *Vaccine*. 2014:32(43);5531–5539.

3 The malaria human challenge model: After a malaria vaccine candidate has been tested for safety in a small number of healthy adult volunteers, it may be put through a "challenge" phase of testing. Under this model, volunteers vaccinated with a malaria vaccine candidate are deliberately "challenged" with malaria—under controlled conditions—through the bite of malaria-infected mosquitoes to assess whether the candidate vaccine can prevent or delay malaria infection. The current malaria vaccine challenge model—developed for testing vaccines that prevent malaria infection—does not apply to TBVs, which are a novel type of vaccine that aim to prevent transmission of the malaria parasite to mosquitoes.