

MVI's strategy for developing a second generation of malaria vaccines

The PATH Malaria Vaccine Initiative's (MVI) research and development strategy represents a multi-pronged approach to developing a next-generation malaria vaccine that would support efforts to move beyond reducing malaria disease and death to the longer-term goals of elimination and eradication. Malaria caused by *Plasmodium falciparum*, the deadliest of the malaria parasites affecting people, is the principal target of MVI's efforts, due to the heavy toll of *falciparum* malaria in sub-Saharan Africa, where the bulk of malaria deaths occur.

Looking forward to the next five years, MVI's R&D efforts will focus on two priority areas: vaccines that prevent infection, and those that block or interrupt transmission—the latter aimed at stopping the parasite before it even enters the human body.

Currently, the world's most clinically advanced malaria vaccine candidate, RTS,S, is under development through an innovative partnership among PATH, GSK, and research centers across Africa. RTS,S is now undergoing regulatory review, following completion of a Phase 3 program in sub-Saharan Africa in early 2014. While the final results of the Phase 3 trials have yet to be published, initial results have shown the RTS,S vaccine candidate to reduce episodes of clinical malaria in infants and young children by between one-third and one-half, respectively, over one year of follow-up after the primary vaccination course. In mid-2014, results over 18 months of follow-up were published, which indicate continued efficacy, despite waning, in both age groups.

If the required regulatory approvals are obtained and public health information, including safety and efficacy data from the Phase 3 program, is deemed satisfactory, WHO has indicated that a policy recommendation for the RTS,S malaria vaccine candidate is possible in late 2015, paving the way for decisions by African nations regarding implementation of the vaccine through their national immunization programs.

Cultivating different approaches

However, the road to elimination and eradication of malaria requires additions to the current vaccine pipeline, and MVI has numerous, early-stage studies under way to develop the vaccine candidates of the future. Some seek to build on the success of RTS,S to date, while

others take different paths toward immunization. Only the most promising of these will advance to clinical testing, with key decisions being made based on the latest scientific evidence available. In all, MVI is supporting more than two dozen feasibility studies and the clinical development of six vaccine projects. MVI's more than 50 partners include academic and non-profit research groups, biotech and pharmaceutical companies, and US government agencies.

Since its founding, MVI has terminated dozens of projects, learning valuable lessons along the way—among them, the need for new targets on the malaria parasite. Today, several of MVI's early-stage projects are focused on identifying new pre-erythrocytic vaccine targets (antigens). Like RTS,S, these are anti-infection vaccines that aim to trigger the immune system to defend against the parasite as soon as it enters a person's bloodstream or infects liver cells. This prevents the parasite from infecting, maturing, and multiplying in the liver, so that there are fewer—or ideally no—parasites to reenter the bloodstream and infect red blood cells, and thus trigger symptoms of disease. MVI is also evaluating potential vaccines that would interrupt the cycle of parasite transmission between mosquitoes and humans, such as by preventing the parasite from maturing in the mosquito and thus making impossible its transmission back into a person. The benefit of such a vaccine to the person vaccinated would be delayed. It would confer community immunity to a susceptible population by significantly limiting the spread of infection.

While a much smaller part of the current portfolio, MVI has also supported vaccine projects that target the malaria parasite when it is most destructive: at the blood stage, when the parasite replicates rapidly in red blood cells. While highly efficacious blood-stage vaccines have the potential to prevent humans from being infectious to mosquitoes, and therefore serving a role in elimination, they are primarily being developed to decrease the number of parasites in the blood, reducing the severity of malaria. MVI has made limited investments in this area, but sees this effort as yielding additional components that could be combined with a pre-erythrocytic vaccine, for example, to further boost its effectiveness.

Taken together, MVI's vaccine development efforts are broadly consistent with the vision of the 2013 *Malaria Vaccine Technology Roadmap*, which calls for the development of vaccines that prevent disease and death, and prevent transmission to enable malaria eradication.

Developing tools to measure success

As new potential malaria vaccine candidates enter the pipeline, scientists need robust and consistent technologies to assess the potential efficacy of these approaches and thus decide which should advance through development. MVI continues to support the refinement and development of both laboratory tools and methodologies for evaluating vaccine candidates in humans, as well as reference centers to provide these services to scientists around the world. MVI supports one such reference center at the Laboratory of Malaria and Vector Research at the US National Institutes of Health, thereby enabling systematic comparisons of trial results for different vaccine approaches, including transmission blocking vaccines.

Continuing need for collaboration, flexibility

For more than a decade, MVI has worked with a wide range of partners and the numbers continue to grow. The program seeks collaborators both inside and outside the malaria research community, investing aggressively in approaches and technologies that are at earlier stages of

development. This approach involves many smaller investments in projects that are evaluated as quickly as possible for their feasibility, another way that MVI seeks to maximize efficiency and use of scarce resources.

This partnership-based approach has yielded positive results, as seen in the advancement of RTS,S through Phase 3 trials, the upgrading of clinical trial and research capacity in locations across Africa, and the decisions by several African countries to put in place mechanisms to facilitate informed decision-making on malaria vaccine use, once one becomes available.

Another key to MVI's continued success is its ability to shift resources among different projects in its portfolio as new data become available, thanks to the flexibility of MVI's donors and investors. This so-called portfolio approach allows for the sharing of information across projects, so that the lessons learned can inform overall vaccine development efforts. As a result, MVI is able to look for success across its entire R&D portfolio, rather than depend on the results from a specific project. And of course, MVI continues to be on the lookout for promising vaccine projects to add to the portfolio.

THE PATH MALARIA VACCINE INITIATIVE (MVI) is a global program established at PATH through an initial grant from the Bill & Melinda Gates Foundation. MVI's mission is to accelerate the development of malaria vaccines and catalyze timely access in endemic countries. MVI's vision is a world free from malaria. For more information, please visit www.malariavaccine.org.

PATH is the leader in global health innovation. An international nonprofit organization, we save lives and improve health, especially among women and children. We accelerate innovation across five platforms—vaccines, drugs, diagnostics, devices, and system and service innovations—that harness our entrepreneurial insight, scientific and public health expertise, and passion for health equity. By mobilizing partners around the world, we take innovation to scale, working alongside countries primarily in Africa and Asia to tackle their greatest health needs. Together, we deliver measurable results that disrupt the cycle of poor health. Learn more at www.path.org.

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