# In the Public Eye

## Beyond Our Borders

### Are we there yet? The road to a malaria vaccine

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**Summary points**

- Malaria kills three children per minute in developing countries and contributes substantially to economic underdevelopment
- Although a complex challenge, developing a safe, effective, and long-lasting malaria vaccine is feasible
- The return on any industrial investment in malaria vaccine development is uncertain, so major public sector investment is required
- The Malaria Vaccine Initiative is using focused funding and partnerships to accelerate the development and availability of promising malaria vaccine candidates
- Vaccine developers in many countries are advancing several promising malaria vaccine candidates; one or more could be ready for introduction in about a decade

Every minute, a parasite transmitted by *Anopheles* species mosquitoes kills three children. Every day, 2.4 billion people in 100 countries—40% of the world's population—are at risk of this infectious disease.[1] Malaria causes fever, shaking chills, anemia, and fatigue; in its severest form, it can cause coma and death.[2] Every year, it affects 300 to 500 million people worldwide, killing 700,000 to 2.1 million, mostly children and mostly in Africa (figure 1).[3]

This disease is not new, "fashionable," or emerging. Its vector lives well in much of the world, including the United States. The long-term consequences of malaria—chronic anemia; debilitating recurring infection; and renal, liver, and central nervous system impairment—mean that endemic countries spend many of their limited resources on combatting the disease and its aftermath. Malaria is directly associated with profound economic deprivation. The Malaria Network, a partnership of the World Bank and World Health Organization, estimated that in 1997, direct and indirect expenditures for malaria cost sub-Saharan Africa more than US$2 billion.[4]

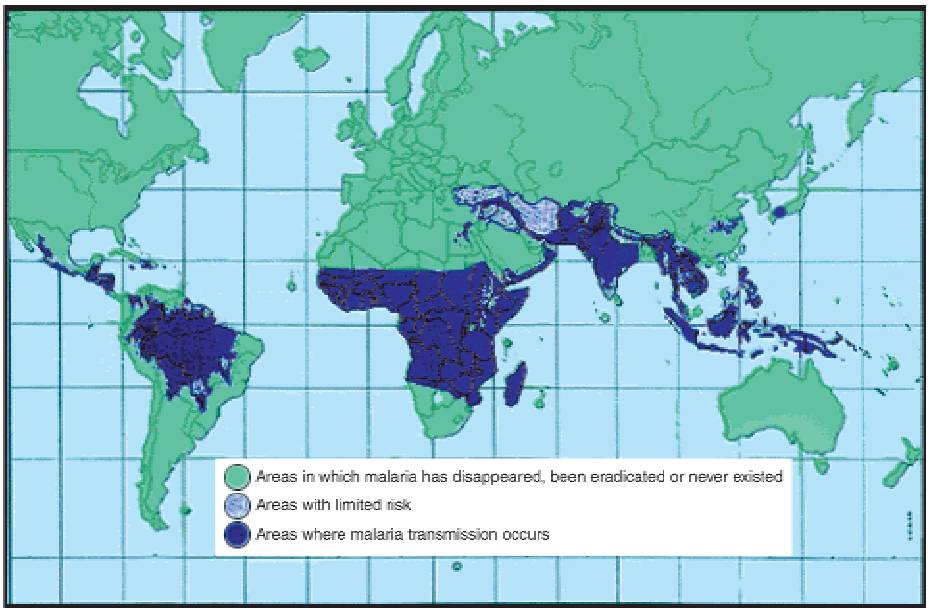


Figure 1 Malaria is endemic in more than 40 countries

Whereas malaria has been earmarked by the United Nations and the global health community as one of the three big infectious disease killers—along with HIV/AIDS and tuberculosis—and thus a priority for action, it has not received the attention needed to effect change. Spearheaded by Roll Back Malaria, countries currently employ limited tools that include insecticide-treated bed nets, antimalarial drugs, and vector control measures that have sometimes been controversial, such

as the use of DDT, a highly effective but harmful pesticide. As a package, these are thought to be cost-effective and to have significant effects where well implemented.[5,6]

The disease, however, is a worthy adversary and has evaded many of the tools that at one time could control it. Drug resistance by the parasite, pesticide resistance by the mosquito, and community resistance to interventions that require continuous financial and human resources point to the nature of the challenge. An effective vaccine that could safely prevent infection, disease, or transmission would add immensely to this armamentarium.

Although no licensed vaccine against a parasitic disease exists, vaccines should be viewed as a critical part of the solution. Vaccines have been used extensively to control many previously common diseases, making vaccination one of the most effective and cost-effective public health interventions known.[7]

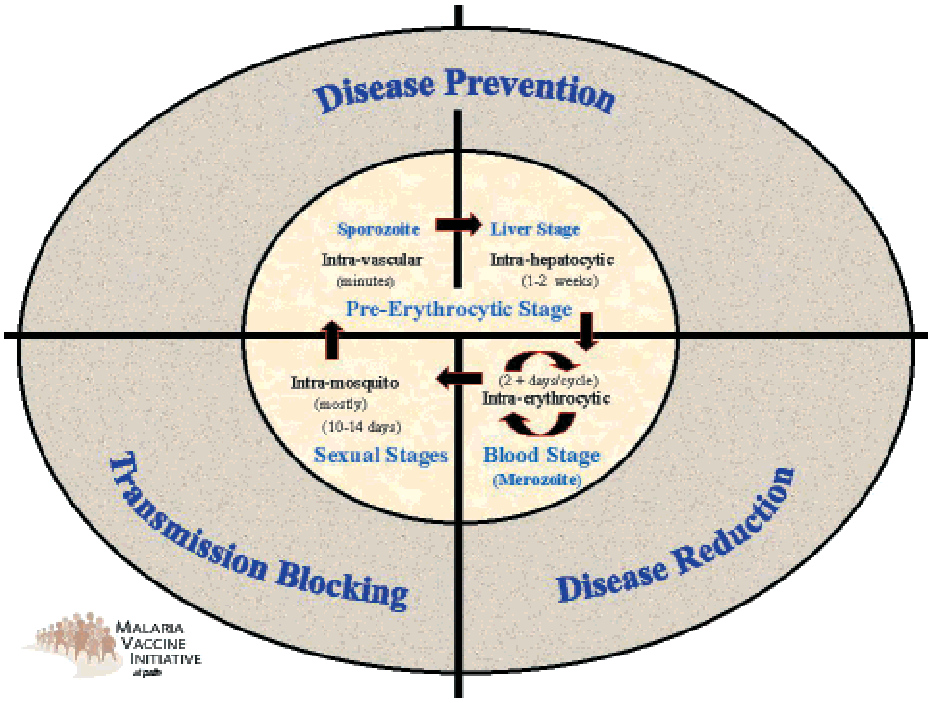


Figure 2 Life cycle of the malaria parasite: possible vaccine targets and how a vaccine would affect disease

## A MALARIA VACCINE IS FEASIBLE

Paradoxically, the very complexity of the parasite's life cycle that presents a considerable challenge for vaccine development also presents multiple opportunities to attack the parasite (figure 2). Several observations indicate that humans can, indeed, generate such an immune response. First, people living in endemic areas gradually develop resistance to disease, despite active parasitemia.[8] Second, experiments by New York University investigators in the 1970s demonstrated that irradiated sporozoites generate protective immune responses.[9] Third, candidate vaccines have been recently demonstrated to prevent disease for a short time, both in human studies and in endemic areas.[10]

Thus, the critical question is not whether an immune response can prevent disease, but how to increase the breadth and scope of that protection. A number of strategies can be reasonably pursued—varying the target antigens, the platform for presenting antigens to the immune system, and the technology for strengthening the immune response. Even with this, before 1998, rigorous efforts to assess malaria vaccine candidates had dwindled. Promising approaches languished in research laboratories without adequate resources for their evaluation in humans.

## THE DOG THAT DIDN'T BARK: WHO DIDN'T MAKE THE VACCINES?

Traditionally, a symbiotic partnership between academia and pharmaceutical companies has allowed for great ideas from the laboratory to find their way to products in the pharmacy. What drives this process, however, is the perception that after an expensive and long development process (perhaps $300 million and 20 years), there is a market that will eagerly purchase the product. Instead, vaccines primarily for a developing-world population would require a large production volume, entailing substantial capital investments for a relatively low return per dose. This does not offer the touted necessary incentive for the return on investment sufficient to spur development (figure 3). The possible market for malaria vaccines may be—or is perceived to be—different from that for commercially successful vaccines, whose primary market is in the United States and Europe. Public investment of targeted funding can alter the balance of interests—of the public and private sector—and allow both large and small companies to invest their own technologies and staff in pursuit of antimalarial vaccines.

## MALARIA VACCINE INITIATIVE

In 1999, the Bill & Melinda Gates Foundation granted Program for Appropriate Technology in Health funding to create the Malaria Vaccine Initiative. The initiative's mission is to accelerate the development of malaria vaccines and ensure their availability and accessibility for the developing world. The initiative evaluates possible candidate antigens and approaches, considering not only the scientific approach but also the vigor of the business development plan, allied resources, product development strategy, and commitment of the organizations' leadership. Each focused vaccine development project is a varying mix of partners from industry, academia, and government. Through directed funding, the Malaria Vaccine Initiative supports the development of quality, well-characterized candidate vaccines in robustly powered studies and trials.

Cited as a possible predictor of future efficacy in humans, various vaccine candidates can induce protective immunity against primate malaria.[8] Progress will depend on the evaluation of preliminary efficacy in trials conducted in areas where malaria is endemic

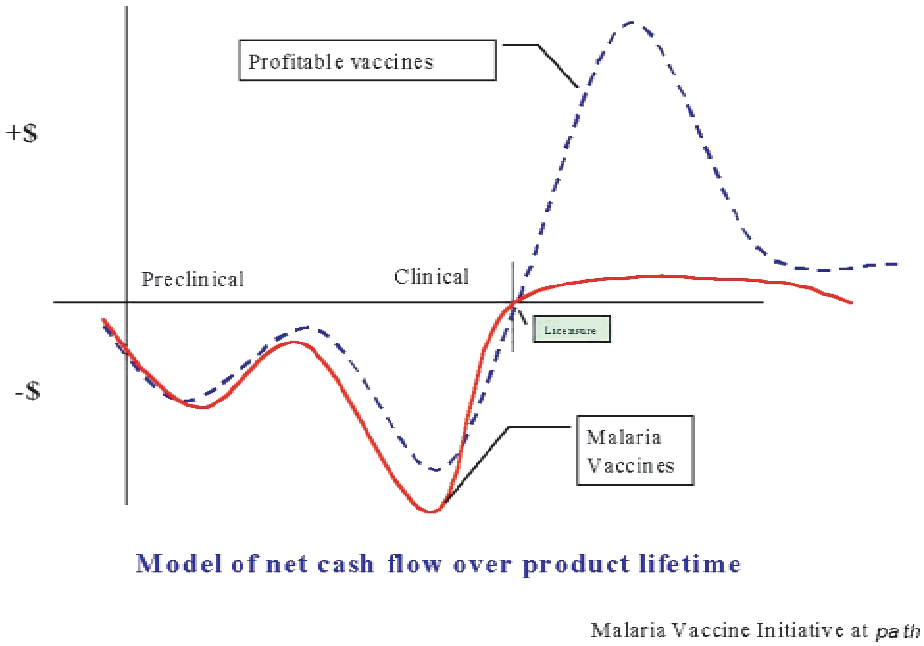


Figure 3 Anticipated return on investment normally drives vaccine development

until a credible, validated proxy for efficacy (a serologic correlate) is found.

Not only do Malaria Vaccine Initiative projects advance the development of each candidate, but discussions with partners and the broader public health financing community also set the stage for future access to these vaccines if development succeeds. Access is defined first by access to a technology by the malaria vaccine developers; second, by creation of a licensed product; third, by manufacturing capacity sufficient to reach the target population; and last, by delivery mechanisms to deliver the product to those at risk of disease. Working with other partners such as the London School of Tropical Hygiene, the US Agency for International Health, and the National Institutes of Health, the Malaria Vaccine Initiative is independently assessing the possible global market for malaria vaccines and the market forces that will affect procurement of eventual vaccines. It would be a tragedy indeed if a credible vaccine were left in storage because of inadequate planning for financing its procurement and delivery. The creation of new health purchase funds (such as the Vaccine Fund and the Global AIDS, Tuberculosis, and Malaria Fund) for the developing world is an important element of malaria vaccine development. The success of efforts such as the Global Alliance for Vaccine and Immunization will increase our ability to deliver vaccine to the most fragile and difficult-to-reach populations in Africa, Asia, and Latin America.

## ARE WE THERE YET?

The good news is that several vaccine development efforts are underway. Projects and partnerships are working on several antigens in a variety of formulations using assorted platform technologies. Malaria Vaccine Initiative partners are developing recombinant proteins, viruslike particles, and a viral vector strategy that uses one vaccine to prime the immune system and a second to boost the immune response. They are also evaluating vaccines with novel adjuvants. The most advanced candidate resulted from a long-term collaboration between SmithKline Beecham (now GlaxoSmithKline) and Walter Reed Army Institute of Research; that vaccine is currently in small trials conducted by the United Kingdom's Medical Research Council unit in The Gambia. The Malaria Vaccine Initiative and other global partners, such as the US Agency for International Development, the European Community, and the National Institutes of Health, plan trials of additional candidates over the next few years.

This sounding of future progress is balanced by the need for realism. Success will be neither quick nor simple. Although it may be possible that a single-antigen or single-vaccine strategy would prevent a large amount of disease, combining several antigens for a more powerful vaccine will more likely be required. The potential for iterative Phase 2 trials required to make a combination vaccine will add to the possible time frame for success. A single-antigen vaccine is feasible this decade. An efficacious combination vaccine could take longer.

The partners in the Malaria Vaccine Initiative believe that, with new resources, growing global concern, and mounting commitment to a "global health" agenda, progress will be made over the next decade. As they emerge, future approaches based on unraveling the malaria genome and the ability to finely target the human immune system must be incorporated into vaccine development. Although the end is not yet in sight, the path to measurable and credible progress is clear.

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