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Perspective

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Betting on a Malaria Vaccine

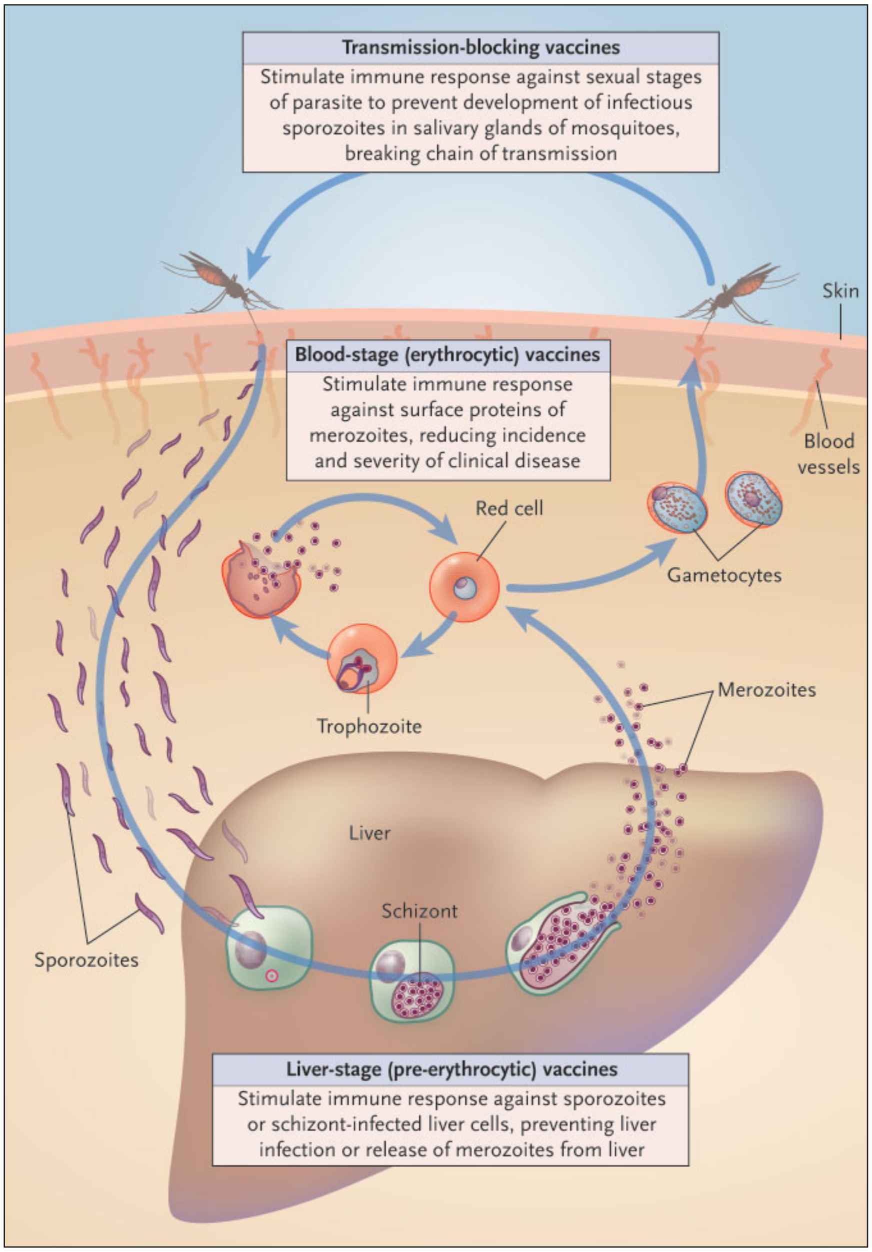
Susan Okie, M.D.

Sometime within the next two years, clinical researchers are expected to begin inoculating at least 2000 African infants in the largest trial ever undertaken of an experimental vaccine for malaria.

The planned efficacy trial will mark a milestone in the multidecade effort to make a vaccine against one of the world's greatest killers of children. It also represents a high-stakes gamble for the company hoping to license the product, GlaxoSmithKline Biologicals, as well as for funding agencies and the international research community. If the vaccine — known as RTS,S — is found to reduce significantly the rates of death and severe illness in children with malaria, it will be viewed as a public health triumph. An expensive failure, on the other hand, could slow progress toward controlling the disease.

Malaria causes at least 1 million deaths per year, most of them of children younger than five years of age in sub-Saharan Africa who are infected with the parasite *Plasmodium falciparum*. Although child mortality in Africa has declined in recent years, malaria's share of that mortality has increased because of the spread of drug-resistant strains of the parasite, the breakdown of health services in many affected areas, the interaction of the disease with human immunodeficiency virus (HIV) infection, and possibly the effects of climate change.[1] Infants and young children with malaria often die from severe anemia, cerebral involvement, or prostration caused by overwhelming infection; many newborns die from complications of low birth weight caused by maternal malaria during pregnancy.

Yet a protective immune response eventually develops in people who survive repeated bouts of malaria during early childhood. In the geographic areas with the highest malaria rates, most deaths occur among children younger than two years of age, and most cases of severe disease among children younger than five or six years of age. Older people in such areas, although almost universally harboring the parasite in their red cells during seasons of high transmission, rarely become clinically ill. Transfusion of serum from adults with acquired immunity to the disease can reduce the severity of parasitemia in infected children, and researchers reported in 1973 that a vaccine made from whole malaria parasites killed by irradiation could protect healthy persons from infection. Although manufacturing large quantities



Vaccine Targets in Malaria.

Liver-stage vaccines are designed to prevent malaria infection, but they must be 100 percent effective to protect people with no natural immunity (such as soldiers and travelers). They include vaccines containing whole killed sporozoites and those based on antigenic portions of sporozoite proteins. Most blood-stage vaccines seek to elicit antibodies to merozoites (the blood-cell–infecting stage of the parasite), since in people with natural immunity, such antibodies are associated with protection from clinical illness. Variability of blood-stage antigens among parasite strains has complicated vaccine development. Transmission-blocking vaccines would not protect the recipient but could help to prevent the spread of malaria. Sexual-stage parasite antigens are complex and have been difficult to produce. Multistage vaccines target antigens from multiple stages of the parasite's life cycle. Some malaria researchers believe such a cocktail may be necessary for high efficacy, but these vaccines are complicated and expensive to make.

of a whole-parasite vaccine was judged at that time to be impossible, the discovery spurred efforts to make a practical malaria vaccine.

Since then, scientists in many countries have been working — until recently, on lean budgets — to develop a vaccine that could prevent malaria infection or at least reduce the frequency of severe illness and death among infected persons (see diagram). As Louis H. Miller, cochief of the Malaria Vaccine Development Branch at the National Institute of Allergy and Infectious Diseases, explained the goal for a pediatric vaccine, “We want to make a young child be like an older child” in the way that the host's immune system responds to the parasite.

From time to time, initial clinical testing of a vaccine has yielded promising results, and reports predicted that an effective vaccine for malaria was only a few years away. In each instance, the early findings have not held up, and veterans in the field have grown wary of over-optimism. “Watching this story for 30 years now, it goes up and down like a malaria fever chart,” said Brian M. Greenwood, a professor of tropical medicine at the London School of Hygiene and Tropical Medicine.

Now, the fever is rising. In recent years, worldwide funding for malaria vaccines has increased from less than \$50 million per year to about \$70 million, in part because of the 1999 establishment by the Bill and Melinda Gates Foundation of the Malaria Vaccine Initiative, as part of the Program for Appropriate Technology in Health (PATH–MVI). (Other major funders of such research include the National Institutes of Health, the European Malaria Vaccine Initiative, the European Commission, and Britain's Wellcome Trust.) The mission of PATH–MVI is to break through barriers that have impeded the commercial development of malaria vaccines and to help in the manufacturing and larger-scale testing of candidates that look promising in pilot studies.

Since 2001, PATH–MVI has contributed about $10 million toward the upcoming efficacy trial of RTS,S. It is also funding 15 other vaccine projects and has influenced the priorities of other sponsors, so that the number of vaccines entering clinical trials has greatly increased. In addition, it has been instrumental in bringing together funding agencies and researchers to agree on a Malaria Vaccine Technology Roadmap that lays out strategic goals for developing malaria vaccines. A July 2005 draft (www.malariavaccineroadmap.net) sets an interim goal of licensing a malaria vaccine by 2015 that has a protective efficacy of more than 50 percent against severe disease and death, with protection lasting longer than one year; the goal for 2025 is a licensed vaccine with 80 percent efficacy lasting longer than four years. "I think those are realistic goals," said Greenwood.

Malaria researchers are heartened by the increased funding and public attention to the disease, but not everyone agrees that the roadmap's timetable is realistic. Pierre Druilhe of the Institut Pasteur in Paris points out that scientists still know little about which components of the natural immune response to malaria confer protection against disease. "It's not a technological problem or a money problem, it's a knowledge problem," Druilhe said. He noted that the malaria parasite is a complex organism containing some 5300 separate proteins, yet 60 percent of the almost 100 vaccines under development are based on just 4 of those proteins.[2] If none of these vaccines prove effective, Druilhe said, "the danger is that in the end people will say, 'Oh, a malaria vaccine is not feasible,' whereas it might have been feasible" if different components had been used.

No malaria vaccine has ever progressed as far along the road to manufacture and licensing as RTS,S has. Developed over the course of two decades, it contains a polypeptide chain corresponding to part of the circumsporozoite protein, a major cell-surface protein found on the form of the parasite that is injected into the bloodstream by mosquitoes. This chain is fused to the hepatitis B surface antigen, creating a hybrid molecule called RTS. The vaccine also contains a separate polypeptide (S) corresponding to the hepatitis B surface antigen, as well as proprietary adjuvants developed by GlaxoSmithKline to stimulate an immune response. The company hopes to license the vaccine (under the brand name Mosquirix) to protect young children against both malaria and hepatitis B. Ideally, it would be given as part of the routine childhood immunization regimen in order to improve the chances of providing the vaccine to all African infants who are at risk for malaria — a formidable logistic and financial challenge.

In a pilot study involving 360 Gambian men,[3] the vaccine's efficacy in protecting against malaria infection was only 34 percent overall, and protection rates had waned to 0 by the end of the 15-week follow-up period. In a larger double-blind efficacy trial conducted in Mozambique,[4] about 2000 children one to four years of age were assigned to receive three doses of either RTS,S or a control vaccine. The primary end point was the time to the first episode of symptomatic *P. falciparum* malaria during a six-month surveillance period; the vaccine's efficacy in preventing clinical malaria was 29.9 percent. However, only 11 of 745 children in the RTS,S group had at least one severe episode of malaria, as compared with 26 of 745 children in the control group — demonstrating a 57.7 percent relative efficacy rate against severe disease. Because of the short follow-up period and the seasonality of malaria transmission in Mozambique, it is not clear how long this protection lasts.

Since RTS,S was not particularly successful at reducing the rate of mild episodes of fever, the finding that it appeared to reduce the rate of severe disease came as a surprise. Although the incidence of severe illness was not a predefined end point of the study, W. Ripley Ballou, vice president for emerging diseases vaccines at GlaxoSmithKline Biologicals, said that the unusual intensity of malaria transmission during the trial period led to enough severe cases to produce a statistically significant result. Ballou said that the vaccine may have an effect somewhat like that of insecticide-impregnated bed nets, which do not completely prevent malaria transmission but which, because they reduce the number of mosquito bites, do reduce the frequency of clinical illness and death. "We feel very secure that we had a very real impact on an important medical end point in this trial," he said.

The company is currently conducting studies in Africa to determine the optimal dose and schedule in infants and is gearing up to manufacture enough vaccine for a large phase 3 trial. "Our hypothesis is that reducing the infectious burden by vaccination during the first year of life will lead to a substantial reduction in the incidence of severe disease and . . . a reduction in the number of deaths," Ballou said. "A vaccine that would reduce severe disease by 50 percent would be a huge success." Nevertheless, the decision to move ahead with a full-scale pivotal trial is risky, scientifically and financially. "Vaccines fail," said Melinda Moree, director of PATH–MVI. "We could take this forward, and it could be that it doesn't show the kind of impact that we're looking for."

An effective malaria vaccine has proved elusive because the malaria parasite, like *Mycobacterium tuberculosis* and HIV, has developed elaborate strategies to evade detection by the immune system. "The parasite has evolved to a stage where it's got antigens that are not particularly immunogenic," explains Adrian Hill, a professor of human genetics who studies malaria at Oxford University. "That's how it has survived millions of years." Among people who live in areas where malaria is endemic, natural protection against clinical disease apparently depends on maintaining high levels of antibody to multiple antigens present on the form of the parasite found in the bloodstream. Vaccines based on some of these "blood-stage" antigens are being developed, but the work has proceeded slowly because the proteins are highly variable and have been difficult to produce.

In contrast to the whole-parasite approach, most vaccines contain portions of only one or two malaria proteins, to which they must somehow induce a vigorous T-cell or antibody response. Hill's group uses an unusual strategy called "prime–boost," in which malaria antigens are combined with one or more attenuated viruses in order to stimulate a powerful T-cell response. A trial of one such vaccine in Gambian adults failed to reduce the natural infection rate,[5] but Hill and his collaborators are currently testing a more promising formulation, using a fowlpox virus and a modified vaccinia virus as serial vectors, in 400 Kenyan children. "We're beginning to build a picture that it's central memory T cells" that may correlate best with long-term protection by a vaccine, he said.

Other vaccines being tested include some containing multiple antigens from different stages of the parasite's life cycle, one based on whole killed parasites, like the vaccine that proved effective in the 1970s, and transmission-blocking vaccines designed to induce an immune response against the stage of the parasite that develops inside the mosquito. Members of this last group are considered "altruistic" vaccines, because they would not protect the recipient but would prevent that person's blood from infecting a mosquito, thus preventing transmission of the parasite to someone else.

Once a malaria vaccine is licensed, there will still be the problem of paying for it: the children who make up the potential market live in some of the world's poorest countries. At the G8 Summit in Gleneagles, Scotland, this past July, representatives of donor countries expressed support for advanced purchase commitments to encourage vaccine development, and British chancellor of the exchequer Gordon Brown has promised that his government would pay £300 million to prepurchase a malaria vaccine if one is licensed. Last June, President George W. Bush also called on Congress to appropriate $1.2 billion in new funding over five years to reduce malaria deaths in Africa.

Public health experts emphasize that even if a vaccine becomes available, reducing malaria's toll will continue to require drugs, bed nets, mosquito-control efforts, and other measures. To be cost-effective, a vaccine would probably need to protect infants and toddlers for at least two or three years. Perhaps, during this period, episodes of low-level infection would allow children to develop longer-lasting natural immunity. "If [RTS,S] costs, say, $10 and it gives you three or four months' protection, then that really is not a viable option," said Brian Greenwood. Nevertheless, he and other veterans of the research effort say they feel more hopeful than ever before. Greenwood ventured a prediction: there will be a vaccine in use that gives at least partial protection against malaria by 2015, "but we don't know which one it will be and whether it will be affordable."

Dr. Okie is a contributing editor of the *Journal*.

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Beyond Red Lake — The Persistent Crisis in American Indian Health Care

Yvette Roubideaux, M.D., M.P.H.

On March 21, 2005, at the high school on the Red Lake Indian reservation in Minnesota, a troubled American Indian teenager went on a shooting rampage, killing nine people before turning the gun on himself. Most of the news reports highlighted his past, including a history of depression and suicide attempts, and the daunting socioeconomic conditions in his reservation community. Reporters mentioned high rates of poverty, alcoholism, unemployment, and violence among young people as possible factors in the tragedy. Although similar events have occurred in wealthier communities — the shootings at Columbine High School in Littleton, Colorado, leap to mind — this calamity seems to have reminded our country that many American Indian and Alaska Native communities face deep-rooted challenges every day and continue to be affected by significant socioeconomic and health disparities.

An American Indian physician, I spent three years in the 1990s working in an Indian Health Service hospital in rural Arizona and witnessed the harsh realities of life on an Indian reservation. Having spent 11 years in Boston for my education and training, I felt I was embarking on a great adventure as I drove the desolate stretch of highway that led to the reservation. As I entered it, however, I noticed a change in scenery. Scattered along the road were small houses in various states of disrepair, often with litter and beer cans scattered about the high desert landscape around them. Even some of the newer homes had wooden outhouses close by, and small children played in a yard full of trash and abandoned cars. Some of these houses, no larger than 500 square feet at best, had at least six cars parked in front of them, and as I later discovered, many housed more than one family.

As I drove into the center of town, I found that the main street was only about three blocks long. The town center was framed by the elementary school, the hospital, a small café, a grocery store, tribal offices, and an abandoned gas station. I breathed a sigh of relief when I arrived at the hospital and spotted the government-owned houses for hospital staff across the street — in much better condition than the homes I had passed on my way into town. Driving into this community, I was reminded of my family's visits to my grandmother on an Indian reservation in South Dakota, but the poor living conditions had not been as striking to a child as they were to a physician.

During a brief orientation, my supervisor described the community of approximately 10,000 people and the challenges it faced. The unemployment rate hovered around 80 percent, and alcoholism, substance abuse, injuries, accidents, and violence were common. National statistics show persistent disparities in socioeconomic conditions between the people who live on most Indian

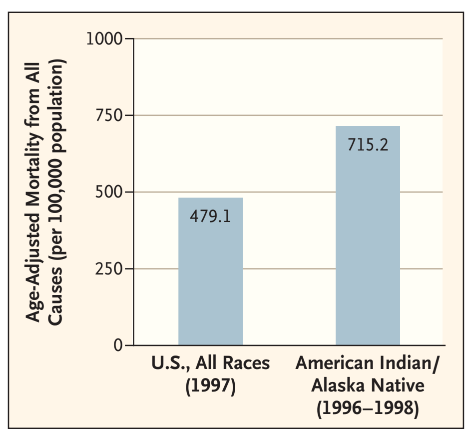

Figure 1. Disparities in Mortality Rates.
Data are from *Trends in Indian Health, 2000–2001.*[1]