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Producing A Successful Malaria Vaccine: Innovation In The Lab And Beyond

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ABSTRACT With approximately 225 million new cases and 800,000 deaths annually, malaria exacts a tremendous toll—mostly on African children under the age of five. Late-stage trials of an advanced malaria vaccine candidate—which, if approved, would become the world’s first malaria vaccine—are under way, and it may be ready for use by 2015. This article recounts the pivotal roles in that achievement played by collaborations of nonprofit organizations, pharmaceutical companies, private and public donors, and countries whose citizens would benefit most directly from a vaccine. Just as it takes a village to raise a child, it has taken a huge number of stakeholders around the world to reach this point. Developing even more effective vaccines for malaria and other diseases will require continued hard work and creative thinking from scientists, regulators, and policy makers.

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Malaria has afflicted humankind for millennia, killing—among many others—an Egyptian pharaoh, a Roman emperor, and the poets Dante Alighieri and Lord Byron. Eight American presidents, including Theodore Roosevelt and John F. Kennedy, had at least one bout of malaria. Today malaria affects the health and wealth of many of the world’s most impoverished nations.

More than one-third of the global population is at risk of contracting malaria. Each year the disease sickens 225 million people and kills nearly 800,000, with the vast majority of deaths in African children under age five.¹ Malaria is responsible for about 10 percent of Africa’s entire disease burden; it inflicts severe economic consequences on the continent, accounting for up to 40 percent of public health expenditures, 30–50 percent of inpatient admissions, and up to half of outpatient visits. A high incidence of malaria can reduce a country’s economic growth rate by 1.3 percent a year.²

The first campaign to eradicate malaria, launched by the World Health Organization in

1955,³ led to the disease’s elimination from many countries in the Americas, Europe, Asia, and Oceania. It was based on extensive use of DDT as an insecticide and chloroquine as the drug of choice for treatment and prevention. Multiple factors led to the cessation of this campaign. They included growing resistance to chloroquine and a decline in political and financial support in the 1960s—in particular from the United States, the primary funding source at the time.⁴ Malaria came back with a vengeance in Asia and remained a serious problem in Africa.

What Having A Malaria Vaccine Would Mean

The availability of substantial financial resources over the past five years or so—as well as the coordinated use of existing malaria interventions, such as insecticide-treated bed nets, indoor residual spraying of insecticides (meaning that the insecticide’s intended impact lasts after the spraying), and drugs to treat patients—has reduced illness and mortality in many regions where the disease is endemic. Funding has come

from international organizations such as the World Bank and the Global Fund to Fight AIDS, Tuberculosis, and Malaria; bilateral donors, including the US President's Malaria Initiative; and other sources.

But no existing intervention has been shown to be completely effective in preventing malaria infection and disease. Vaccines are widely viewed as a critical missing tool.⁵ After all, vaccination is considered one of the most important modern medical advances, and the most important one for preventing infectious diseases.⁶ In the last century, vaccines saved more lives than any other health intervention.⁷ Today they prevent more than two million deaths each year.⁸

One malaria vaccine candidate is currently undergoing Phase III trials. It is known as RTS,S, an abbreviation for the names of the vaccine's key chemical constituents. Still another generation of vaccines is now in the very early stages of development. These have as a goal eradicating malaria—an objective that will require developing a vaccine that effectively ends the parasite's life, thereby stopping the cycle of transmission that depends on sequential infection of human and mosquito hosts. In effect, the target of these vaccines shifts from protecting individual humans against disease to ending the cycle of transmission.

There are now two leading vaccine strategies aimed at blocking transmission. They focus on inducing immune responses that target the parasite when it is at its most vulnerable—that is, when there are fewest of it—at the point of transition either from mosquito to human or from human to mosquito. Should these vaccines ultimately prove successful, eradication will depend on achieving high vaccination rates across a broad population and on using a vaccine in conjunction with other interventions, such as insecticide-treated bed nets. Also, the vaccines will need to be safe, inexpensive, and easy to use with people of all ages.

This article describes the recent history of the discovery and development of malaria vaccines; chronicles successes to date; and focuses on scientific, regulatory, and other hurdles that must be overcome to develop a new generation of vaccines that could help eradicate the disease.

Barriers To Vaccine Development

Efforts to develop a vaccine for malaria face two distinct challenges. One is the scientific challenge of producing a vaccine against a parasite, *Plasmodium falciparum*, that changes form as it moves between and through its human and mosquito hosts—and that also has more than 5,000 genes⁹ that may vary from one parasite to

another.

The second challenge is the absence of a market that is lucrative enough to attract private-sector drug manufacturers. Malaria primarily afflicts people in poor, developing countries. This lack of a market “pull” was a key factor in the 1999 creation of the Malaria Vaccine Initiative at PATH (a nonprofit organization based in Seattle, Washington, that focuses on global health and that was formerly named the Program for Appropriate Technology in Health).

In addition to providing funds and thus increasing the “push” toward the development of a vaccine, the initiative acts as a product development partner with other private- and public-sector organizations around the world that are trying to produce a vaccine for malaria. The initiative provides scientific, managerial, and other technical support, as well as applying private-sector portfolio management practices to the development process.

The PATH Malaria Vaccine Initiative was founded on the premise that promising vaccine concepts already existed, but they needed help getting out of the laboratory and on a path toward clinical trials. Indeed, a number of academic and governmental organizations and pharmaceutical companies had been working on vaccines for malaria. However, progress was hampered either by insufficient funding—because neither government nor academic institutions typically undertake large-scale manufacture or late-stage clinical development of medicines—or by the lack of a market “pull,” a disincentive for the private sector.

For example, US military laboratories have long been at the forefront of malaria vaccine research, and a collaboration between the Walter Reed Army Institute of Research and what is now GlaxoSmithKline Biologicals worked on early stages of the development of RTS,S. Research at Walter Reed and the Naval Medical Research Center now continues under the US Military Malaria Vaccine Program, which has collaborated with the PATH Malaria Vaccine Initiative on a number of projects.

In its first decade, the initiative evaluated existing vaccine approaches on which work was progressing slowly and terminated support for many projects as a result of its evaluation. As other approaches failed in the lab or in early clinical trials, a leading candidate emerged: RTS,S. Phase II studies of the candidate vaccine indicated that it had an additive impact. In other words, when used in combination with current interventions, it increased the cumulative effect on the prevention of infection and the treatment of clinical malaria—loosely defined as the phase of disease that begins seven to eighteen days

after infection and results in symptoms such as fever.¹⁰ That candidate vaccine has now moved into a pivotal Phase III study.

Hope On The Horizon?

RTS,S is the culmination of forty years of research, and it has generated considerable optimism that a malaria vaccine may finally be on the horizon. Ruth and Victor Nussenzweig conducted work at New York University in the 1960s and 1970s that resulted in the identification of a key protein on the surface of the malaria parasite, which the Nussenzweigs then reproduced and tested in animals and humans. Work on this approach was continued at Walter Reed in collaboration with GlaxoSmithKline.

A critical hurdle at that point was to increase the immune response. Key to success here was the decision by GlaxoSmithKline scientists, led by Joe Cohen, to include in the malaria vaccine a component of the company's hepatitis B vaccine, to help boost the body's immune system. Later the company scientists also added a proprietary adjuvant system—adjuvants are frequently added to vaccines to enhance the body's immune response.¹¹

Clinical trials of RTS,S began in adults in the United States in 1992 and in Africa in 1998. A Phase II trial initiated in 2003 with more than 2,000 children ages 1–4 years in Manhica, Mozambique, found that the vaccine reduced the risk of clinical malaria by 35 percent, and the number of cases of severe malaria by 49 percent, thereby providing initial evidence of RTS,S's efficacy in young children.^{12,13} A follow-up study demonstrated that the vaccine may protect against malaria for up to forty-five months.¹⁴ And another trial with infants ages 10–18 weeks showed that the vaccine worked with that age group, too.¹⁵

Two other important studies were published in December 2008.^{10,16} The first showed that RTS,S reduced the risk of clinical malaria by half in children ages 5–17 months. The second demonstrated that the vaccine was efficacious in infants ages 8–16 weeks and could safely be administered together with commonly used childhood vaccines. Simultaneous administration is critical because it would allow RTS,S to piggyback onto established immunization regimes in African countries, sparing nations as well as parents the burden of a separate vaccine schedule.

The positive results of the Phase II studies led to the launch of a large-scale Phase III efficacy trial in May 2009. A Phase III trial—critical for regulatory approval—aims at confirming with more accuracy both the safety of an intervention and the level of protection that previous trials

have demonstrated. Eleven trial sites were chosen for RTS,S, all in sub-Saharan Africa. The sites—in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania—finished enrolling more than 15,000 infants and young children in January 2011.

The results will be reported in three stages, with initial findings for children ages 5–17 months expected in late 2011. If Phase III results confirm the safety and efficacy of the vaccine, the World Health Organization has indicated that a recommendation on the use of RTS,S is possible as early as 2015. That would pave the way for countries where malaria is endemic to decide on vaccine approval, adoption, and implementation through their expanded programs on immunization, which collectively aim to ensure full and routine immunization of young children worldwide.

Innovation As A Measure Of Success

Ultimately, the success of any malaria vaccine will be measured by reductions in illnesses and deaths due to the disease and by the resulting decrease in economic burden. Obviously, these outcomes cannot be fully assessed until a vaccine has been introduced. An earlier measure of success is the innovative thinking that has already characterized the process of developing a malaria vaccine. Examples include RTS,S's design and plans for its clinical development—in particular, the vaccine candidate's chemical makeup and the phased enrollment of older, then younger, children in a single, large efficacy trial in Africa.

More broadly, innovation in malaria vaccine development has also included the creation of tools to guide, inform, predict, and increase the vaccine's impact, from both the economic and the public health standpoints. Some of these tools are described in the following sections.

INNOVATIVE TOOLS TO SUPPORT DECISION

MAKING Before a vaccine can be used, policy makers need estimates of its probable cost-effectiveness and public health impact. Since 2003 the Swiss Tropical and Public Health Institute, with support from the PATH Malaria Vaccine Initiative, has been working on a model of malaria vaccination that could be used by potential funders and national decision makers, among others. Such models are designed to provide estimates of how many cases of illness and deaths would be averted by the use of a vaccine in different transmission settings—such as the seasonal transmission in the highlands of western Kenya and the year-round transmission near Lake Victoria—and with current malaria control interventions.

In addition, health economics studies in

Africa are collecting comprehensive data on the direct and indirect costs of malaria to individual households and national health systems—data that can be used by the model to produce estimates of a vaccination campaign's cost-effectiveness and impact on a country's budget.

Another kind of innovation can be seen in efforts to support early decision making on introducing a malaria vaccine into African health systems. Vaccines often are available in developed countries long before they are used in poorer parts of the world. To avoid similar delays, the PATH Malaria Vaccine Initiative began working with national health officials and other stakeholders in 2006 to support the development of the Malaria Vaccine Decision-Making Framework.

First the initiative worked with African ministries of health to identify the information that their countries will need to make decisions about the appropriate use of a malaria vaccine once it is available. The initiative and the World Health Organization—using the latter's guidelines on the introduction of new vaccines as a basis—worked with African countries to develop a framework that identified the necessary data and the processes through which national leaders will decide whether or not to implement a future malaria vaccine. Financial support for the project came from the US Agency for International Development.

Technical experts from some thirty African countries have developed a regional version of the framework, and at least six African countries—Burkina Faso, Gabon, Ghana, Kenya, Mozambique, and Tanzania—have developed country-specific versions. Burkina Faso, Ghana, and Tanzania have established formal working groups to advance the decision-making process, and Kenya, Nigeria, Uganda, and other countries have held preliminary meetings.

INNOVATIVE POLICY AND REGULATORY PATHWAYS Once the World Health Organization has recommended a vaccine for use by developing countries, other international organizations, national authorities, regulatory bodies, manufacturers, and various experts need to collaborate on its implementation. For example, the GAVI Alliance—a global health partnership that brings together national and international stakeholders from the private and public sectors, formerly known as the Global Alliance for Vaccines and Immunization—may be able to provide funds that can be used to buy the vaccine. At the other end of the process are the countries that will decide whether or not to adopt a vaccine and, finally, the parents who decide whether or not to have their children vaccinated.

The PATH Malaria Vaccine Initiative and

Once a malaria vaccine has been recommended for use, countries will need funding to support its use.

GlaxoSmithKline began discussing the vaccine with the World Health Organization and relevant regulatory agencies well before the Phase III trials, including the efficacy trial, began. As a result, that and other Phase III trials—which are looking at such issues as the administration of RTS,S with newer vaccines and its use among HIV-positive children—were designed to meet the requirements of these organizations.

The Phase III data will be submitted to the European Medicines Agency—the European Union equivalent to the US Food and Drug Administration—under a specific regulatory provision called Article 58. This is an innovative solution to the requirement that a World Health Organization policy decision must follow approval by the regulatory body in the country of manufacture, and the regulatory body's requirement that a medicine be approved only for use within its own borders. This provision allows the agency to assess—in collaboration with the World Health Organization—the quality, safety, and efficacy of a medicinal product intended for use exclusively outside the European Union and against a disease of major public health interest. Article 58 has not yet been used for a vaccine.

In this approach, products must meet the same standards as those intended for use in the European Union, but the assessment takes the form of a scientific opinion rather than regulatory approval from the European Medicines Agency. The pathway to implementation also involves reviews by national regulatory agencies and public health authorities across Africa. Ideally, the process will be relatively speedy in this case because concerns will have been addressed through the consultations that have occurred regularly during the Phase II and Phase III trials.

INNOVATIONS IN FINANCING AND DELIVERY Once a malaria vaccine has been recommended for use, countries will need funding to support its use. Since its establishment in 2000, the GAVI Alliance has played a leading role in securing

The RTS,S project provides an example of innovative partnerships in the governance of Phase III trials.

money to support vaccine use by low-income countries. But it does not have enough funds to cover even vaccines that are already available for use. Moreover, not all countries likely to use a malaria vaccine will have access to GAVI financing, as a few have per capita incomes above GAVI's threshold.

Additional funding mechanisms may be required to ensure that a first malaria vaccine does not sit on the shelf after passing all its regulatory hurdles, as happened with other vaccines prior to GAVI's founding. One such creative approach is that employed by UNITAID, an international aid organization, which raises money—largely through a tax on airline tickets—to increase access to treatments for HIV, tuberculosis, and malaria.¹⁷ In addition to the possible role of similar funding mechanisms, the funders listed at the beginning of this paper, including the Global Fund to Fight AIDS, Tuberculosis, and Malaria and the President's Malaria Initiative, may all need to help African countries obtain the new vaccine.

INNOVATIVE FUNDING MODELS AND PARTNERSHIPS For many years, the lack of a lucrative market for malaria interventions hobbled the development of products such as vaccines. In response, the Bill & Melinda Gates Foundation began investing in malaria research and development in the late 1990s. The foundation's role in vaccine development has been transformational, paving the way for a rate of progress not seen in the previous thirty years. One important vehicle for investment has been the product development partnership, described by David Bishai and others in this issue of *Health Affairs*.¹⁸

The initiative's place in the spectrum of product development partnerships can best be described as "virtual," because it does not own labs or manufacturing plants and relies instead on those of its partners. The initiative's assets include the technical, scientific, and managerial expertise of a staff of some fifty people who man-

age an annual budget of more than \$60 million. Funding comes primarily from the Gates Foundation, but also from the US Agency for International Development, the ExxonMobil Foundation, and some smaller donors.

The RTS,S project provides a further example of innovative partnerships in the governance of the Phase III trials. The Clinical Trials Partnership Committee brings together local clinicians as well as representatives of GlaxoSmithKline and the PATH Malaria Vaccine Initiative to oversee the efficacy trial, while the steering committee responsible for the whole RTS,S project has similar diversity.

Some observers doubted that a trial so large and complex—with its eleven sites in seven African countries and scheduled to last several years—could succeed. But the doubters were proved wrong, as the initiative, GlaxoSmithKline, and the African scientists and institutions met every challenge, thanks in part to the ownership afforded by the approach to governance.

Bringing Benefits To The Community

The partnership model outlined above has also worked to provide short- and long-term benefits to the communities at the trial sites. For example, the PATH Malaria Vaccine Initiative and the Malaria Clinical Trials Alliance—a project of the Ghana-based INDEPTH Network that aims to strengthen clinical trial capacity and codify clinical best practices—provided funds for new or upgraded facilities, radiology and other equipment, improved telecommunications, and training programs to familiarize the trial's staff with protocols and procedures.

These efforts have bolstered home-grown research capacity, manifested both in new or refurbished research facilities and in the increased participation by the African scientists in international conferences and other forums. A trial site in Ghana illustrates this point.

The study center is located in a well-regarded Presbyterian hospital in the small town of Agogo, Ghana. The hospital's research infrastructure was extremely limited, making it difficult to recruit scientific staff and students, particularly from the teaching hospital in nearby Kumasi. A new, well-equipped facility was built at Agogo, attracting a flood of motivated students and staff (interview by David Poland with Tsiri Agbenyega, co-principal investigator at Agogo, March 14, 2010). Better diagnostic equipment and trained medical staff meant better care for the Agogo community, and lives have been saved as a result.

The viability of Nanoro, in a remote area of

Burkina Faso, as a trial site was thrown into question because the town was not on the electric grid. Recognizing the importance of clinical research capacity, the national government extended the electric grid out to Nanoro and electrified the town as well as the research facility. The process strengthened connections—both literally and figuratively—between the research site and the community.

New Vaccines, New Partnerships

The success of RTS,S so far makes it likely that an important development milestone for 2015 outlined in the Malaria Vaccine Technology Roadmap will be met: a malaria vaccine with 50 percent efficacy against severe disease that lasts longer than one year.¹⁹ It has also laid the foundation for a three-way approach to developing new vaccines with even higher efficacy.

The first of the three ways is to further boost the immunity conferred by the key component of RTS,S: the circumsporozoite protein. The second is to target other parts (antigens) of the parasite during the same initial stage of infection, thus complementing RTS,S. And the third is to more effectively block the parasite's entry into red blood cells—the so-called blood stage, which is when symptoms of the disease typically first appear—after it leaves the liver. (For more information about the complex life cycle of the malaria parasite, see the Appendix.)²⁰ This strategy requires coordinated investments in identifying and prioritizing new targets on the parasite, developing delivery mechanisms or platforms to reach these targets, and creating better tools to evaluate the potential success of vaccine approaches.

In addition to developing more-effective vaccines, the PATH Malaria Vaccine Initiative and other organizations in the field are supporting longer-term efforts to eliminate the disease by targeting malaria transmission.²¹ In particular, the initiative seeks to combine the malaria research taking place in academe, the novel vaccine technologies being developed by biotech companies, and the extensive product development expertise of large pharmaceutical companies.

For example, the initiative is collaborating with academic and government partners such as the Johns Hopkins University, New York University, the National Institutes of Health, and the US military to develop new vaccine targets and evaluation tools. It has formed partnerships with biotech companies such as Inovio, in Pennsylvania, and Liquidia, in North Carolina, as well as Merck, Crucell, and other large pharmaceutical companies, to develop more-effective mecha-

nisms of delivering vaccines. And it has created a partnership with Gennova Biopharmaceuticals, a division of Emcure that is based in India, to capitalize on the product development expertise that is emerging in that country.

Future Challenges

Although the ultimate reason to create a new malaria vaccine is to improve public health, the development process has already produced important benefits for future efforts and, we hope, for the malaria field overall.

Work on the RTS,S vaccine candidate has clearly shown the importance of collaboration. As the field moves toward the development of vaccines with a greater number of components, collaborations are likely to involve even more partners, and creative licensing arrangements for intellectual property may be needed.²¹ Experience has shown that maintaining the collaborative relationships requires both time and trust. Planning the introduction of a new health intervention is also a lengthy process. It's important to get started on work such as this in a timely fashion.

If data available in 2014 allow the World Health Organization to recommend the use of RTS,S in 2015, the world's first malaria vaccine could be available soon after that. Reaching this point has required large financial resources, new ways of partnering, and innovative regulatory approaches. Now we face other challenges, such as helping low-income countries make the new vaccine available as a complement to existing malaria interventions, along with an impressive list of other new vaccines.

In addition, the development of the next generation of vaccines, with increased emphasis on interrupting the transmission of malaria, will take time. Trials involving transmission-blocking approaches are still in the very early stages of planning. Many questions remain: Will any transmission-blocking vaccine be as effective as a vaccine that targets illness? Can we prevent mosquitoes from being infected? Would regulatory agencies—and, ultimately, families—accept vaccines that didn't provide direct protection for an individual, but that instead protected the community in general? The PATH Malaria Vaccine Initiative is already contemplating such questions.

Perhaps the greatest challenge is whether today's enthusiasm and funding levels can be sustained. Half a century ago, the drive to eradicate malaria had stalled. Resistance to insecticides and drugs had emerged, and investments in research and development were insufficient. Especially in the current economic climate, the half-

billion dollars or more typically required to develop a vaccine seems like a hefty price to pay. We need further innovation in funding models and partnerships, as well as in the science itself. ■

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In this issue of *Health Affairs*, Christian Loucq and coauthors write about the PATH Malaria Vaccine Initiative's success in spearheading testing and possible distribution of an experimental vaccine against malaria. The

parasitic infection annually sickens 225 million people and kills 800,000. Most of the victims are in Africa, where the not-for-profit PATH Malaria Vaccine Initiative is helping coordinate trials in seven countries where malaria is endemic.

Although insecticide-treated bed nets and medicines have reduced malaria incidence in many regions, a vaccine is widely regarded as the critical missing tool to control the disease.

Loucq joined the PATH Malaria Vaccine Initiative in 2007 as director of strategy and operation;

later that year, he became director of the initiative itself. He worked previously in product development, marketing, and manufacturing for large vaccine companies, including GlaxoSmithKline and Sanofi Pasteur, as well as for biotech companies, including Rhein Biotech and Acambis. He has extensive experience building partnerships with local governments, private industry, and philanthropies.

Born and raised in France, Loucq earned his doctorate in human medicine at the University of Paris and a diploma in public health and

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Ashley Birkett is director of pre- and early clinical research at the PATH Malaria Vaccine Initiative. He oversees the identification of promising malaria vaccine technologies and collaborations with for-profit and nonprofit partners. He previously worked with biotechnology companies, where he advanced influenza and malaria vaccines from research through early clinical trials. He holds a doctorate in biochemistry and molecular biophysics from Virginia Commonwealth University.



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David Poland is the PATH Malaria Vaccine Initiative's senior communications officer and concentrates on activities related to the RTS,S malaria vaccine

discussed in this paper. He has worked in science communications since the mid-1980s, and before that was a newspaper reporter and photographer. He has a master's degree in communications from Cornell University.



Carla Botting is director of product development and access at the initiative.

As director of product development and access, Carla Botting incorporates the needs of developing countries into the PATH Malaria Vaccine Initiative's vaccine activities and ensures that the products will be accessible to populations in need. She also leads the group's RTS,S program. Previously, she headed government business relations at Cangene Corporation. She has an undergraduate honors degree in commerce from the University of Manitoba.



Julia Nunes is a program officer at the initiative.

A program officer at the PATH Malaria Vaccine Initiative, Julia Nunes models the impact of malaria interventions to guide international policy and new vaccine development. She previously served as a technical adviser for the Clinton Foundation in Ecuador, where she focused on a proposal for an HIV vaccine. Nunes studied immune responses to malaria at the Harvard School of Public Health and received her doctorate in immunology and infectious diseases from the Harvard Graduate School of Arts and Sciences.



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Sally Ethelston is director of communications and advocacy at the PATH Malaria Vaccine Initiative. Before joining the initiative in 2007, she was communications director for Population Action International, which advocates for access to contraception. She also headed the group's financing project. She has served as a consultant for the World Bank and International Planned Parenthood Federation, and she has a master's degree in Arab studies from Georgetown University.