

Quest for malaria vaccine revs up, but much work remains

After upwards of 75 human trials — mostly small-scale, but a few full-scale, field trials — and with dozens more being planned, malaria vaccines are coming of age. Money has begun to pour into vaccine trials from both public and private sources, and new ideas and approaches are proliferating. Researchers are upbeat, but how long will it be before a good malaria vaccine becomes available. Robert Walgate investigates.

With the influx of new money — probably ten times as much as was available over the last decade — malaria vaccine research and vaccine development are booming. And with the new knowledge of the human genome, and the almost complete sequencing of the malaria genome, hundreds of new components of the malaria parasite are being discovered that might stimulate the immune system, to add to the mere dozen or so that have been worked on by vaccine researchers to date.

So far, the most promising results, in the view of the majority of experts interviewed for this article, have been seen with a vaccine that has emerged from a 17-year collaborative effort involving several teams. The vaccine, code-named “RTS,S”, is a combination of molecules from the malaria parasite and others from the hepatitis B virus, combined into a single particle that incorporates a specially designed immune-stimulating, or *adjuvant*, substance. It was developed by the drug firm GlaxoSmithKline (and its predecessors), in partnership with, among others, the Walter Reed Army Institute of Research. In a preliminary trial, the vaccine protected 70% of adult volunteers in the Gambia against infection with *Plasmodium falciparum*, the most lethal of the four malaria parasites that infect humans, but the protective effect waned rapidly after two months.

Dr Joe Cohen, head of vaccines for emerging diseases at GlaxoSmithKline told the *Bulletin* that the vaccine is “targeted to infants and children living in malaria-endemic regions”. An early-stage (Phase 1) trial is currently under way in children in the Gambia, primarily to test the vaccine for safety. “If all goes well, an efficacy, or Phase 2b, trial will take place in an African country in 2002 to tell us to what extent the vaccine reduces malaria disease.” Much larger (Phase 3) trials would then be started “to evaluate the impact of the vaccine on morbidity and mortality in children and infants.”



In a rural Vietnamese hospital, a father tries to rouse his daughter from a malaria coma.

WHO/Lysiane Maurice

The initial series of Phase 1/2b trials, which will cost nearly US\$ 7 million, is being conducted in partnership with the US\$ 50 million Malaria Vaccine Initiative (MVI) launched 18 months ago by Microsoft entrepreneur Bill Gates and based at the Seattle headquarters of the Program for Appropriate Technology in Health (PATH).

The second most promising vaccine candidate, according to many experts, is an Australian “combination B”, vaccine, that combines immune-stimulating molecular structures (antigens) from the asexual blood stages of the malaria parasite’s life cycle (see Box). It has been tested in children in Papua New Guinea by a team from the Papua New Guinea Institute of Medical Research and their collaborators at the Swiss Tropical Institute in Basel, Switzerland. In this trial, still to be published, the vaccine induced a substantial reduction in parasite densities in the bloodstream over a period of at least four months, and could, say the researchers, be potentially life-saving, especially in

children. The duration of protection, however, has not yet been studied.

To create a useful vaccine against such a complex organism as the malaria parasite, with its different life cycle stages, each involving a distinct set of immunologically operational antigens (see Box), is far from easy. Dr Tom Richie, head of clinical trials at the Naval Medical Research Center’s malaria program in Silver Spring, Maryland, which hosts one of the world’s largest malaria vaccine research programmes, points out that malaria is a chronic infection, whereas successful human vaccines so far “are almost all against acute infections or the acute stage of an infection. In other words if you get smallpox naturally or chickenpox, you develop a sterilizing immune response naturally”. After surviving one infection you will usually not be infected again. “But in malaria that doesn’t happen. So a basic problem we face with a malaria vaccine is that we are harnessing as our weapon the immune system, but the parasite already knows how to avoid it.” Scientists, he says,

“have to understand the mechanisms of immune evasion in malaria, and we have to short-circuit those mechanisms.” A good vaccine able to do this, he believes, is ten years away.

There is, however, strong evidence that a malaria vaccine really could work. For one thing, it is clear that in malarious areas a degree of natural immunity builds up after many infections. For another, research which began in the early 1970s and was expanded during the 1990s has shown that 90–95% of people exposed over several months to irradiated mosquitos carrying malaria parasites develop protection against the infection and that protection can last for ten months. This approach though is too crude and impractical to produce a vaccine for wide application.

Scientists are divided, however, as to how to move forward to make a better vaccine. Some believe that enough malaria parasite antigens have been identified and that all that is needed now is to find the right way of presenting them to the immune system in order to elicit a protective immune reaction.

Among the many research programmes working with different sets of antigens are the Institut Pasteur in Paris, where Dr Pierre Druilhe is focusing on blood-stage vaccines. One candidate vaccine is now in an early stage (Phase 1) trial in Lausanne, Switzerland, with support from the three-year-old European Malaria Vaccine Initiative, and 11 other candidates are in the pipeline. Then, at Walter Reed, Dr Christian Ockenhouse is working on vaccines against *P. vivax* malaria (see Box), as is Dr Chetan Chitnis of the malaria research group at New Delhi’s International Centre for Genetic Engineering and Biotechnology. At the National Institute of Allergy & Infectious Diseases (NIAID), part of the US National Institutes of Health, a new malaria vaccine development unit headed by Dr Louis Miller has started work on several blood-stage and sexual-stage antigens for a vaccine against malaria disease and a transmission-blocking vaccine, respectively.

And in Bogota, Dr Manuel Patarroyo, at the Colombian Institute of Immunology Foundation, is still full of enthusiasm after the disappointing results in human trials with his famous “SPf66” vaccine. He is reportedly working on a second-generation vaccine made up of a ring-shaped molecular structure that mimics a merozoite, or blood stage, surface protein (see Box).

With the considerable funding now available, some of these efforts are likely to reach the human trial stage.

Some scientists are working not with antigens but directly with the genes, the DNA, that code for the antigens. At the



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A health worker in Thailand takes a blood sample from a woman suspected of having malaria.

University of Oxford in the UK, Dr Adrian Hill is using so-called “naked DNA”, which, injected into the host’s own cells, can make the protein components of the vaccine. A harmless virus package engineered to carry the same genes more efficiently into the body’s cells is administered some time later. This so-called “DNA prime–virus boost” technique was tested in adults in the Gambia and the results are “encouraging,” Hill says. At the US Naval Center’s malaria lab, the leading candidate, called MUSTDO-9, is also a DNA vaccine, containing nine antigens from the sporozoite and liver stages of the parasite.

Some scientists say a large array of antigens should be used in these DNA vaccines. After all, the sporozoite has about 5000 genes, while current candidate vaccines work with the antigens produced by less than a handful of genes. Others point out that adding too many elements can be counterproductive. Walter Reed researchers, for example, discovered that when a pre-erythrocytic antigen (see Box), called TRAP, was added to RTS,S, it did not add to, but diminished, the vaccine’s efficacy. Yet others stress the importance of developing vaccine delivery systems that induce specific immune responses. The US Naval Center group has reported that a DNA vaccine they are working on has induced in human subjects interferon-gamma responses that are thought to be critical to the protection against malaria produced by the irradiated sporozoite vaccine.

Optimism also stems from the advent of new tools, like genomics and proteomics. Dr Stephen Hoffman, former director of the Naval Medical Research Center’s malaria program and now with Celera Genomics, is

enthusiastic about his work with proteomics, a systematic, exhaustive approach to the analysis and identification of parasite proteins. “Now, for the first time, we have the possibility to begin to identify the real targets of irradiated sporozoite immunity or naturally acquired immunity to malaria.” And using the *P. falciparum* genome sequences published so far, Richie at the US Naval Medical Research Center says his team already has identified “hundreds of new [antigen] candidates”. Dr Michael Hollingdale of the London School of Hygiene and Tropical Medicine sounds a more cautious note: “I think [genomics] is a very exciting approach, but while you may dramatically increase the number of vaccine candidates they’ve still got to be turned into vaccine products, manufactured and tested. Many of the candidates we’re using now were identified 10–15 years ago, so there’s a big role for finding new ones. But you still come down to the engineering job.”

For some researchers, there are just too many ideas around. Dr Stephanie James, at the NIAID’s parasitology and international programs branch, says: “We already have so many different antigens, expression systems and delivery systems under examination, all of which carry some degree of ego investment by both the investigators and those who have funded the research so far, that it has been very difficult to sort out. One may well assume that this will be magnified by the expedited discovery of more candidates through genomics and post-genomics research. It will be increasingly important for the field to come together to agree on some fundamental selection criteria for putting candidates on the path to clinical trials.”



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A mother and her child, both with malaria, in a Viet Nam country hospital.

Another testing question is how effective a usable malaria vaccine must be. Dr Marcel Tanner of the Swiss Tropical Institute says: “Maybe we need to rethink what we mean by an effective vaccine. We can aim at something which is 99% efficacious. But if we see the vaccine as part of an integrated strategy, a vaccine which reduces morbidity and mortality by just 50% could be a tremendous addition. Maybe the way forward is to rethink the concept of vaccines, and to look at packages of measures that can really be implemented, not just theoretical ways of reducing malaria.” A recent study in the United Republic of Tanzania, for example, showed that anti-malarials plus iron supplements administered preventively to infants through routine immunization programmes, can reduce the incidence of malaria by nearly 60% in these children (see *Bulletin of the World Health Organization*, 2001, 79: 688).

At the bottom line, though, comes the price tag. To develop and produce a usable vaccine may take about US\$ 500 million, says MVI director, Dr Regina Rabinovich. “There is certainly a lot more money now than in the past, but malaria remains a neglected disease with only a fraction of the funding HIV/AIDS gets.” So where’s the money for malaria going to come from? “We are going to have to seek other sources, because you don’t get that level of funding directly from government. There’s going to have to be a clear development initiative, and there may be potential from philanthropy, and a package [from different sources] that will make it feasible.”

At the end of June, the birth of such an initiative hit the news. Three donor agencies — the European Malaria Vaccine Initiative, the United States Agency for International Development (USAID) and the MVI — announced that they had “joined

forces in facilitating malaria vaccine development, from testing and manufacturing vaccine candidates to ensuring their accessibility and affordability in developing countries”. In a press comment, Rabinovich said: “Current global resources are not sufficient to defeat [malaria], making concerted action imperative...Today’s agreements extend our efforts to replace competition with strategic collaboration.” ■

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A brief background to malaria vaccine research

Of the four main species of *Plasmodium* parasites that cause human malaria, two are particularly troublesome and are the targets of vaccine research: *Plasmodium falciparum*, which causes the most lethal form of malaria (anywhere between 700 000 and 2.7 million deaths a year, 75% in African children), and *P. vivax*, which causes comparatively few deaths but is extremely debilitating.

When an infected female *Anopheles* mosquito bites, it injects the malaria parasite into its victim’s bloodstream in the form of rod-shaped *sporozoites*, which quickly invade the liver. This is the *pre-erythrocytic* stage of the parasite’s life cycle, and includes the *liver* or *hepatic stage*. Over the next few days the parasites multiply in the liver and turn into roundish *merozoites*, which burst out from the liver and enter red blood cells in the bloodstream: during this *blood* or *erythrocytic stage*, the merozoites undergo several cycles of multiplication, eruption and reinvasion, causing the cyclic fevers characteristic of malaria. Finally — if the patient remains alive — some of the merozoites go on to develop into *gametocytes*, or *sexual forms* of the parasite (all other forms or *stages* of the parasite’s life cycle are, therefore, often referred to as *asexual stages*). During this *sexual stage*, the gametocytes can be picked up by another biting mosquito, and the deadly cycle continues. At each of these stages of the life cycle, the parasite presents on its outer coat a distinct set of molecules, or antigens, capable of stimulating the host’s immune system.

The different candidate vaccines under research or in development contain these or parts of these antigens. Some, like the RTS,S vaccine (see main text), use sporozoite antigens, and aim to stop infection in its infancy. Others, like the Australian vaccine, may use merozoite antigens, aiming to reduce disease by limiting the development of the asexual blood stages of the parasite, which cause the symptoms of malaria. Yet others, called “altruistic” or transmission-blocking vaccines, because they would be of no direct use to the individual patient, would act against the gametocytes and stop transmission of the infection, thereby putting a crimp on an epidemic or lowering the level of malaria infection in a community.

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