A vaccine for malaria?

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A child receives the third and final dose of a malaria vaccine as part of a field trial to test its efficacy under African conditions. African children stand to gain most from an effective malaria vaccine. Photo WHO/TDR/A. Crump

Improved knowledge and the availability of new technologies give us reason to believe that vaccination against malaria is possible.

In the last decade, considerable progress has been made in the search for a malaria vaccine, and the turn of the century is expected to see one or more such vaccines being actively developed by the pharmaceutical industry.

Globally, malaria is a major public health problem. The story of mosquito resistance to insecticides and parasite resistance to drugs impeding malaria control is a familiar one. And while there are renewed efforts to combat malaria both through conventional and novel drugs and through vector control activities, an effective vaccine would constitute a powerful addition to these tools.

Natural exposure to malaria leads to the development of partial immunity in humans, but repeated re-infection is required to maintain this immunity. Inactivated sporozoites (parasite forms living in the mosquito which are infective to humans) have been shown to be highly effective at inducing immunity in humans. Unfortunately, it is not possible to produce inactivated sporozoites in the enormous numbers required to make this a feasible method of vaccination. However, we now have new technologies at our disposal. Nucleic acid-based DNA vaccine technology, for example, allows us to identify promising immunogenic molecules much more rapidly, and this considerably expands the number of potential vaccines. Novel adjuvants – neutral substances that enhance the body’s immune response to antigens – are becoming available for clinical use. Other delivery systems (live vectors such as salmonella or vaccinia which incorporate antigen gene sequences, and DNA vaccines) are under development and starting to be evaluated in humans.

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What sort of vaccines are being developed?

The malaria parasite has a number of different stages in its life cycle (see figure on page 13). Candidate vaccines are based on various antigens derived from these different stages: Pre-erythrocytic vaccines prevent the malaria parasite sporozoite stage from entering or developing within liver cells. Such vaccines would prevent the severe and life-threatening consequences of malaria in non-immune individuals. About 20 human clinical trials with various Plasmodium falciparum pre-erythrocytic vaccine candidates have been conducted to date. One highly promising candidate, “RTS,S”, is currently in field trials in the Gambia.

Asexual blood-stage vaccines prevent the parasite merozoite stage from entering or developing within red blood cells. Immunity against the asexual blood stages of the parasite, which are responsible for the symptoms of malaria, would have a direct impact on disease morbidity and death in the individual but would not necessarily prevent people from getting infected. At least six asexual blood stage vaccines have been tested clinically or are currently undergoing human trials.

Transmission-blocking vaccines inhibit development of the sexual stages of the parasite within the mosquito. The sexual forms of the malaria parasite develop in the red blood cells a few weeks after infection, and are infective for mosquitoes biting infected individuals. With wide coverage these vaccines could reduce transmission of the disease in endemic regions by reducing the number of mosquitoes infected. Several transmission-blocking candidate vaccines are already undergoing clinical trials for safety and immunogenicity in the USA.

Vaccines currently under development include:

- Vaccines based on cocktails of antigens (multicomponent vaccines). The first multicomponent synthetic peptide vaccine SPf66, developed by Dr Manuel Patarroyo in Colombia (repre-
senting three asexual blood stage antigens and a sporozoite antigen), is the most widely tested vaccine to date. It has given mixed results in field trials in South America, Africa and South-East Asia.

- Another multicomponent vaccine, engineered in attenuated vaccinia virus and expressing three pre-erythrocytic proteins, three asexual blood-stage antigens and a transmission-blocking candidate, gave limited protection in a human clinical trial in the USA.
- A third multicomponent asexual blood-stage vaccine under development by Australian scientists is currently undergoing clinical trial in Papua New Guinea.

Second-generation vaccines include those that contain modified malarial peptides or novel adjuvants; DNA vaccines (nucleotide sequences encoding the antigen in question), which have shown promising results in rodent models; and antitoxic or anti-disease vaccines.

**Why is a vaccine for malaria proving so elusive?**

We don’t yet have a vaccine for any human parasitic disease. For malaria, there is the problem of not being able to grow malaria parasites in large enough quantities to make vaccines in the traditional way, either from live but weakened organisms or from crude antigen preparations. Hence the focus on synthetic peptides, recombinant proteins or DNA vaccines. One difficulty is that, in clinical trials so far, most vaccines have failed to live up to the potential they have shown experimentally in animal models. This situation may be overcome when novel, more powerful adjuvants for human use become available.

Then there is the difficulty of evaluation. The fact that there are no good in vitro surrogate screening systems to assess the efficacy of different vaccines in the laboratory is a significant limitation, and means that vaccines have to be tested experimentally, often in expensive, time-consuming animal model systems, including monkeys.

Another problem is that, unlike less complex organisms, parasites have developed ingenious ways of avoiding the host’s immune response. For instance, the malaria parasite expresses different antigens at each stage of its life cycle, and is often able to change these antigens when the host mounts an immune response towards them. Different strains or isolates of the parasite can also express different forms of the same antigens. A multicomponent vaccine, aimed at covering several of the antigens, could overcome this problem but would be highly complex and difficult to develop. And finally, there is the complexity of conducting the clinical and field trials themselves, when researchers are confronted with measuring the reduction of morbidity and mortality following vaccination with a candidate vaccine.

Research on vaccines against malaria is mainly supported by a variety of international agencies, organizations, foundations and national funding agencies, including the governments of some countries and various research institutes. There is also greater involvement of the private sector when vaccine candidates have reached advanced stages of development.

**Where do we go from here?**

There is no guarantee that the current promising approaches to malaria vaccine development will result in a cost-effective malaria vaccine. Nevertheless, new technologies are becoming available and there is intensified political and financial support for research on malaria. The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) is committed to evaluating the currently available leading *Plasmodium falciparum* malaria vaccine candidates in clinical trials by 2005. If all goes well, a malaria vaccine could be ready for use sometime in the next decade.

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