Malaria vaccines

Increased funding for vaccine research aims to accelerate the transition to phase I clinical trials

MALARIA REMAINS A GLOBAL CRISIS that kills at least one to two million people per year, mainly children in sub-Saharan Africa.[1] Forty per cent of the world's population is at risk of malaria, and each year more than 300 million people have episodes of acute malaria. In recent times, there has been a breakdown in malaria control programs. This has been caused by failure of health systems in the poorest countries, as well as the emergence of mosquitoes resistant to insecticides and malaria parasites resistant to cheap, widely available drugs. In addition, population movements, large-scale development projects, civil wars and conflicts, as well as environmental changes, have all acted in concert to increase the number of individuals at risk of malaria.

In Papua New Guinea, for example, malaria is the commonest cause of outpatient presentation and accounts for an estimated 27% of all attendances at health facilities.[2] In some Papua New Guinea provinces, malaria is the reason for more than 40% of health centre attendances, and equals pneumonia as a primary cause of death.[2]

In recognition of the need for a renewed attack on malaria, a global strategy for malaria control was presented to a World Health Organization Conference of Health Ministers in 1992.[3] The strategy, now incorporated into the Roll Back Malaria Campaign, promoted a new philosophy emphasising malaria control (in contrast to eradication), and acknowledging the need for different approaches to disease control in different populations. For example, the approach to malaria control in children and pregnant women in Africa is different to that in adult refugee populations. The strategy emphasised the importance of political commitment, such as that given by the heads of State and governments of African countries in Nigeria in 2000 (the Abuja Declaration).[4] All participants resolved to commit to an intensive effort to reduce the burden of malaria by strengthening health systems, implementing action plans, improving local capacity, promoting early recognition and treatment of clinical malaria, and reinforcing efficacious preventive measures such as the use of impregnated bednets and chemoprophylaxis. An important

component of the strategy is the development of new antimalarial drugs and vaccines.

Vaccines have been shown to be one of medicine's most cost-effective interventions. A malaria vaccine that protects for one to five years with 50% efficacy could substantially reduce all-cause child mortality in endemic areas. The cost of such an intervention compares very well with that of using insecticide-treated bednets, and is likely to have major economic as well as social benefits for the populations currently threatened by malaria.

An "experiment of nature" suggests that developing a vaccine should be possible. Although many children die of malaria, the majority survive the life-threatening risk of the first few years of exposure and develop clinical immunity. Provided they continue to be exposed to malaria, this immunity protects them from severe disease for the rest of their lives, except during pregnancy.

Unfortunately, the immune response that correlates with protection in these lifelong residents of endemic areas has not been identified, so development of a vaccine that mimics this immunity will be difficult. Moreover, malarial parasites demonstrate extreme antigenic diversity. Recent developments, including better methods for antigen production, improved adjuvants and novel delivery systems, provide optimism that sustained and appropriate long-lived immunity can be achieved.

Vaccines could be directed against the sporozoite stage of the malaria parasite to prevent infection, or against the stages in human blood — the asexual stage to prevent clinical disease, or the sexual stage to prevent transmission. The malaria vaccine which has been studied in most detail is designed to induce immunity to the sporozoite and the infected liver cell (ie, to stop sporozoites invading liver cells and to kill sporozoite-infected liver cells). In early studies it was shown to induce protective immunity against experimental challenge.[5] Under conditions of natural exposure (in semi-immune adult men in The Gambia),[6] the vaccine was shown to be safe and well tolerated, with an estimated efficacy (decrease in malaria infection) of 70% in the first nine weeks of follow-up. However, over the 15 weeks of observation, the efficacy fell to 34%. Further trials will determine whether improved efficacy can be achieved in young children.

Australian research efforts have led to a multicomponent recombinant protein vaccine targeting the asexual blood stages. This vaccine was tested recently by the Papua New Guinea Institute of Medical Research and its collaborators. The vaccine caused a 62% reduction in parasite density in children, without any harmful side effects.[7] Further development will be necessary to produce a vaccine sufficiently efficacious for routine use.

In the past there has been a serious lack of funding for research into malaria, partly because companies engaging in this type of research did not expect it to be profitable. A major change has occurred of late, with increased funding from the Wellcome Trust in the United Kingdom, and from the United States through the National Institutes of Health. A grant from the Bill and Melinda Gates Foundation has funded the Malaria Vaccine Initiative of the Program for Appropriate Technology in Health (PATH) (http://www.malariavaccine.org). This worldwide initiative has the specific goal of enhancing the transition of the many promising candidate vaccines from the laboratory to "proof of principle" research in phase I clinical trials. It has funded Australian projects developing vaccines from asexual stage (merozoite) antigens by researchers at Monash University, La Trobe University and the Queensland Institute for Medical Research, partnered by Biotech Australia (New South Wales), the Cooperative Research Centre for Vaccine Technology (Queensland) and Progen Industries Limited (Queensland).[8]

There are still many challenges in developing a malaria vaccine, such as the need to cope with diverse antigenic types and the importance of stimulating a lifelong response that is boosted by natural infection. Vaccine-induced sterilising immunity that is not boosted by exposure to malaria could put an individual at increased risk when the vaccine-induced immunity wanes. Most importantly, we need vaccines that can be incorporated into national immunisation programs as part of a coordinated, holistic approach to malaria control. Research to find new methods for vector control and new drugs must also continue, as we know from past antimalarial campaigns that a single technology will not be sufficient to control this devastating disease.

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