A Malaria Vaccine–Necessary But Not Sufficient

In 1983 there were 220 million cases of malaria world-wide – mostly caused by *Plasmodium falciparum*. In tropical Africa alone there were one million malaria deaths among children. At the present time 2 billion people live at risk in malarious areas of the world. Malaria is without doubt the most destructive of infectious diseases and the harm it does is not only measured in cost to human life but also in the destruction of human potential.

During the 1970s the World Health Organisation's strategy for the eradication of malaria began to deteriorate. National malaria programmes mounted in the 1950s and 1960s were based on the availability of new and effective residual insecticides for the control of the mosquito vector and antimalarial drugs for prophalaxis and treatment of infection. Implementation of these programmes required major resource and financial expenditures. Erosion of these efforts came about basically in three ways. First, partial successes in the eradication strategy produced a false optimism which reduced national health priorities and expenditures for malaria control. Second, the anopheline mosquito began to develop resistance to residual insecticides. Third, the major human malaria pathogen, *Plasmodium falciparum*, developed resistance at an alarming pace to the available armamentarium of antimalarial drugs. These factors and others have combined to produce a situation today that WHO characterises as stagnant.[1]

It is, therefore, no surprise that the current prospect for the development of a malaria vaccine has been received with much hope and enthusiasm. The idea of a malaria vaccine is of course not new, but since about 1980 a critical effort has been underway to field a product for human use. Work on developing a vaccine has been spurred by major scientific advances occuring throughout the 1970s – hybridoma techniques for producing monoclonal antibodies, recombinant DNA methodology essential to gene cloning and, in the specific case of the malaria parasite, the technique for cultivating *P. falciparum*.

Work on developing a vaccine has progressed along three lines of attack on the complex malaria life-cycle targeting specifically the sporozoite, blood stage and gamete forms. The most promising development has been towards the production of a sporozoite vaccine. The prospect for a vaccine against the gamete is also good. Identification of the relevant blood stage antigens has proven more difficult, although a number of candidate antigens are under intensive study.

Malariologists have, however, recognised that there are practical problems involved with a vaccine directed at only one point in the malaria organism's life-cycle. A sporozoite vaccine must have an "all-or-none effect," since a single surviving sporozoite reaching the host's liver has the potential for causing infection. A gamete vaccine which would act to block transmission of infection is at best a tool for use in the long-range control of malaria. In the case of a blood stage vaccine, infection would not be prevented but attenuation of clinical symptoms would be achieved. Because of these individual vaccine considerations, there is a consensus for a combination or polyvalent vaccine aimed at all three stages in the life cycle of *P. falciparum*.[2]

Even if the ideal of a polyvalent malaria vaccine is achieved, there will be, nonetheless, serious problems with its practical application. The issue is whether a malaria vaccine will be effective in a malaria endemic population. For nonimmune individuals even a monovalent vaccine may provide limited but useful protection, but for a malaria endemic population it is questionable whether immunisation can be achieved in a majority of individuals.

Under natural conditions protective immunity to infection with *P. falciparum* is poorly acquired, often incomplete and transient. Immunosuppression is a major feature of falciparum malaria and immunisation even with heterologous antigens can be difficult. In addition the parasite may introduce complications through antigenic heterogeneity or other mechanisms for eva-

ding host defences.

Success against these rather formidable problems regarding a malaria vaccine will only be achieved through a long process of field testing and refinement. The message here is that while the development of a prototype malaria vaccine may be imminent, an efficacious vaccine for most of the world's at-risk population may be expected at best in the distant future.

We must not, therefore, allow our enthusiasm for a vaccine solution to the malaria problem to obscure the immediate and near future realities of malaria's actual and potential destructive force. The lessons of past failures in our struggle against malaria should teach us that we must bring to bear on malaria all the weapons we can muster. This means not only a vaccine but innovative means of vector control and new and noval chemotherapeutic agents.

In particular we need new antimalarial drugs. It must be recognised that we have reached the point where *P. falciparum* has demonstrated resistance to all the clinically proven drugs – including the newest, mefloquine. What should be most disturbing is that after mefloquine there are only a few candidate drugs under development and most of these are structually related to mefloquine and thus are potentially subject to cross-resistance. So there is a very real possibility that in 5-10 years we may have exhausted our chemotherapeutic resources against malaria.

Thus it should be obvious that concurrent with vaccine development there should be a programme for the production of antimalarial drugs. Yet during the past 20 years there has been only one sustained effort for antimalarial drug development: the US Army's Walter Reed programme which produced mefloquine. The basic approach in this programme is empirical search for lead compounds which are then rationally developed. Given the current malaria situation this approach cannot be counted upon to produce the diversity and number of drugs needed. One or two more drugs in the next 20 years – even if achieved by empirical search – will not solve the problem. What is needed is a truly rational approach to the development of antimalarial drugs.[3] By rational is meant the design of agents based on a detailed understanding of the malaria parasite's biochemistry whereby parasite-unique metabolic features are selected for drug targeting. In addition, biochemical targeting and agent design must in the case of malaria be complemented by an understanding of the molecular basis of resistance to current drugs.

The new biotechnology provides a powerful tool with which to pursue the objective of rational drug development. What is needed is a "critical mass" of scientific talent sensitised to the unique problems of malaria drug development with long-range institutional support and international coordiation.

A rational approach to antimalarial drug development is an achievable goal. But it is a costly and demanding one and therefore must compete with other approaches such as vaccine development. At the current time a first generation malaria vaccine may be a soon-to-be achievement. This is not the case for a rationally developed new antimalarial drug. It is a matter of concern that the prospect of a vaccine will devalue the emphasis and hence support for drug development. We must not let this happen. For, while a malaria vaccine is necessary, it is not alone sufficient to control and eventually eliminate the world malaria problem.

H. Kyle Webster, Ph.D.
Department of Immunology & Biochemistry, US Army Medical Component, Armed Forces Research Institute of Medical Sciences (Bangkok, Thailand), APO San Francisco 96346

REFERENCES

1. World Health Organization Report of the Steering Committees of the Scientific Working Groups on Malaria (June 1980-June 1983).
2. Wernsdorfer WH. Prospects for the development of malaria vaccines. Bull Wld Hlth Org 1981;59:335-41.
3. Webster HK. Antimalaria drug resistance: problems and prospects. Thai J Pharmacol 1982;4:171-91.