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Malaria Vaccines: Current Status and Future Prospects

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Malaria is a mosquito-borne protozoal disease which is endemic in many tropical and subtropical regions of the world. *Plasmodium falciparum* and *Plasmodium vivax* are the most common species of human malaria and the most pathogenic. *P. vivax* causes the classical recurrent/relapsing febrile illness which is widely recognized as typical of malaria; although it causes severe morbidity, it is rarely fatal. *P. falciparum*, on the other hand, presents a much more variable picture. Symptoms may be severe or deceptively mild but the disease is fatal in approximately 1% of cases. Death may follow an acute infection (endotoxic shock or cerebral malaria) or may be the result of severe anaemia following chronic infection. The World Health Organization (WHO) estimates that up to 300 million cases and 3 million deaths occur worldwide each year. Malaria has traditionally been controlled either by preventing contact between the mosquito vector and human host or by chemotherapy (as discussed elsewhere in this volume). The only significant breakthrough in malaria control in the last decade has been the introduction of pyrethroid-impregnated bed nets: in controlled trials, treated bed nets have been shown to reduce *P. falciparum*-related deaths by up to 40% and national bed net programmes are being implemented in a number of sub-Saharan African countries (D'Alessandro et al 1995a). However, it is widely accepted that long-term control of malaria depends upon the development of a safe, cheap and highly immunogenic vaccine.

It has long been known that residents of highly malaria endemic areas acquire protective (but non-sterilizing) immunity to malaria. Young children are susceptible to disease and death but, following infection, parasite prevalence, parasite density and the number of clinical episodes decline progressively. Adults are more or less resistant to the pathologic effects of infection (McGregor 1986). If this process could be mimicked by vaccination, severe malaria and malaria-related deaths could be prevented. Such a vaccine would need to target the intra-erythrocytic stage of the life-cycle, which is responsible for the clinical symptoms and severe pathology of the disease, and would need to induce lifelong immunity which could be boosted by periodic reinfection. The aim of vaccination would be to inhibit merozoite replication or erythrocyte invasion, thereby keeping parasite density below the threshold required to trigger an inflammatory response. An alternative approach, from a public health perspective, is to limit the spread of malaria by targeting the transmission stages of the life-cycle which infect mosquitoes. Finally, a vaccine which effectively targets the infective (sporozoite) stages would completely prevent infection and may also be suitable for travellers from non-endemic countries.

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Early Vaccine Studies

Early attempts to produce a malaria vaccine were largely empirical and followed the tried and tested approach of pathogen attenuation—in this case irradiation of sporozoite-infected mosquitoes. Irradiated mosquitoes were allowed to feed on (and infect) non-immune human volunteers who were then challenged with bites from infected, non-irradiated mosquitoes and monitored for signs of infection. Protective immunity was induced but was short lived and species specific (Rieckmann et al 1979). Protected individuals had serum antibodies to the surface-coat protein of the sporozoite, the circumsporozite protein, and it seemed plausible that these antibodies were mediating protection.

Malaria vaccine research was revolutionized in the late 1970s by the development of methods for long term in-vitro culture of *P. falciparum* and by recombinant DNA technology. The gene for the *P. falciparum* circumsporozoite protein was cloned in 1984 and human clinical trials, with a recombinant protein vaccine and a synthetic peptide vaccine, commenced in 1986. Unfortunately, these first generation anti-malaria vaccines were poorly immunogenic and did not confer protection to most vaccinated individuals (Ballou et al 1987; Herrington et al 1987). It was subsequently realized that highly immune individuals living in endemic areas, who had very high titres of anti-sporozoite antibodies, were not actually protected against infection and would periodically be infected by blood-stage parasites (Hoffman et al 1987). At about the same time, it was realized that heavily irradiated sporozoites, which failed to invade hepatocytes, were not able to induce protective immunity. Attention moved from the sporozoite itself to intrahepatic parasites and non-antibody-mediated immune mechanisms were explored.

These early studies were extremely instructive. Firstly, it became clear that although the attenuated vaccine approach might be theoretically possible, it was not feasible to produce parasites on the scale required and the only way forward was through recombinant DNA or synthetic peptide technology. Secondly, the simplistic approach of identifying an antigen on the basis of its recognition by immune serum, genetically engineering its production and injecting it with a standard adjuvant (alum) (Ballou et al 1987) or carrier antigen (tetanus toxoid) (Herrington et al 1987) was probably not going to work. Thirdly, there was a lot that could be learned about immune effector mechanisms in malaria by studying naturally acquired immune responses in malaria-exposed populations.

More recently, workers have had a much more focussed idea of what they expect a particular malaria vaccine to achieve, what the longterm benefits and potential hazards of vaccine implementation might be, how the vaccine should be formulated and how it can be evaluated.

Requirements for a Malaria Vaccine

The main market for a malaria vaccine will be in developing or newly industrialized countries. The health budgets of such countries are small and already overstretched. A malaria vaccine will need to provide a clear cost benefit—i.e. the cost of implementing a vaccine programme must be recoverable in terms of decreased treatment costs. This means that the vaccine must be cheap to buy and easy to administer. It should be stable at ambient temperatures (which can rise above 40°C in many endemic countries) to avoid the cost of cold storage and the risk of vaccine failure after breaks in the cold-chain. Ideally the vaccine should be highly immunogenic, protecting more than 90% of individuals after a single dose and being boosted by re-exposure in the field. In countries with poor infrastructure and highly mobile populations, vaccine programmes which require multiple injections and frequent boosting will rapidly breakdown. Maximum uptake of the vaccine will be achieved if it can be integrated into the existing WHO-sponsored expanded programme of immunization (EPI) for childhood diseases. Finally, the vaccine must be able to protect against all genotypes of malaria parasites, which means targeting conserved or semi-conserved antigens.

To date, most of the research effort has been put into a vaccine against falciparum malaria—partly because it is the most serious and most widespread of the human malarias but also because the development of in-vitro culture techniques for this parasite has made it much more accessible to laboratory workers. *Plasmodium vivax* is now receiving more attention and, with the benefit of experience gained with *P. falciparum*, research is moving ahead rapidly. There is still considerable debate about the extent of cross-immunity between the two species. In areas where both diseases occur together, there is a tendency to assume that some cross-immunity exists, although much of the data is anecdotal. There are regions of genetic sequence conservation between different *Plasmodium* spp but little evidence for widespread antigenic conservation, although the endotoxin-like molecules produced by rupturing schizonts are immunologically cross-reactive (Bate et al 1992)—which may explain why the clinical symptoms of falciparum malaria appear to be ameliorated in individuals with previous experience of vivax malaria. For the most part, however, it seems that separate vaccines will be required to protect against the two species of malaria.

Evaluation of Vaccine Candidates

Thus far, there are no reliable in-vitro tests which will predict whether an individual is protected against further malaria infection or disease. Response to vaccination can be monitored by sero-conversion or activation of various cellular mechanisms but these parameters do not necessarily correlate with protective immunity. Antibody screening may be of use for confirming vaccine viability and general immunogenicity during the implementation phase of a vaccine programme but may be of little use in monitoring vaccine efficacy during clinical or pre-clinical trials. The most promising surrogate measure of protection against blood-stage parasites seems to be the ability of immune serum to mediate antibody-dependent killing of intra-erythrocytic parasites (Bouharoun-Tayoun et al 1990) but the correlation only holds at a population level and will not predict whether specific individuals are protected. Also, this method is too cumbersome for wide-scale use in the monitoring of vaccine trials.

There are no completely appropriate animal models of human malaria. Immunization and challenge of New World monkeys is useful, although variation in individual monkey susceptibility to *P. falciparum* infection means that several animals need to be used in each experiment to assure a statistically significant result (Anon 1988). In the limited number of cases where human malaria vaccine trials have followed apparently successful monkey experiments, correlation between protection in monkeys and humans has been disappointing and some researchers are now questioning the value of such experiments.

The only certain way to evaluate new malaria vaccines is in clinical trials, which is time consuming and expensive. There are also ethical problems. On the whole, the countries where malaria vaccines are to be tested do not have their own indigenous vaccine development programmes. Health officials in these countries are being asked to make difficult decisions about the relative merits of different vaccine candidates and may be under pressure to cooperate with overseas funding agencies. Fortunately, WHO has undertaken the role of vaccine trials coordinator, acting as an independent scrutineer of preclinical data, defining trial protocols and matching candidate vaccines to appropriate trial sites.

Selection of Immunogens

Malaria parasites are genetically complex. Their genome contains somewhere between 3000 and 4000 genes, compared with an average of 30–40 genes in a relatively complex virus. Malaria parasites are also extremely genetically diverse and have demonstrated the ability to adapt rapidly to adverse circumstances, for example the spread of drug resistance (Walliker 1994). Antigenic polymorphism is the rule rather than the exception for malaria antigens, particularly for antigens on the surface of the parasite or infected host cells which are exposed to the immune system. Anti-malarial immunity is believed to be at least partially strain-specific although definitive epidemiological studies of the relative importance of strain-specific responses are only now being undertaken.

Although some malaria antigens are expressed throughout the life-cycle, each stage of the life-cycle expresses novel antigens. For example, the circumsporozoite protein is expressed on the surface of sporozoites and can be found in early liver-stage parasites and in the mature oocyst. Specific antigens are expressed on liver-stage schizonts which differ from those expressed on intra-erythrocytic schizonts and the sexual stages express another set of surface antigens. These antigens are not immunologically cross-reactive so that immunity raised to one parasite stage will not protect against other stages. Thus a vaccine based on the circumsporozoite protein would not protect against blood-stage parasites and if a single sporozoite successfully matured into a liver schizont, a

full blown blood-stage infection could follow. Similarly, a vaccine which reduced the development of asexual stages would not affect sexual-stage parasites—which may lead to selection for highly transmissible strains of parasite which have evolved to very early gametocyte production, as is believed to have occurred after the introduction of mass chemoprophylaxis in Africa, reviewed by Carter & Graves (1988). On the other hand, the formulation of a multi-stage vaccine, simultaneously targeting several different antigens, would allow the various immune responses to act synergistically, increasing the overall efficacy of the vaccine and hindering the spread of vaccine escape mutants.

For an antigen to be targeted by antibody-mediated immune effector mechanisms, it has to be expressed either on the surface of the parasite itself, or on the surface of the infected hepatocyte or erythrocyte. Malaria parasites are intracellular for most of the time, but sporozoites are vulnerable during the infection process, merozoites are extracellular during schizont rupture and reinvasion and gametocytes give rise to extracellular gametes in the midgut of the mosquito, where they are exposed to all the components of the blood meal including antibody, cells and complement (Carter et al 1988). In order to survive within the host cell, the parasite must modify the cell in various ways. This includes the insertion of parasite-derived antigens, such as specific transporter molecules, into the host cell membrane. In the case of *P. falciparum*, specific adhesion molecules are expressed on the surface of the parasitized erythrocyte which allow schizont-infected cells to adhere to the endothelium of post-capillary venules and thus avoid immune clearance in the spleen (Schlichtherle et al 1996). These cell-surface antigens are exposed to the immune system throughout the period of infection of the cell and are thus tempting targets for immune intervention to induce antibodies which inhibit cytoadherence and facilitate immune clearance of parasitized red blood cells.

Cell-mediated effector mechanisms can be triggered by virtually any parasite antigen. Dead parasites are phagocytosed and their constituent proteins expressed on the surface of antigen-presenting cells where they activate T cells. When these T cells subsequently come into contact with dead or dying parasites, or parasite antigens expressed on host cells, they may be directly cytotoxic (cytotoxic T lymphocytes, CTLs) or may induce the production of inflammatory mediators and parasiticidal molecules such as nitric oxide (Long 1993). The only parasite stage which is susceptible to $CD8^+$ CTLs is the intrahepatocytic stage, as human red blood cells do not express class I major histocompatibility complex (MHC) antigens. There has been considerable interest in the possible role of CTLs in anti-malarial immunity ever since these cells were found to confer immunity to malaria in mouse models (Romero et al 1988), however recent evidence throws doubt on the role of direct cellular cytotoxicity as the effector mechanism and it now seems likely that the effects are partly cytokine-mediated.

Another logical approach to vaccine development would be to target molecules which perform vital parasite functions. Such molecules tend to be functionally constrained in their structure and are thus less polymorphic. Potential targets include parasite-specific enzymes (such as those within the folate pathway, which have been inhibited pharmacologically) or molecules involved in the cellular invasion process (Holder & Blackman 1994). Finally, many of the pathological effects of malaria infection are believed to be mediated by parasite-derived endotoxin-like molecules, phospholipoproteins which may be derived from the glycophosphoinositol anchors attaching proteins to the parasite surface membrane (Schofield & Hackett 1993). The toxins of different malaria species are immunologically cross-reactive and neutralizing antibodies to them inhibit the induction of pro-inflammatory cytokine responses (Bate et al 1992). An anti-toxic vaccine thus has the potential to protect against clinical malaria but would need to be used in conjunction with an anti-merozoite vaccine to limit parasite growth. One disadvantage of this approach is that the toxins tend to induce T-cell-independent immune responses which are of low affinity and short duration (Bate et al 1990)—although this problem could be overcome by coupling the toxin to a protein carrier molecule. More problematic is the likelihood that these complex glycolipoproteins may be very difficult to synthesize.

Identification of potential vaccine targets is only part of the process; selecting which ones to follow up requires additional information. In the early days (1985 or thereabouts), candidate molecules were identified by immunoblotting with immune serum and their genes were cloned by screening expression libraries with the same serum. Some of these antigens are still prime candidates but many others have been exhaustively characterized but finally abandoned because, although they were highly immunogenic, the immune responses to them were not protective. Protective responses can be differentiated from non-protective responses by a variety of means including in-vitro testing of their ability to inhibit parasite growth or infectivity, or by immuno-epidemiological methods, looking for associations between immune responses and clinical immunity in endemic populations. As discussed above, these methods are by no means foolproof, but they do provide some objective criteria by which candidate antigens can be prioritized for further study. The immunological approach to malaria vaccine development has recently been extensively reviewed (Hoffman 1996).

Current Status of Candidate Vaccine Antigens

Pre-erythrocytic stage vaccines

Currently, two sporozoite surface antigens, the circumsporozoite protein and sporozoite surface antigen 2 (SSP2), and a number of liver-stage specific antigens, including liver-stage antigen 1 (LSA1), LSA2 and the sporozoite and liver-stage antigen (SALSA), are being evaluated as potential vaccine antigens. For the sporozoite proteins the main problem appears to be generating a construct which induces very high titre antibodies. Numerous approaches have been tried including expression in vaccinia virus, use of immuno-stimulating complexes (ISCOMS) and multiple antigenic peptides (MAP). More recently DNA vaccines have been explored (Hoffman 1996). Small-scale (Phase 1) human trials have been, and are being, conducted with a variety of immunogens but no large-scale clinical trials have been undertaken.

For the liver-stage antigens, formulations to induce cell-mediated immune mechanisms (CTL- and cytokine-mediated) are being evaluated (Nardin & Nussenzweig 1993). Although there is no direct evidence that CTLs are involved in protective immunity to malaria in humans, cloned CTLs are able to

confer protection in murine malaria, and lymphocytes from malaria-immune humans mediate lysis of target cells loaded with sporozoite or liver-stage antigen-derived peptides (Malik et al 1991). Given the diversity of HLA Class I alleles in human populations, defining a peptide vaccine which will induce CTLs in all, or a majority, of potential recipients may prove difficult.

Antigenic polymorphism does not appear to be such a major problem for pre-erythrocytic antigens as for blood-stage antigens. Variation in T-cell epitopes of the circumsporozoite protein has been described (Good et al 1988) but conserved T-cell epitopes have been identified which are recognized in association with most MHC class II alleles (Sinigaglia et al 1988). There are subtle variations in the sequence and number of tetrapeptide repeats which form the immunodominant B-cell epitopes, but these sequence variations do not appear to translate into significant antigenic polymorphism. LSA1 is highly conserved and contains well recognized T- and B-cell epitopes, including epitopes for CTLs (Fidock et al 1994).

Erythrocytic stage vaccines

Approaches to blood-stage vaccine development include induction of antibodies which mediate phagocytosis or cellular cytotoxicity of free merozoites, inhibit ligand-receptor interactions involved in merozoite invasion of erythrocytes or target essential enzymes. Antibody-independent mechanisms include induction of inhibitory cytokines and toxic radicals (Long 1993). Currently, two merozoite surface membrane antigens (merozoite surface protein 1, MSP1, and MSP2) and the apical membrane antigen (AMA-1) are undergoing safety and immunogenicity trials in humans, and efficacy trials in monkeys. Of these, a 19 kDa fragment from the C-terminus of MSP1 ($MSP1_{19}$) induces antibodies which are associated with protective immunity in humans (Riley et al 1992; Egan et al 1995). $MSP1_{19}$ has been expressed as a correctly folded protein in bacterial, yeast, insect (baculovirus) and vaccinia expression systems. The first three of these yielded highly immunogenic proteins but only the yeast and baculovirus products were able to induce protective immunity in monkeys and protection was dependent on the use of Freund's adjuvant (Kumar et al 1995; Chang et al 1996). Phase 1 human trials have begun with the yeast product, using alum as adjuvant, but no results have yet been reported.

The family of genes encoding the parasite-derived erythrocyte membrane proteins (PfEMP1) , which are believed to be involved in parasite cytoadherence and sequestration, have recently been identified (Borst et al 1995), opening up the possibility of exploiting these antigens as vaccines. The antigens appear to be highly immunogenic but they are extremely polymorphic and undergo clonal antigenic variation such that several different antigens are sequentially expressed by a single parasite clone during the course of a single blood-stage infection. From the data collected so far there appears to be very little sequence conservation between different members of the family, making it difficult to conceive how they might form the basis of a strain-independent vaccine. However, the function of PfEMP1 (cytoadherence to a small number of host adhesion molecules) is relatively conserved implying that there is conservation of crucial structures at the three-dimensional level even if there is little in the way of linear sequence homology. Recently described techniques such as random display of peptides on the surface of bacteriophage may be one way of identifying such 3-D structures (Schlichtherle et al 1996).

To date, the only asexual-stage malaria vaccine to have undergone multiple field trials is the synthetic peptide vaccine developed in Colombia by Dr Manuel Patarroyo (Moreno & Patarroyo 1989). The vaccine has been, and still is, the focus of unprecedented controversy (Maurice 1995). SPf66 was developed empirically by immunizing wild-caught *Aotus trivirgatus* monkeys with affinity-purified merozoite-derived proteins and challenging them with *P. falciparum*. Proteins which conferred some degree of immunity were partially sequenced and synthetic peptides derived from these sequences were used to immunize more monkeys. Promising peptides were combined and the most effective combination synthesized as a single hybrid polypeptide which was then polymerized (SPf66). The polymer contains sequences derived from three separate merozoite antigens (including an *N*-terminal sequence of MSP1) linked by a sequence derived from the repetitive B-cell epitope (NANP) of the circumsporozoite protein. Partial protection in some animals was observed in monkey trials (Patarroyo et al 1987) but two independent research teams were unable to reproduce these results (Herrera et al 1990; Ruebush et al 1990). In the first human trial of SPf66, levels of protection similar to those observed in the original monkey trial were obtained (Patarroyo et al 1988); 3 of 5 volunteers resolved a challenge infection without treatment but all volunteers developed clinical symptoms of malaria (fever, headache, nausea). There was no correlation between protection and any measured immunological parameter.

In the course of four combined safety, immunogenicity and efficacy trials in South America between 1988 and 1993, approximately 18 000 people received the SPf66 vaccine (Tanner et al 1995). Although the vaccine seemed safe, and estimates of efficacy varied from 30 to 80%, significant doubts remained. In the first three trials, estimates of efficacy were based on rather small numbers of clinical cases and the trials were either not properly randomized or had inappropriate controls. An independent randomized, double-blind, placebo-controlled trial of SPf66 was conducted in Tanzanian children in 1993. The vaccine had no effect on the incidence of infection or parasite density in asymptomatic infections but 58 cases of clinical malaria were identified in 274 vaccinated children and 88 cases in 312 placebo recipients—giving a risk ratio of 0·72 and an estimated vaccine efficacy of 31% (95% confidence interval, 0–52%) (Alonso et al 1994). A second independent trial in The Gambia (D'Alessandro et al 1995b) showed no protective effect of SPf66 vaccination in children under one year of age (7·1 clinical cases per 1000 child days at risk in the vaccinated group, 7·2 cases per 1000 days at risk in the unvaccinated group). Vaccinated children did, however, have high titres of specific antibody, indicating that they had responded well to the peptide immunogen. No protection against clinical malaria was observed and there were no significant differences between vaccinated and unvaccinated children in terms of parasite prevalence, parasite density or any other measure of malaria-related morbidity. A third independent trial in children in Thailand was similarly disappointing (Nosten et al 1996).

Despite their shortcomings, the first five trials all suggested that vaccinated individuals are at marginally lower risk of

clinical malaria than are unvaccinated individuals, but the protective efficacy is exceedingly small – too small to be measured accurately even in large field trials. The Tanzanian trial was restricted to children aged to 1 to 5 years but previous studies in the same population have shown that most malaria-attributable morbidity occurs in children under 1 year of age (Smith et al 1995). In contrast, the Gambian trial targeted children aged 6–9 months, precisely the time at which maternal immunity wanes and children become highly susceptible to infection—and the children were not protected. This suggests that the vaccine may be able to boost an existing immune response but is not able to immunise essentially naive individuals. There is no evidence so far that the vaccine prevents severe disease or death; mortality trials are necessarily very large and it is regarded as unethical to proceed with such a trial unless there is convincing evidence of protection against infection or clinical disease. The SPf66 vaccine is currently being redesigned and new peptide constructs are being evaluated.

Transmission blocking vaccines

The next malaria vaccine to reach full-scale clinical trials is likely to be directed against transmission stages (Kaslow et al 1992). A recombinant, yeast-derived polypeptide representing a zygote-specific surface antigen (Pfs25) induces transmission blocking antibodies which pass into the mosquito midgut, as part of the blood meal, and inactivate the developing ookinete. Human safety and immunogenicity trials of Pfs25 have been completed and preparations are underway for field-based efficacy trials. One disadvantage of Pfs25 as a vaccine antigen is that this protein is not expressed by parasite stages within the human host. Thus, a vaccine-induced immune response will not be boosted by natural reinfection. On the other hand, Pfs25 has a major advantage over other transmission-blocking vaccine candidates in that it has a relatively simple secondary and tertiary structure, allowing its expression as a conformationally correct protein which induces antibodies which bind to the native antigen on the parasite surface. In contrast, the two major surface antigens of gametocytes and gametes (Pfs230 and Pfs48/45), which are both targets of transmission-blocking antibodies, have a complex disulphide-bonded secondary structure which is essential for antibody recognition (Carter et al 1995). It has not yet been possible to express these two antigens in the appropriate conformation for recognition by transmission-blocking monoclonal antibodies or for use in immunization studies. Novel expression strategies may need to be exploited—for example, phage display—to recreate these complex epitopes.

Epidemiological Consequences of Malaria Vaccination

There are several possible outcomes of a successful malaria vaccine programme. Significant reduction of malaria transmission, morbidity and mortality would be considered a major achievement, but there are potential hazards.

Firstly, in endemic areas, the impact of malaria is greatly ameliorated by a high degree of naturally acquired immunity in the population, which is maintained by periodic subclinical infection. Stable endemic malaria is generally less of an acute health-care problem than is unstable epidemic malaria (although the chronic effects of persistent or repeated infections are frequently underestimated). Significant reduction of malaria transmission after introduction of a vaccine will reduce this natural boosting of immunity and delay the development of naturally acquired immunity in individuals who have not been vaccinated or who have not responded to vaccination. If the vaccine programme fails, and malaria transmission increases, these individuals are vulnerable to infection and are likely to develop symptoms at the severe end of the spectrum of clinical malaria. Importantly, a vaccine which is only partially protective but nevertheless reduces malaria transmission, could transform a stable situation into an epidemic one with a consequent increase in morbidity and mortality. Thus, vaccine programmes need to be integrated into a wider programme of malaria control and vaccines must be evaluated in comparison with and in conjunction with, alternative control measures, such as insecticide-impregnated bed nets.

Secondly, as discussed above, malaria parasites are genetically diverse with the capacity to evolve rapidly in response to a changing environment. The development of vaccine-resistant mutants is to be expected, particularly if the vaccine is based on a single antigenic peptide. In the long term we need to consider multivalent vaccines, targeting different stages of the parasite life-cycle and, preferably, including a transmission-blocking component.

The Future for Malaria Vaccines

In the 1970s and 1980s, numerous pharmaceutical companies, government-sponsored research agencies and international development organizations were investing in malaria vaccine programmes. Rapid progress in the sporozoite vaccine programme held out the prospect of a cheap synthetic vaccine with wide-scale applicability and large profits. However, it is already ten years since the results of the first clinical trials were published and there is still no firm evidence that a protective vaccine is in sight. Lack of definitive progress within the time frame originally envisaged has already led to a reduction in funding by most organizations and some have pulled out altogether. Most of the pharmaceutical companies are now just keeping a close eye on progress within the academic research community rather than investing directly in research and development.

The most successful vaccine programmes have been those where academic research programmes have had long-term financial support for both field-based and laboratory-based research coupled with access to industrial product development. The WHO continues to play a major role in motivating and coordinating the various research programmes, but has little in the way of financial resources to drive the process forward. These financial and political issues will need to be resolved if we are to stand a realistic chance of implementing a vaccine programme in the next 10 or even 20 years.

On the positive side, the last 15 years of intensive effort have paved the way for more rapid progress in the near future. Apart from the antigens highlighted here, there are numerous others which have been identified as potential vaccine candidates (e.g. SERA, EBA-175, RAP1, RAP2). Some of these are now being characterized while others have been shelved due to lack of resources. Several research teams have gained considerable expertise in conducting malaria vaccine trials and more precise definitions of clinical disease have been obtained

using data collected during the recent African SPf66 trials (Smith et al 1994). The methodology for conducting multicentre trials is much more sophisticated than it was 5 years ago and the next generation of trials should be quicker to get off the ground and easier to compare.

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