

## Towards a malaria vaccine for Papua New Guinea

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### SUMMARY

**Malaria is a major problem in Papua New Guinea, where it accounts for a high proportion of sickness and death. In addition to the human suffering, malaria also puts severe stress on the health services, and may directly hinder economic growth. A malaria vaccine would be the best, most cost-effective and safest public health measure to reduce the burden of malaria. Though considerable technical challenges are present, much natural and scientific evidence suggests a vaccine is achievable. Through the malaria vaccine program at the Papua New Guinea Institute of Medical Research, Papua New Guinea is playing a significant role in the global effort to develop a malaria vaccine, and ensuring that the malaria patterns of the Asia-Pacific region figure strongly in vaccine development strategies. Discussed here are some of the major issues to be considered as we work towards a malaria vaccine for Papua New Guinea.**

### The public health problem of malaria

Malaria continues to be a major cause of disease and death in tropical regions, including sub-Saharan Africa, Oceania, and South and Southeast Asia. Some 300,000,000 people become infected by malaria each year and as many as 3,000,000 people may die, the majority of deaths occurring in children under the age of 5 years. Malaria is also one of the major disease problems of Papua New Guinea and if the disease did not have a geographical restriction to low-lying areas, it might well have been the country's principal health issue.

The importance of malaria is acknowledged by the prominence of the disease in the Government of Papua New Guinea (PNG) National Health Plan 2001-2010. The national statistics presented show that malaria is the commonest cause of outpatient presentation and accounts for 27% of all attendance at a health facility. Furthermore, it is the second most common reason for admission to a health facility (15%) after obstetrics and the second most common cause of death (12%) after pneumonia. Serious as these statistics appear, they still do not reflect the full burden on the affected communities, as a large proportion of the PNG population live in the interior highlands that are largely malaria free. In an

area such as the East Sepik Province, where the Papua New Guinea Institute of Medical Research (PNGIMR) conducts malaria research, malaria accounts for more than 40% of health centre attendance and equals pneumonia as the primary cause of death (19/100,000). It should also be noted that the rural areas bearing the brunt of the disease also have less access to health facilities and it has to be assumed that the real figures for malaria mortality are much higher since many people die at home without receiving attention.

In response to this problem the PNG Department of Health has pledged to revitalize control programs and improve diagnostic and treatment services. However, this must be done against serious obstacles, such as growing resistance to drugs and insecticides, the extremely challenging logistics of serving remote rural populations and of course considerable financial constraints.

### The economics of malaria

Malaria takes an enormous toll on human health and well-being and in many regions this burden has been increasing even further in recent years. In addition to the human cost of pain and suffering, the costs of malaria are also enormous when measured in economic terms

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(1). Highly malarious countries are among the very poorest in the world, and typically have very low rates of economic growth. Malaria has played a significant role in the poor economic performance of these countries.

Traditional estimates have looked at some of the short-term costs of malaria without taking into account the long-term effects of malaria on development. Short-term costs, including lost work time, economic losses associated with infant and child mortality and morbidity, and the costs of treatment and prevention are typically estimated to be higher than 1% per year of a country's gross national product. Beyond these high and rising short-term costs, malaria restricts economic growth in many other ways. Malaria may impede the flows of trade, foreign investment and commerce, thereby affecting a country's entire population.

The effect of malaria on infected individuals may greatly exceed the direct costs of any single episode of the disease. Repeated bouts of malaria tend to hinder a child's physical and mental development, and may reduce their attendance and performance at school. Chronic malaria may also expose individuals to chronic malnutrition, anaemia and to increased vulnerability to other diseases. Additionally, as a consequence of the unequal social and economic burden of the disease on women (2), malaria may be contributing to the continuing gender inequity of development initiatives.

There have been no specific data gathered on the economic burden of malaria in Papua New Guinea. However, for a disease that accounts for between 25% and 35% of all outpatient attendances and is the second most common cause of death, it is likely that the situation reflects the global figures and that malaria has a significant impact on gross domestic product (GDP) and hinders economic growth.

The difficulty of making such a calculation is that the majority of the PNG population are rural subsistence farmers, with a complex relationship to the cash economy. For this reason the social impact of the disease is the primary indicator of its effect and typically this is the most difficult factor to quantify in cash terms.

There clearly must be a direct economic impact on the health budget of this widespread illness. Drugs must be dispensed, additional health workers and health posts must be maintained and hospital beds taken. However, as the budget is severely limited in PNG, pressure on the health system will be reflected in resources directed away from other areas, rather than cost increases. Thus this chronic, widespread and potentially controllable disease is holding back the more general health development of PNG.

### **The advantages of a malaria vaccine**

It is widely believed that a malaria vaccine would be the best, most cost-effective and safest approach towards radically reducing the burden of malaria (3). A vaccine that could be given to community groups, particularly in rural areas, on a scheduled basis, offers much more reliable protection than gambling that a health facility with appropriate drugs will be accessible to the patient at the time of a malaria attack. The logistics of vaccine delivery might also be simpler than the supply, constant use and regular maintenance of insecticide-treated bednets. Furthermore, the anticipated reduction in insecticide spraying activities may allow DDT usage to be discontinued, which would have beneficial environmental implications.

A malaria vaccine with even a modest efficacy of more than 50% would be a highly cost-effective measure for many endemic areas. Recent calculations estimate that a malaria vaccine that costs US\$1-7 per child per year, with a duration of protection of 1-5 years, distributed within the expanded program of immunization (EPI) and reducing all-cause childhood mortality by 30% or more would be a cost-effective intervention. The cost per disability-adjusted life year (DALY) of such a vaccine is US\$1-14, which compares very well with the use of insecticide-treated bednets at US\$7-14 per DALY (4).

### **The challenges of developing a malaria vaccine**

A number of pieces of scientific evidence justify the continued search for a malaria vaccine:

- i) Individuals living in endemic areas acquire functional immunity following continuous exposure
- ii) Passive transfer experiments show that immunoglobulins from semi-immune individuals can protect against clinical malaria
- iii) Specific antibodies suppress growth and multiplication of malaria parasites in vitro
- iv) Immunization with irradiated sporozoites of *P. falciparum* and *P. vivax* resulted in protective immunity in humans.

However, there are a number of reasons for not having an effective vaccine in hand at present. Despite the identification of an increasing number of potential parasite target antigens it is difficult to screen the effectiveness of these candidates and determine which should be carried forward into clinical development. The difficulties are mainly based on the complexity of the parasite and its life-cycle. Distinct immunological effector mechanisms are responsible for eliminating different forms of the parasite and in spite of careful analyses of the humoral and cellular immune responses of human trial volunteers, no immunological correlate of clinical protection has been identified so far.

This lack of knowledge hinders the selection of defined antigen and adjuvants and forces researchers to screen and extensively test a number of potential vaccine candidates, both in the laboratory and in the field, which involves considerable time and cost. Given the lack of surrogate measures, it is also very difficult to establish the criteria that lead from one clinical testing phase to the next. Lastly, malaria vaccine trials are conducted in countries where the perception of the disease and of clinical research in general may be very different from the one of the investigators, who often belong to industrialized nations. This difference has to be taken into account in the study design and implementation, and can only be dealt with appropriately by involving indigenous organizations and scientists very early in the process of research.

In order to compress the time scale of the

eventual development of a global malaria vaccine, more candidates must be brought to the field and tested in a timely fashion. This will require investment in production of clinical grade material for trial and an increased field capacity for culturally appropriate community-based trials.

### Which malaria vaccine?

There is a large bank of literature on potential vaccine candidates and it is not the intention here to provide a comprehensive review; rather to discuss some generally applicable points that have bearing on the vaccines given priority for testing in PNG.

All vaccine candidates are designed to mimic targets of the immune system and to boost the host immune response through exposure to them. Although many bacterial vaccines use whole-cell preparations, the technical difficulties of preparing large production runs of *Plasmodium* cultures makes this approach impracticable for malaria vaccines. The majority of vaccine candidates under investigation are therefore recombinant subunit vaccines.

Another important aspect of malaria vaccine technology is the delivery platform, that is to say, the way in which the vaccine is given to promote the most effective host response. This requires the parallel investigation of various adjuvants and vectors alongside the vaccine itself.

One of the major divides in the types of vaccines being delivered is the stage of the parasite life-cycle that they target. Much work has been done on the pre-erythrocytic stages (ie sporozoites and liver stage) that would produce sterilizing vaccines, preventing the parasite from establishing in the blood. However, the disadvantage of these vaccines is that they would prevent the development of any natural immunity and thus may prove to be more useful for visitors to malarious areas than for long-term residents. In contrast, vaccines that target the blood stages of the parasite imitate the acquisition of natural immunity. They allow infection of the blood but their effect should mitigate the progress of disease. The great advantage of this type of vaccine for an

endemic area is that there is constant boosting of the immune response by malaria infection, a state that reflects the natural balance of a semi-immune adult in a malarious area. The philosophy of these vaccines is not to prevent infection, but to protect from clinical disease while accelerating the process of acquiring natural immunity.

The third category of vaccines consists of transmission-blocking vaccines that do not provide any protection to the infected host, but prevent them transmitting the disease to another party. Combined with other measures or as a component of a multistage vaccine these might be useful in a malaria control program.

The choice of the PNGIMR has been to place its priority on the investigation and testing of blood-stage vaccine candidates. This type of vaccine, which assumes natural boosting, is the most applicable to the year-round transmission in PNG. However, the PNG malaria vaccine testing program will not totally exclude candidates from the other stages, if they show promise as components of a multistage vaccine, or for specific usage such as control of outbreaks in nonimmune populations.

One of the limiting factors of vaccine development is the availability of candidates produced in the quantity and quality required for testing. However, there are a large number of credible contenders which should be available for testing in the next few years, driven on by such funders as the Bill and Melinda Gates Malaria Vaccine Initiative (<http://www.MalariaVaccine.org>), whose mission is to accelerate the movement of antigens into clinical trial.

#### **Field trials of malaria vaccine candidates**

Only three important malaria vaccine trial programs took place in endemic areas in the last five years.

#### **SPf66 (South America, Africa and Asia)**

The multistage (sporozoite and asexual blood stages), multicomponent, synthetic peptide vaccine SPf66 (5) has undergone

several comprehensive trials. The results of 6 double-blind, randomized controlled trials undertaken in areas of different malaria endemicity ranging from Latin America to Asia and Africa revealed overall efficacy estimates of 23% (95% CI: 12-32) in reducing the incidence of the first and only attack of clinical *P. falciparum* malaria.

As the best use of a vaccine in Africa will be achieved if it can be delivered through the existing EPI, a large trial among infants of SPf66 administered at 1, 2 and 7 months of age alongside the EPI vaccines was undertaken in an area of high perennial transmission in Tanzania. While the vaccine was safe and did not modify the humoral immune responses to EPI vaccines, it did not, however, reduce the risk of clinical malaria (vaccine efficacy 2%; 95% CI: -16-16) (6).

Considering all of the results of the comprehensive clinical testing of SPf66, this vaccine in its current formulation does not appear to have a role in malaria control in sub-Saharan Africa. While these results are disappointing for malaria vaccine development, the experience with SPf66 has greatly enriched our understanding of steps, criteria and prerequisites of clinical tests with malaria vaccines. In addition, it may provide the basis for future developments with synthetic peptides.

#### **RTS,S (Belgium, Africa)**

Field testing of the recombinant pre-erythrocytic vaccine RTS,S/SBAS2 has not only shown its potency for inducing effective cellular and humoral immune responses, but also promising efficacy against both artificial challenge (7) and natural challenge (8). A recently completed study among male adults in The Gambia showed an overall vaccine efficacy of 16% (95% CI: -16-39) to reduce malaria infection or clinical episodes during the full trial period. However, during the first two months, efficacy was 65% (95% CI: 38-80). These promising results justify the conduct of further trials in younger children with this component. At the same time progress is needed to extend the period of protection, maybe through the inclusion of a new antigen, or through the use of a new delivery platform.

### **Combination B (Papua New Guinea, Australia, Switzerland)**

The PNGIMR, along with the Cooperative Centre for Vaccine Technology (Australia) and the Swiss Tropical Institute, has just completed analysis of a vaccine efficacy trial performed in the Wosera, East Sepik Province during the end of 1998 (B. Genton et al., submitted manuscript). This was a full-scale testing of the infrastructure at the test site. The exercise not only proved the system's capacity to perform trials effectively but also produced very encouraging results.

The vaccine on trial was an asexual blood-stage vaccine comprising merozoite surface protein 1 (MSP1), the 3D7 allele of merozoite surface protein 2 (MSP2) and the ring-infected erythrocyte surface antigen (RESA). Following convincing safety and immunogenicity trials (9), this combination was tried in a double-blind randomized placebo-controlled trial in 120 Papua New Guinean children aged between 5 and 9 years.

All of the 120 children completed the full vaccination schedule and of the 1080 planned blood samples only one was missed. This extraordinary compliance rate is a clear indicator of the level of community education and the enthusiastic volunteer participation at the Wosera site. The surrogate marker for vaccine effect was reduction in parasite density, as the small sample size and low incidence of disease prevented meaningful assessment of clinical malaria. The result of a 62% (95% CI:13-84) efficacy of the vaccine in reducing density of parasitaemia is the best effect of a malaria vaccine seen in any malaria-endemic area in the world so far. However, a genetic shift was subsequently observed in the parasite population away from the 3D7 form of MSP2 included in the vaccine and towards the complementary FC27 allele that was not included. This phenomenon clearly indicates that much further work needs to be done on these and other candidates and a greater mix of antigens included in the vaccine 'cocktail'.

### **The importance of a malaria vaccine testing site in Papua New Guinea**

Malaria is a complex disease, involving not only the infective agent but also its interplay

with the human immune response, which in turn is intimately related to vector transmission dynamics. Also, whilst the target of a vaccine to reduce mortality is the parasite *Plasmodium falciparum*, the deadliest form of malaria, the interplay with other *Plasmodium* species such as *Plasmodium vivax* is important in determining disease outcome.

Though by virtue of the actual numbers of victims, Africa has been the focus of the majority of research on malaria vaccines and other interventions, Africa in general has a very different disease pattern from that of the Pacific and Southeast Asia. The transmission in Africa tends to be seasonal, with wet seasons of intense transmission punctuated by dry seasons of little or no malaria in which natural immunity wanes. There is also little influence of *Plasmodium vivax* in the African context. Papua New Guinea has a general pattern of year-round transmission with significant levels of co-infection with *Plasmodium vivax* (10).

It is thus extremely important that vaccine trial results obtained in Africa are not assumed to be globally effective. It is imperative that candidates are also tested in the Asia-Pacific context, in order to ensure that the 'final' product of the international effort meets the needs of our region. The international malaria vaccine testing program should not be seen as a race to own a working vaccine, but a collaborative effort to make sure that good candidates are tested in multiple sites with different malaria patterns so the choice of an eventual global vaccine can be made.

### **The PNGIMR malaria vaccine testing program**

As early as 1979 PNGIMR expanded its long-established malaria program to initiate epidemiological studies as a background to malaria vaccine trials. From 1987 to 1994, funded by USAID, the Malaria Vaccine Epidemiology and Evaluation Project was undertaken (11). First in Madang and then in the Wosera, baseline studies in demography, epidemiology, genetics, immunology, parasitology and entomology were undertaken as an essential prerequisite to vaccine studies (10,12). During this period a substantial IMR

infrastructure was built up in the town of Maprik to support the predominantly community-based activities. From 1995 onwards, the Australian government has provided support to maintain and improve this infrastructure and given PNG the capacity to perform its first major trials, moving from safety and immunogenicity (phase I) to efficacy with natural challenge (phase IIb) testing.

The experience gained and the infrastructure built as well as the level of community involvement achieved has made the PNG malaria vaccine trial site a world-class facility. As new vaccine candidates emerge there is no doubt that PNG will be high on the list of testing priorities for vaccine developers worldwide. The strength of the site is that it is maintained and run by a PNG organization, which means it will be able to participate in such testing under its own terms. The funding of the site will not be dependent upon the groups promoting particular vaccines. We will therefore be able to set our own agenda and prioritize vaccines that may have eventual deployment in PNG, and make sure that malaria vaccines which are useful for PNG are pushed to the front row of international vaccine development strategies.

### Future directions

The future plans of the PNGIMR malaria vaccine program will clearly involve following up on the promising results of the previous trial, especially the testing of a formulation of MSP2 including both dimorphic types and of other MSP1 alternatives. As other candidates emerge, these will be trialed in a variety of combinations in a similar population to Combination B in order to develop an optimal formulation. Such a formulation will then be used in trials in 6 month to 4 year old children, the eventual target group.

It is important for PNG to exercise a global perspective and to use the valuable resource of the trial site to its full potential. To this end the PNGIMR will consider introducing into its testing schedule the trial of promising malaria vaccine candidates from around the world. Access to such candidates will undoubtedly be made easier through the facilitation of the

Malaria Vaccine Initiative, which will be supporting vaccine developers to get antigens ready for testing and promoting the use of the PNG site.

In the longer term the most successful of the antigens and combinations tested will progress through to large-scale trials that will be the strongest indicators of whether a particular vaccine will have substantial impact on malaria in PNG.

Much more work lies ahead for the PNGIMR malaria vaccine testing program, capitalizing on its experience and infrastructure, to further investigate the components of Combination B, to test new promising antigens, singly and in combination, and to move forward into trials in the younger target populations. With continuing support the PNGIMR will be well positioned to make an important contribution to the global malaria vaccine effort and to push towards a malaria vaccine to advance the health and development of Papua New Guinea.

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