

Is vaccination the only option for possible global malaria eradication?

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In the last century, vaccines, together with the discovery of antibiotics have been powerful tools in the management of infectious diseases. Both were of particular importance in reducing the morbidity and mortality associated with infections prevailing in the early 20th century. Whereas antibiotics were useful in treating the infection, vaccines worked by priming the uninfected individual against future infections. The success of vaccination can be seen through numerous examples. The World Health Organisation (WHO) was able to certify that smallpox had been eradicated in 1980¹ whereas the European Regional Commission for the Certification of the Eradication of Poliomyelitis declared the European Region polio-free on 21 June 2002.² On the other hand, measles has been reduced to very low levels in many regions of the world.³ This led to the speculation that such a good result could be extended to other diseases. Tuberculosis, human immunodeficiency virus (HIV) and malaria are currently three infectious diseases requiring urgent attention due to their serious consequences especially in less developed countries (Figure 1).

Preventing and treating malaria

The current measures used to prevent and treat malaria are:

1. Use of suppressive drugs for chemoprophylaxis
2. Pharmacological treatment of malaria cases
3. Vector control

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Although many of the above measures have been successful in controlling the spread of malaria in developed countries, the problem remains as severe as ever in most of the less developed countries.

Thus, one might argue that the current measures are not effective in such countries and innovative ideas are needed to combat malaria. This is where pro-vaccine scientists are advocating their cause for further vaccine research. Others argue that the current measures would be adequate to control the infection if used correctly.

Why develop a malaria vaccine?

“The malaria problem is too great to be overcome by the meagre resources traditionally devoted to health.”⁴ In his editorial, Graham Brown suggested that the control of malaria should become a national and international priority. Despite the various failures seen in trying to develop a good malaria vaccine there are two lines of evidence to suggest that such a vaccine could be attainable. Naturally acquired immunity can be acquired following natural exposure to infection.⁵ In fact, it has been shown that children living in areas of very high malaria transmission throughout the year in Africa (holoendemic areas) and who survive up to the age of 10 have a much lower probability of developing subsequent severe disease.⁶ Various immunisation strategies have been successful (in whole or in part) in inducing protection against experimental infection in animal models. Moreover, in humans it has been shown that using irradiated sporozoites, one can induce a 95% protection lasting for at least 9 months.⁷ However, these vaccines are strain and stage specific.

Using currently available control measures, it has been possible to eradicate malaria from a number of countries throughout the world without the benefit of a vaccine. These include many European countries and the United States.⁸ However, these strategies have had far less success in stifling malaria from tropical and subtropical countries. The problems encountered here include the biology and behaviour of certain species of anopheles (the vector responsible for the transmission of malaria), intricate immunological and host factors, poverty and unsettled political conditions, problems with accessing health care facilities and unexpected population movement

around the world.⁹ Therefore, in order to achieve better control in the latter countries, novel strategies are required. The development of an effective vaccine may be one such initiative.

A malaria vaccine is unlikely in the near future

The prospect of a malaria vaccine has been hampered by numerous obstacles. Although there were a number of vaccine trials in the past, many of them did not have the desired impact. Up to the present day, none of them could be launched as a preventive tool. In a study on Gambian infants¹⁰, a synthetic malaria vaccine, SPf66, was administered in a phase III trial to 55 children and compared to 32 infants who were given injected polio vaccine. It was shown that SPf66 did not protect Gambian children against first attacks of malaria or overall incidence of malaria infection.

If a vaccine were to be produced, it should target the various pathogenic species of *Plasmodium*. There are four major pathogenic organisms and a good vaccine should protect against all of them. However, since *Plasmodium falciparum* is the only one associated with significant mortality, development of a vaccine against it might be considered the major target. Moreover, there are multiple stages in the life cycle of *Plasmodium falciparum*. Each stage expresses a different repertoire of antigens (Table 1) and many of these exhibit

remarkable polymorphisms. Hence, any vaccine would need to include multiple targets which are normally expressed during the different stages of the life cycle, but this is very difficult to attain.

Organisms from different stages are present in different compartments of the host. Some are present intravascularly and these stimulate a humoral-mediated immune response. Others are present intracellularly and hence stimulate the cellular immune system. A good vaccine would induce both the humoral and cellular arms of the immune system. Unlike other currently available vaccines, such as hepatitis B vaccine and BCG (where only one arm is activated), this presents a major challenge.

The success in studies on animal models does not necessarily mean that it can be replicated in the human model. Pre-erythrocytic vaccines are straightforward since immunised volunteers can be tested for their ability to prevent blood-stage infection after exposure to infected mosquitoes. Even if it were shown that such a vaccine was useful, it would still be difficult to assess whether it acts similarly in people visiting endemic areas or in locals who are constantly exposed to malaria infections. Blood stage vaccines are more difficult to evaluate since studies will have to assess the level of parasitaemia following infection. This exposes volunteers to potential life-threatening infection and it is ethically necessary to treat as soon as parasitaemia approaches symptomatic levels. Hence, there is no way of knowing what level of parasitaemia would otherwise have

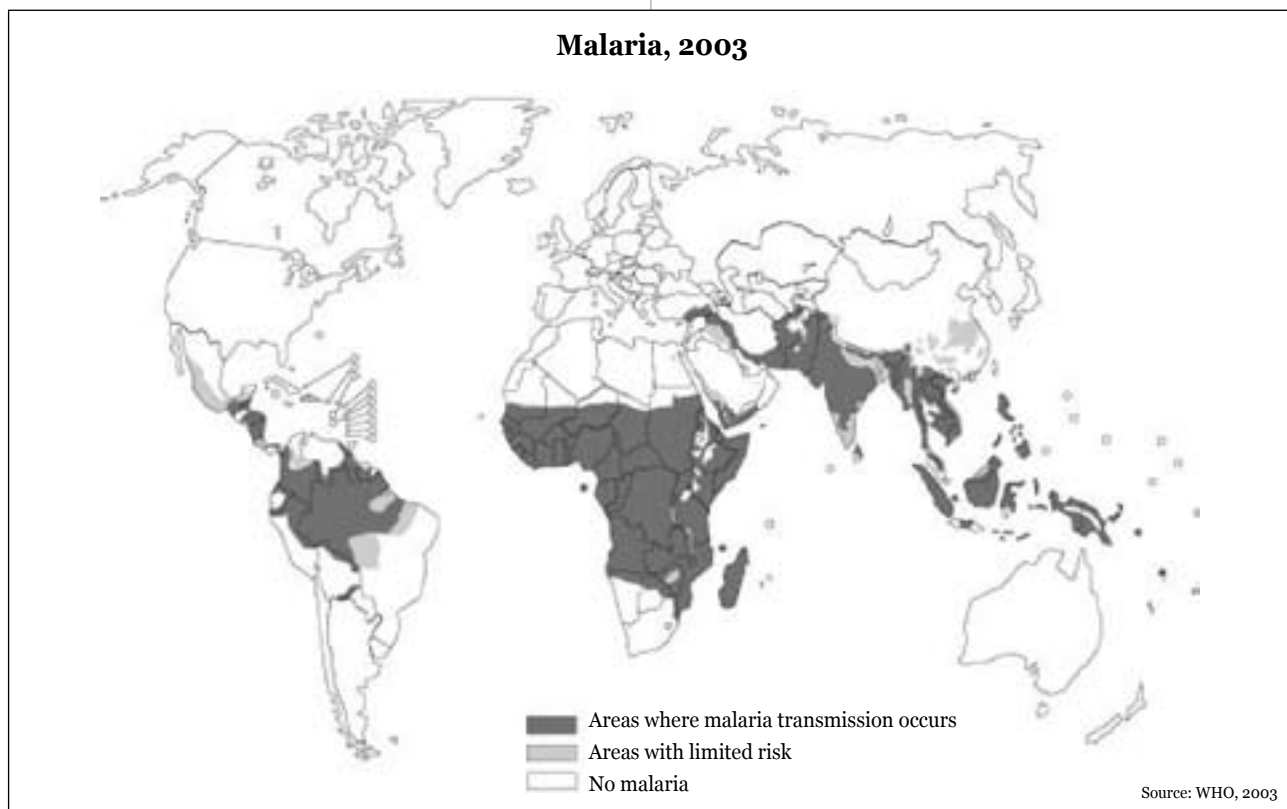


Figure 1: Areas of the world in which transmission of malaria occurs or where the transmission of malaria is a risk. (Source: WHO available at: http://www.who.int/ith/chapter05_mo8_malaria.html)

been reached in vaccinated people and those who are given a placebo.

Lastly, there has been reduced interest shown by the pharmaceutical industry to develop a malaria vaccine. A major driving force may be the fact that the vaccine will be used mainly in developing countries necessitating that the price of the final vaccine be affordable to such populations. Visitors to areas affected by malaria are few compared to visitors to other "safer" countries and this may result in too small a market.

Is the development of a malaria vaccine a priority?

A number of factors determine the priority of developing a vaccine. These are listed in the results of the Joint Global Alliance for Vaccines and Immunisation / World Health Organisation (GAVI/WHO) meeting held in Geneva in 1999¹¹ and they will be used here to assess the importance of malaria vaccine research around the globe.

- **What is the magnitude of disease burden?**

About 40% of the world's population live in malarious areas. It is estimated that 300-500 million people are infected by malaria per year and of these 1.5-2.7 million die. In the year 2000, malaria was estimated to be the cause for the loss of nearly 45 million Disability Adjusted Life Years (DALYs) and this accounts for 13% of all DALYs associated with infectious diseases.¹²

- **What is the public perception of the disease?**

Since so many patients are affected per year and the cost of disease is so high, the public perception is that if a vaccine is not readily produced, then the battle against malaria is eventually lost.

- **Is the science sufficiently mature to generate rational vaccine candidates?**

The life cycles of malaria and its vector have been known in detail for a number of years. Nowadays, the quest is to describe the life cycle at the molecular level and find target molecules which can be utilised in vaccine development. Malariologists are divided as to the best way to produce vaccines. One group believes that the parasite antigens already discovered should be enough to be able to elicit the immune response.¹³ Other scientists believe that with the sequencing of the parasite's genome, other candidate molecules could be found which may be more important than the ones already known.¹⁴

- **Are there already candidate vaccines in clinical trials or approaching launch into clinical field trials?**

Numerous malaria vaccines have been tested but none have withstood the test of time. For example, a clinical trial with a pre-erythrocytic vaccine made up of a fusion protein called RTS,S did show protection over the first 60 days after the third dose of vaccine, but the immunity waned with time such that the vaccine did not afford significant protection by the end of the study period of 105 days.¹⁵ The main problem is that different stages of the malaria parasite activate different branches of the immune system and most of the vaccines tested will only activate one arm of the immune system. A promising new approach is known as heterologous prime-boosting. Using this strategy, an antigen is presented in a series of different delivery systems that are administered sequentially.¹⁶ In fact, animal studies have been carried out using a regimen consisting of an initial vaccination with a plasmid containing a gene coding for the *Plasmodium falciparum* antigen thrombospondin-related adhesion protein (TRAP) as well as several other peptide sequences that might provoke an immune response, followed by a vaccination with recombinant modified vaccinia virus Ankara (MVA), which contained similar plasmodium genes.¹⁷ It is still to be seen whether the same vaccine would be effective in human beings.

- **Are there microbiological or parasitological factors that make vaccine development difficult?**

Multiple serotypes or antigens from different stages of the parasite must be included in the vaccine. It would be physically impossible to include all the possible variants in the vaccine. One would have to choose the most important ones and these may vary between different countries. The result may be that one would need a different malaria vaccine which is specific for the geographical area in which he/she lives.

- **Are alternative public health measures available?**

In the case of malaria, such measures are available but not fully effective. In other instances, they are not affordable.

- **Does an effective treatment exist?** It is common knowledge that effective treatment for malaria exists. However, the rapid emergence of resistance to treatment makes the issue of finding alternative means of control more urgent.

Table 1: Surface and secreted antigens produced at the different stages of malaria life cycle.

Life cycle stage	Stage specific antigen
Sporozoites	Circumsporozoite protein (CSP) Thrombospondin-related adhesive protein (TRAP)
Liver stages	Liver stage antigen 1 (LSA-1)
Merozoites	Rhoptry-associated protein-1 (RAP-1) Apical membrane antigen 1 (AMA-1) Erythrocyte-binding antigen (EBA-175)
Infected red blood cell	<i>Plasmodium falciparum</i> erythrocyte membrane protein 1 (PfEMP1)
Gametocytes	Pfs 48/45
Gametes	Pfg 25/27

- **Is there a traveller’s market in industrialised countries?**

There has been an increase in tourism to tropical countries recently. Although still not sufficient, this would increase the demand for a vaccine, particularly since the current method of chemoprophylaxis is not without its hazards.

- **Can the vaccine be combined or concomitantly delivered with other vaccines?**

This has not been dealt with yet since there has not been an effective vaccine tested on humans as yet. Theoretically, this is possible. In fact, it could be hypothesised that plasmids coding for antigens from different organisms would be genetically engineered and incorporated in vectors, such as MVA to deliver antigens from more than one organism.

- **Can the vaccine be attractive to developing countries?**

This will need to be addressed once a viable vaccine is found. The possibility of administering the vaccine parenterally or in 1-2 doses only would be preferable.

- **Can the vaccine be cost-effective, assuming optimal implementation?**

In an analysis comparing the cost-effectiveness of vaccines and insecticide impregnation of mosquito nets for the prevention of malaria, Graves¹⁸ estimated that the costs per death averted for a vaccine would be US\$252 compared with US\$771 with nets impregnated with insecticide every six months. On the other hand, if one had to use an insecticide-impregnated wash-proof mosquito net (which could be sold for the same

price as an untreated net), the cost would be nil.¹⁹ Thus, the conclusion that malaria vaccine research and development should be the highest priority for investment might need to be reconsidered.

Possible unexpected consequences of a malaria vaccine

With all the major benefits of a malaria vaccine, possible problems could still arise. After the introduction of a vaccine, the pathogen might evolve in response to selection pressure. A major concern is “escape mutants” which are variants expressing epitopes that vaccinated individuals fail to recognise. This is best seen in HIV, where the difficulty with producing a vaccine is the high mutation rate of the virus such that new clades arise which are not recognised by the host’s immune system.

The worst scenario is seen when a parasite with a higher virulence evolves. In such cases mortality in those affected by malaria would be increased, hence abolishing the effectiveness of the vaccine.²⁰

Alternatives to vaccination

Due to the difficulties in developing a commercially available malaria vaccine, other approaches to eradicate the disease need to be considered.

Widespread use of insecticides has resulted in selecting anopheline mosquitoes that are resistant to the most affordable insecticides.²¹ Similarly, attempts to reduce the incidence of malaria by improved access to treatment have selected parasites that are resistant to the most affordable drugs.²²

There is an urgent need to find ways of re-establishing the efficacy of previous tools and preserving existing ones. Unfortunately, certain measures being adopted encourage further resistance. For example, when analysing the latest figures on malaria treatment in Africa, it can be seen that more

money is being spent on chloroquine which, although costing \$0.10 per dose, is largely ineffective in this area. Combination treatments based on artemisinin would be highly effective in Africa, but costs at least ten times as much.²³ Chloroquine use in such areas is also exposing patients unnecessarily to the side effects of the drug.

The alternatives are:

1. Use of the **best available drug treatment** to treat all malaria cases. This involves
 - a. choice of appropriate treatment depending upon the patient and resistance pattern of the parasite. Quinine is the recommended drug treatment for acute falciparum malaria provided that the patient was not on any quinine-based chemoprophylaxis or living in areas of reported quinine resistance.²⁴
 - b. use of combination therapy to increase efficacy and reduce emergence of resistance. Two particularly promising examples are atovaquone with proguanil²⁵ and artemisinin-based combinations.²⁶ The latter group offers an exciting prospect in the management of malaria and use of such combinations is advocated by WHO.²⁷
 - c. Use and development of alternative dosage forms and formulations. There is plenty of ongoing research to develop drug formulations that are efficacious and enhance patient compliance. Included are the use of rectal formulations of artemisinin²⁸ and quinine²⁹, and research into a transdermal mode of delivery of the drug.³⁰
2. Encourage **home-based management of malaria** in areas where treatment of uncomplicated malaria starts at home.³¹ It has been recognised that, in endemic countries, most episodes of malaria are first managed outside public health facilities, usually by the parents of affected children. Research has shown that a number of factors can improve home-based management. These include:
 - a. availability of unit-dose packaging of full-course therapy with pictorial labelling
 - b. training of parents and community health workers to recognise malarial symptoms early and treat promptly
 - c. Training of retailers so that they are able to offer appropriate antimalarial drugs at the right dosage
 - d. Community-targeted information, education and communication (IEC) for behavioural change.

3. In places where the cost of treatment is beyond reach, investing in **prophylaxis against the disease** may be feasible. Thus, making insecticide-impregnated mosquito nets widely available to the population can have a major impact on the incidence of the disease.³²
4. Over the past years, new breeding sites for mosquitoes were created through deforestation, mining, irrigation projects and road building. These environmental changes might be expected to be of economic benefit to the country involved but will definitely lead to a worsening scenario in the context of malaria.³³ **Education, international help and political pressure** might change the situation.
5. The major strategy of using **insecticides to control the mosquito population** has led to the emergence of insecticide-resistant mosquitoes. The high costs of control programmes have forced their reduction or total abandonment in some regions.³³ Such a problem could be dealt with by using more than two insecticides at the same time. This would hopefully prevent the emergence of resistance, just like combined antibiotics are given to treat infection.¹⁹

As it stands now, in addition to suffering and death, malaria penalises poor communities as it perpetuates poverty through loss of work force, school drop-outs and decreased financial investment. It is estimated that Africa's GDP would be up to USD 100 billion greater if malaria had been eliminated years ago.³⁴ Moreover, malaria could be prevented or treated for between \$0.50 and \$10. Many of the developing countries could reduce malaria deaths by half if the already existing tools are wisely and widely used.³⁴

The major problem here is that USD 1 billion annually are necessary to implement, finance and deliver the above recommendations. This is much more than most developing countries could ever aspire to afford.

Conclusion

The hard facts about malaria are far from comforting. Anti-malarial drugs have always been the mainstay of defence against the malaria parasite. If these are to remain effective, it is essential to track drug resistance as it appears. Also it does not matter how effective the next generation of anti-malarials are. If they are administered incorrectly, resistance soon appears and will annihilate a whole generation of drugs.

The Roll Back Malaria campaign initiated by WHO has had some success in curbing the disease, although not all the main targets have been met. Thus, places, such as Vietnam have seen a reduction in malaria deaths by 97% in a five-year timespan. Similarly, in Kenya, efforts to promote the use of bednets have helped to reduce malaria cases.³⁵ More research into developing new antimalarials, vaccines and rapid diagnostic methods is required to halt the progress of such a devastating disease.

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