REVIEW ARTICLE

Malaria Vaccine: The Pros and Cons

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Abstract

Background: Malaria is an important parasitic disease of humans caused by infection with a parasite of the genus Plasmodium and transmitted by female anopheles. Infection caused by P. falciparum is the most serious of all the other species (P. ovale, P. vivax and P. malariae) especially in terms of morbidity and mortality hence the reason why most of the research has been focussed on this species.

The disease affects up to about 40 per cent of the world's population with around 300-500 million people currently infected and mainly in the tropics. It has a high morbidity and mortality especially in resource-poor tropical and subtropical regions with an economic fall of about US$ 12 billion annually in Africa alone.

***Method:** relevant literatures were reviewed from medical journals, library search and internet source. Other relevant websites like PATH, Malaria Vaccine Initiative and Global Fund were also visited to source for information. The key words employed were: malaria, vaccine, anopheles mosquito, insecticide treated bed-nets, pyrethroids and Plasmodium.*

***Results:** several studies have underscored the need to develop an effective human malaria vaccine for the control and possible eradication of malaria across the globe with the view to reduce the morbidity and mortality associated with the disease, improve on the social and economic losses and also protect those at risk.*

***Conclusion:** It is very obvious that the need for effective human malaria vaccine is not only to serve those living in malaria endemic regions but also the non-immune travellers especially those travelling to malaria endemic areas; this would offer cost effective means of preventing the disease, reducing the morbidity and mortality associated with it in addition to closing the gap left by other control measures. It is very obvious that there is no single control measure known to be effective in the control of malaria, hence the need for combination of more than one method with the aim of achieving synergy in the total control and possible eradication of the disease. It suffices to say that despite the use of combination of more than one method (e.g. drugs treating patients, breaking the life cycle of the vector mosquito using larvicides, clearing swamps and other mosquito breeding sites), no much progress was made towards achieving this goal, hence the renewed interest especially with regards to vaccine development.*

***Key words:** malaria, vaccine, anopheles mosquito, insecticide treated bed-nets, pyrethroids and plasmodium*

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Introduction

Malaria is the most important parasitic disease of humans caused by infection with a protozoan parasite of the genus *Plasmodium* of the order Haemosporida in the phylum Apicomplexa. Infection caused by *P. falciparum* is the most serious of all the other species *(P. ovale, P. vivax and P. malariae)* especially in terms of morbidity and mortality hence the reason why most of the research has been focussed on this species[1,9].

Malaria is transmitted between hosts by female mosquitoes of the genus *Anopheles* and affects

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up to about 40 per cent of the world's population with around 300-500 million people currently infected and mainly in the tropics. There are between 1.5 to 2.7 million deaths every year, especially children of the under five group; pregnant mothers are also more vulnerable leading to life threatening complications like anaemia, miscarriages, low birth weight babies and premature deliveries especially in resource-poor tropical and subtropical regions[1,2,9] and furthermore, exacts an economic fall of about US$ 12 billion annually in Africa alone[9].

It cannot be disputed that several attempts have been made in the past hundred years to control, reduce and eradicate the impact of malaria using different methods but with little success made especially in tropical and subtropical Africa and some parts of Asia. The control strategies currently in use using rapid diagnosis and treatment as well as methods to reduce the man-vector contact have had limited success. In view of the increasing morbidity and mortality associated with malaria and also the complex and adaptable nature of the parasite, there is a renewed interest especially with regards to vaccine development[1,9,15].

In Nigeria, a study conducted by Agomo CO on the prevalence of malaria in pregnant women in Lagos, the prevalence was 7.7% (95% confidence interval; 6.2-9.4%)[12]. However, there is no documented study on malaria vaccine trial to date. However, in view of the adverse outcomes often associated with malaria in pregnancy, the commonest prevention strategy in pregnant mothers, as shown in a study by Wagbatsoma VA and Omoike BI in Edo, is either sulphadoxine-pyremethamine combination, insecticide treated bed-nets or both; these preventive measures, either alone or in combination, proves to be effective[13].
In some African countries (including Kenya, Tanzania and Mozambique) where malaria vaccine trials are ongoing,

The epidemiologic, molecular, immunologic and pathologic aspects of the plasmodium species in addition to the life cycle of malaria parasite (as shown in figure 1) are essential to the understanding drug treatment, vaccine development and control measures as well. The intensified effort towards developing a malaria vaccine led to further interest in the understanding of the immune response to malaria. Immunity to malaria, which involves both humoral and cell mediated mechanisms and which may be directed against different antigens, is acquired from natural infections at the rate which depends on the level of exposure. Malaria antigens have polymorphic features thus immune response against one parasite may not cross react with the other leading to strain specific immunity. There is production of antibodies to sporozoites, cell mediated immune responses to early exoerythrocytic liver stage and antibody production to surface antigens to the infected red blood cells[1]. The immune response in malaria infection is not very effective because it fades easily and cannot eliminate the parasites completely. The life cycle presents a number of immunologic problems for the host and development of effective and safe vaccines[1,3].

Furthermore, the knowledge of the molecular biology has greatly contributed to the understanding of potential target antigens to be synthesized in large quantities for use in vaccine development. Inflammatory cytokines (e.g. IFN-γ, nitric oxide, IL-1, IL-6 and TNF-α) often triggered by the release of toxins during schizogony plays an important role in the symptoms of malaria thus explaining the molecular and pathological aspect of the disease[1]. It worthy to note that low levels of the circulating inflammatory cytokines are of beneficial to the body in malaria attack since they help activate macrophages to engulf infected red blood cells and to further release toxic radicals to be able to kill the malaria parasite. However, high levels of these cytokines lead to fever and other symptoms of malaria which results due to the inhibition of erythropoiesis (leading to anaemia), decrease blood glucose levels (resulting to hypoglycaemia) and adhesions of molecules to the vascular endothelium (leading to sequestration of parasite thus cerebral malaria); it has been documented that about 10 to 15 per cent of hospital malaria admissions due to severe anaemia or cerebral malaria will die despite effective supportive and anti-malarial treatment hence the need for developing an effective malaria

vaccine to be able to prevent the disease from setting in[1].

Control Measures: In discussing the modern concept for the control of malaria, it could be said that it was Ross who conceived the idea that it is necessary to break the chain of transmission by the use of quinine for treatment as well as prophylaxis in addition to other anti-mosquito measures[1]. Thus it is very obvious that there is no single control measure known to be effective in the control of malaria, hence the need for combination of more than one method with the aim of achieving synergy in the total control and possible eradication of the disease. It suffices to say that despite the use of combination of more than one method (e.g. drugs treating patients, breaking the life cycle of the vector mosquito using larvicides, clearing swamps and other mosquito breeding sites), no much progress was made towards achieving this goal[1].

There are basically two main strategies employed in the control of malaria which has been in use for over a century; these are anti-mosquito and anti-parasite measures. The anti-mosquito measures include the use of insecticides against the larvae and adult forms, bed nets, insecticide impregnated bed nets, insect repellent and use of protective clothing. The anti-parasite measures include provision of early diagnosis and treatment using anti-malarial, prophylactic use of chemotherapeutic agents, removal of breeding site, clearing of ditches, use of sterile adult male Anopheles and breeding of fish to feed on the larvae of the parasite. These various methods have been in use for over a century but without being able to effectively control or eradicate the disease especially in Africa where greatest burden of the disease is being felt. There is no doubt that improvement on some or all of these measures would go along way at improving the control notwithstanding the fact that, the development of effective malaria vaccine is not something that cannot be substituted or negotiated easily[1].

It could be recalled that in 1955, the concept of malaria eradication was adopted at the 14th World Health Assembly (WHA) of the World Health Organization (WHO) with an excellent result within 15 years of its operation especially in the Europe, North America, the USSR, Australia and some parts of Asia but less so in the tropical countries (for some obvious reasons which include poverty, lack of commitment of government amongst others).

As a result of this failure especially in the tropical countries, the WHO in 1957 again revised the strategy by improving on disease surveillance, involving the health institutions, development of new and effective anti-malarial drugs and research. In 1969, the emphasis on eradication was switched to control in view of the fact that eradication was not practicable[1].

In 1985 at its WHA 38.24, the WHO recommended that malaria control be part of the primary health care in system in individual governments. In 1998, the WHO introduced the 'Roll Back Malaria' partly because malaria in sub-Saharan Africa has deteriorated and with the aim of developing a sector wide approach in combating the disease. Despite all these, the past decade recorded an alarming increase in the incidence of malaria in several countries especially of the tropical area, and also malaria resurgence in those places where in the past the eradication programmes appeared to be working. The reason for this is multi-faceted and include the issue of drug and or multidrug resistance to virtually all the anti-malarial by the parasite, resistance to the insecticides by the vectors, increase in global warming, uncontrolled urbanization, lack of commitment and political will in some countries, health system reforms with adverse consequences especially in the developing countries with poor per capita income, poverty and to some extent the negative effect of globalisation especially in the sub-Saharan countries of Africa, war and civil unrest and the adverse interaction between HIV and malaria[1,4,6,7]. It should be noted that malaria increases viral load in HIV and also HIV increases malaria fevers[6,7].

The control measures in place are ineffective hence the need for developing an effective malaria vaccine to achieve a good control and possible eradication. There is resistance to and high cost of producing anti-malaria drugs, resistance to insecticides (DDT and pyrethroids)

by the vectors, cost of producing conventional or long-lasting insecticide-treated bed-nets (ITNs/LLINs), uncertainties associated with larval control, and poor compliance and non-adherence to the control measures on the side of the human population[1,4,8].

Malaria Vaccine: In history, modern vaccine development started over 200 years ago and it was Edward Jenner who first developed a small pox vaccine in 1789. Despite this, it was not until 1980 when the WHO declared that small pox was eradicated[5]. There are several other vaccines which were developed by renowned figures in the history of medicine whose contributions tremendously help in the control and spread of life threatening diseases; most of these vaccines were developed empirically and from either killed or attenuated whole organism[1]. It suffices to say that these vaccines were not developed overnight as it took enormous time, energy, patience and resources to be able to do that. However, it could be said that vaccines has had a more positive effect on reducing death and helping populations across the globe.

Historically, attempt to develop an effective human malaria vaccine dates back to about 100 years but because of the complex nature of the parasite and its life cycle, little progress was made in that aspect. In 1900, an Italian Angelo Celli unsuccessfully attempted immunisation with dried infected red blood cells to induce fever and the transfer of serum to prevent fever. There were several successful attempts in experimental animals and in 1961, McGregor and Sydney Cohen showed that children could acquire protection using gamma globulin component of immune sera[1,14].

However, the manufacturing, trial and assessment of malaria vaccine involve complex steps and thus the need to be increasingly redefined to be able to get a multi-component vaccine which has both cellular and humoral components. There are recordable successes made in this regard which include the possibility of using live irradiated sporozoites to induce high levels of antibody directed against sporozoites invading liver cells (CSP[circumsporozite protein]), inclusion of epitopes that stimulate helper and cytotoxic T cells, synthetic peptide vaccine (SPf66) which include part of the N-terminal sequence of the merozoite surface protein, ultra-low dose infected red blood cells and MSP-1 (merozoite surface antigen) and AMA (apical merozoite antigen) acting on blood stage. The latest class is the new generation CSP vaccines with a powerful adjuvant named RTS,S which shows promising results in field trials in Africa.

The RTS,S was the first candidate malaria vaccine to have reached this developmental stage; it has been subjected to extensive clinical studies in humans and have indicated possible protective efficacy especially when used in combination with an adjuvant therapy[11].

In a randomise trial of SPf66 vaccine P. falciparum malaria in children in southern Tanzania, the best estimate of the SPf66 vaccine protective efficacy was 31% (95% CI : 0.52)[15]. In another study, a double-blind randomised trial in Kenya and Tanzania, with a view to evaluate the efficacy of RTS,S given with a more immunogenic adjuvant system (AS01E) in children 5 to 17 months of age, the adjusted rate of efficacy against all malarial episodes was 56% (95% CI, 31 to 72; P<0.001)[16].

Other clinical trials include synthetic, recombinant and DNA vaccines, and vector encoded vaccines. It should be noted that these vaccines are directed either against the development of the parasite before the blood stages appear, asexual blood stages, the sexual cycle of the parasite or against the liver stages[1,8].

It has been observed from trials that the single antigen CSP was not successful which lead to the issue of developing multi-component multi-antigen vaccine (MCMAV). The MCMAV involves the use of more than one antigen with a view to get an additive effect such that together they will be much more effective thus to deal with the issue of antigenic polymorphism. The MCMAV will also ensure attack on different stages of the life cycle of the parasite, and a reduction in the chances of resistance to the vaccine by the parasite[1,8]. However, there are issues which include the possibility of one component interfering with the immune response to another and also the induced immune response may likely be complicated[1].

Figure 2 shows some of the vaccines undergoing trial and their sites of action.

There are several other studies conducted testing different types of malaria vaccines all with differing results. In another randomised controlled trials in endemic areas with the aim of assessing malaria vaccine (in preventing infection, disease and death), four types of malaria vaccines (SPf66 and MSP/RESA against the asexual stages, and CS-NANP and RTS,S against the sporozoite stages) were used. The result showed no evidence for protection by SPf66 against P. falciparum in Africa but modest reduction in attacks in other regions; no enough evidence to evaluate the use of CS-NANP vaccines; there was a promising result with RTS,S and MSP/RESA vaccines[17].

The caveat with most vaccines is on their drawbacks to which malaria vaccine is not an exception. Some of the drawbacks associated with malaria vaccine include:

*Immunopathological complications could arise with malaria vaccine as a result of excess production of inflammatory cytokines[1]. As mentioned earlier, the symptoms of malaria arise due to over production of inflammatory cytokines while only low level of these are required to facilitate killing of the parasite.

*Repeated exposure to malaria leads to acquiring immunity which confers protection to individuals; this immunity wanes out easily if exposure rate reduces. There is possibility of loss of naturally acquired immunity which could result due to loss of reduced malaria transmission in a well vaccinated population. Thus resistance to the malaria vaccine or interruption in the vaccination exercise could lead to drop in immunity and certainly prone the population to malaria epidemic with resultant high morbidity and mortality. This interruption could arise due to either lack of resources, change in political will of governments, natural disasters or war[1].

*Cost implications, administrative, manpower, possibility of vaccine failure and other logistics involved.

Conclusion

I wish to conclusively state that effective human malaria vaccine is urgently needed to serve those living in malaria endemic regions as well as the non-immune travellers especially those travelling to malaria endemic areas; this would offer cost effective means of preventing the disease and death in addition to closing the gap left by other control measures. It is in records that several resources have been sunk in the past decades in an attempt to improve the current available control measures but without achieving much due partly to continuous resistance of malaria parasite to drugs and mosquitoes to insecticides. In spite of the complex life cycle of the malaria parasite, there are great prospects from malariologists on the deployment of an effective malaria vaccine possibly in a decade or two; this is more so especially with the advances recorded in the fields of genomics, proteomics, vaccinology, molecular and population biology, population genetics and quantitative epidemiology. These vaccines should aim at being safe, effective, affordable, to provide a long lasting immunity and to protect against all forms of the disease. In the African continent where greater burden is being felt, it could be dispensed through national immunization programmes. The vaccine developments is feasible but with more support especially in terms of funding to support more scientist and vaccine developers use their intellectual capital to achieve this long awaited goal and government at both national and international levels should also support its delivery and use. The international community has shown their commitment in this regard through the formation of the Malaria vaccine Initiative, Global fund for AIDS, Tuberculosis and Malaria by committing billions of US dollars which is worthy of commendation[9,10].

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