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Malaria vaccine can prevent millions of deaths in the world

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Malaria is a major public health problem, afflicting ~36% of the world's population. The World Health Organization (WHO) has estimated that there were 216 million cases of malaria in 2010, and ~655 000 people died from the disease (~2000 per day), many under age five. Yet the disease, a killer for centuries, remains endemic in many poor nations, particularly in Africa, where it is blamed for retarding economic growth. India contributes ~70% of the 2.5 million reported cases in Southeast Asia. Malaria is also an important threat to travelers to the tropics, causing thousands of cases of illness and occasional deaths. The 5 *Plasmodium* species known to cause malaria are *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Most cases of malaria are uncomplicated, but some can quickly turn into severe, often fatal, episodes in vulnerable individuals if not promptly diagnosed and effectively treated. Malaria vaccines have been an area of intensive research, but there is no effective vaccine. Vaccines are among the most cost-effective tools for public health; they have historically contributed to a reduction in the spread and burden of infectious diseases. Many antigens present throughout the parasite life cycle that could be vaccine targets. More than 30 of these are being researched by teams worldwide in the hope of identifying a combination that can elicit protective immunity. Most vaccine research has focused on the *P. falciparum* strain due to its high mortality and the ease of conducting in vitro and in vivo studies. DNA-based vaccines are a new technology that may hold hope for an effective malaria vaccine.

Malaria Vaccine can Prevent Millions of Deaths in the World

Malaria continues to be a major public health problem, afflicting 36% of the world population in 107 tropical and sub-tropical countries. The WHO has estimated that in 2010 there were 216 million documented cases of malaria. Around 655 000 people died from the disease (roughly 2000 per day), many of whom were children under the age of five, in addition to hundreds of millions of febrile episodes.¹⁻³ Even though the number of deaths has decreased substantially from 985 000 deaths in 2000, the disease remains endemic in many poor nations, particularly in Africa where it is blamed in part for holding down economic growth. India contributes ~70% of the 2.5 million reported cases in the Southeast Asia. It is well known that the greatest burden of falciparum malaria is borne by children and pregnant women in tropical Africa. Yet people living on the Indian subcontinent and in other parts of Asia, Latin America and the Western Pacific also are substantially affected by malaria and malaria-associated deaths, including disease and death caused by *Plasmodium vivax*, the toll of which is under-appreciated.^{4,5} Malaria is also an important threat to non-immune travelers to the tropics, causing thousands of cases of illness and occasional deaths. The actual number of deaths may be significantly higher, given that precise statistics are unavailable in many rural areas, and many cases are undocumented. Malaria is commonly associated with poverty and is also a major hindrance to economic development.

Malaria is caused by infection with *Plasmodium* protozoa transmitted by an infectious female *Anopheles* mosquito

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vector, which is transmitted via the bites of infected mosquitoes. The 5 *Plasmodium* species known to cause malaria in humans are *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*.^{6,7} Timely identification of the infecting species is extremely important, as *P. falciparum* infection can be fatal and is often resistant to standard chloroquine treatment. *P. falciparum* and *P. vivax* are responsible for most new infections. The parasites multiply in the human liver, and then infect red blood cells. Usually, people get malaria by being bitten by an infectious female *Anopheles* mosquito. Only *Anopheles* mosquitoes infected through a previous blood meal from an infected person can transmit malaria. When a mosquito bites an infected person, a small amount of blood is taken which contains malaria parasites. About one week later, when the mosquito takes its next blood meal, these parasites mix with the mosquito's saliva and are injected into the person being bitten.

While most cases of malaria are uncomplicated, infection that is not promptly diagnosed and effectively treated can become severe, even fatal, episodes in vulnerable individuals. Diagnosis has long been based on microscopic detection of asexual malaria parasites on a blood smear from a person suspected to have malaria. But many areas lack laboratory support to provide such microscopy. Even where it is available, many factors affect the quality of microscopic diagnosis: the experience and training of the microscopist; the quality of the slide preparation, staining and reading; the quality of the equipment; and the availability of electricity and reagents.⁶ Malaria diagnosis is frequently based on non-specific symptoms, often resulting in misdiagnosis and unnecessary treatment with anti-malarial drugs. Rapid, accurate and accessible detection of malaria parasites has an important role in diagnosis and in promoting more rational use of increasingly costly drugs. Rapid diagnostic tests (RDTs), which work by detecting specific malaria antigens or enzymes,⁷ can potentially provide accurate diagnosis to all at-risk populations, reaching those unable to access good-quality microscopy services in endemic areas.

Malaria vaccines have long been an area of intensive research. However, no effective vaccine has been introduced into medical practice.⁸ Vaccines are among the most cost-effective tools for public health. They have historically contributed to a reduction in the burden of infectious diseases and have played the major part in the elimination campaign for smallpox and the ongoing polio and measles initiatives. Preclinical and clinical studies have shown some degree of success with attenuated sporozoite (SP) and SP protein as malaria vaccine candidates. The Malaria Vaccine Advisory Committee to the WHO outlined a "Malaria Vaccine Technology Roadmap" in 2006 that has as one of its landmark objectives to "develop and license a first-generation malaria vaccine that has a protective efficacy > 50% against severe disease and death and lasts longer than one year" by 2015.⁹ It appears unlikely that this objective will be met.

The epidemiology of malaria varies enormously, suggesting that it may be necessary to adopt different vaccine development strategies to target different populations. A Type 1 vaccine is suggested for those exposed mostly to *P. falciparum* malaria in sub-Saharan Africa, with the primary objective to reduce the number of severe cases and deaths in infants and children exposed to high transmission rates. A Type 2 vaccine could be considered a "travelers' vaccine," aiming to prevent all clinical symptoms in individuals with no previous exposure. Malaria also presents one of the most substantial threats to travelers' health. Problems with currently available pharmaceutical therapies include cost, availability, adverse effects and contraindications, inconvenience and compliance, many of which would be reduced or eliminated if an effective (> 85–90%) vaccine is developed.

Many antigens present throughout the parasite life cycle could be potential vaccine targets. More than 30 of these are being researched by teams all over the world in the hope of identifying a combination that can elicit protective immunity. Some approaches involve surface expression of the antigen, inhibitory effects of specific antibodies on the life cycle, and protective effects through immunization or passive transfer of hyperimmune

antibodies. Most malaria vaccine research has focused on the *P. falciparum* strain due to its high mortality and the ease of carrying out in vitro and in vivo studies. The earliest vaccines used the circumsporozoite (CS) protein, the most dominant surface antigen of the initial pre-erythrocytic phase. However, problems were encountered due to low efficacy, reactogenicity and low immunogenicity. An initially promising CSP vaccine was based not only on CS protein, but also had recombinant (Asn-Ala-Pro15Asn-Val-Asp-Pro) 2-Leu-Arg (R32LR) protein covalently bound to purified *Pseudomonas aeruginosa* toxin (A9). However, a complete lack of protective immunity was demonstrated in vaccinees; the study group used in Kenya had an 82% incidence of parasitemia while the control group had an 89% incidence. The vaccine was intended to increase T-cell responses, but this was also not observed.¹⁰

The NYVAC-Pf7 multistage vaccine used a different technology by incorporating seven *P. falciparum* antigenic genes from a variety of stages during the life cycle. CSP and sporozoite surface protein 2 (PfSSP2) were derived from the sporozoite phase. Liver stage antigen 1 (LSA1), three antigens from the erythrocytic stage (merozoite surface protein 1, serine repeat antigen and AMA-1) and one sexual stage antigen (25-kDa Pfs25) were included. This vaccine produced encouraging results in Rhesus monkeys: 4 out of the 7 antigens produced specific antibody responses. Despite demonstrating cellular immune responses in > 90% of vaccinees, very poor antibody responses were elicited in clinical trials. Nevertheless, some vaccinees had complete protection from *P. falciparum* challenge. This result has warranted further trials.

A 1995 trial employed (NANP) 19–5, consisting of schizont export protein (5.1) and 19 repeats of the sporozoite surface protein (NANP); thus containing only 20% peptide. This vaccine was weakly immunogenic, and did not contain any immunodominant T-cell epitopes.¹¹

RTS,S is the most recently developed recombinant vaccine. It consists of *P. falciparum* CSP protein from the pre-erythrocytic stage. The CSP antigen elicits antibodies capable of preventing the invasion of hepatocytes and as well as a

cellular response enabling the destruction of infected hepatocytes. The CSP vaccine was weakly immunogenic. The RTS,S vaccine improved on this by fusing CSP with Hepatitis B surface antigen, hence creating a more immunogenic vaccine. As an oil-in-water emulsion with monophosphoryl A and QS21 adjuvants (SBAS2), the vaccine elicited protective immunity in 7 out of 8 volunteers challenged with *P. falciparum*.¹²

Immunity and Genomics

The development of immunity against malaria is very complex in individuals living in areas of high endemicity. People residing in endemic regions over long periods of inhabitation/exposure naturally acquire protective immunity against the disease, although the patterns of immunity vary with malaria transmission patterns. Several studies have demonstrated that purified immunoglobulins from the sera of immune adults living in endemic regions and from experimentally immunized animals can passively transfer protection against live challenge. Clinical studies have demonstrated that experimental vaccination with attenuated sporozoites can induce effective protection against a subsequent challenge.

Immunization in animal studies clearly demonstrated the potential for inducing protective immunity. Different Plasmodial components, e.g., *P. knowlesi* Mz13, can induce immunity superior to that developed from natural human infection. Antibody-dependent mechanisms presumably play an important role in protection, through a wide range of antigen-specific antibodies as well as polyclonal-antibodies. IgG antibodies are important in reducing parasite density during this disease. Genetic mapping of 14 *P. falciparum* chromosomes has revealed ~5300 genes responsible for protein synthesis. Two third of the genes are unique to the parasite, and ~208 genes are responsible for the evasion of parasite from the host immune response.¹³⁻²³

Strategies for DNA Vaccine Development

Since there are no available vaccines that effectively target parasitic infection, the

development of a vaccine of therapeutic and protective benefit against the malaria requires a novel approach. The focus so far has been predominantly on subunit vaccines. The use of live inactivated or attenuated whole parasites is not feasible; thus, antigenic particles or subunits from the parasite are isolated and tested for immunogenicity. The majority of subunits are combined with adjuvants and delivery systems to further increase the immune response.

DNA vaccines are one of the newest technologies that may enable control over some infectious diseases. A DNA vaccine is the source of a stably expressed protein which can induce both antibody- and cell-mediated immune responses to a wide variety of antigens. DNA enters the host cell and produces proteins that elicit antibodies and cellular responses that may control malaria. Moreover, the flexibility of DNA vaccine technology permits the combination of multiple antigens from both pre-erythrocytic and erythrocytic stages. For DNA and recombinant virus subunit vaccines, the DNA sequence for the antigen(s) of choice is inserted into an *E. coli* derived plasmid or into the genome of a double-stranded DNA virus such as vaccinia. The host CD4+ and CD8+ responses can be induced following intracellular synthesis, processing and HLA presentation of class I and II T-cell epitopes.

Many DNA vaccines with genes encoding different parts of malaria proteins have been created; some of these are undergoing clinical trials. MHC class I CD8+ T-cell specific responses could potentially reduce some of the safety concerns associated with vaccination. It is relatively easy and inexpensive to make DNA vaccines. Several DNA vaccines are in clinical trials, having been effective in animal models. The results from these trials will help to determine the likelihood of success of this technology in humans.^{24,25}

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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