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# Malaria vaccine for travellers — where are we now?

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## ABSTRACT

*The authors present a short summary of the current state of malaria vaccine development and the perspectives for the availability of a malaria vaccines for travellers from non-endemic countries. There is currently no commercially available malaria vaccine for travellers. The efficacy of the RTS,S/AS01 vaccine is limited and differs dramatically from the effects of other vaccines administered in travel medicine. In the current recommendations, the use of repellents is deemed the most important measure to prevent malaria infection, and in the high-risk destinations, chemoprophylaxis is strongly advised. Many questions in malaria vaccinology remain unanswered.*

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**Key words: malaria, communicable disease control, protozoan vaccines, travel-related illness**

## INTRODUCTION

Malaria is a parasitic, vector-borne disease transmitted mainly through the bites of *Anopheles* mosquitoes. There are five species of the *Plasmodium* parasite that can infect humans — *P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*. The first one, *Plasmodium falciparum,* is known to be the most serious cause of malaria morbidity and mortality concentrated in sub-Saharan Africa, where limited access to medical services and poor living conditions contribute to intense malaria transmission [1, 2].

The individual susceptibility to the disease varies, depending on the age and the natural immunity acquired as a result of repeated episodes of malaria infection. Young children and non-immune population (e.g. travellers) are at risk of the most severe forms of the disease. The mechanism of this progressive protection against malaria infection is not fully understood [2].

According to the World Malaria Report 2018, there were 219 million cases of malaria worldwide and 435,000 deaths in 2017. Ninety-two per cent of malaria infections and 93% deaths occurred in the World Health Organisation (WHO) African Region. Children under the age of 5 years are the most affected group. The number of malaria infections declined between 2010 and 2015, but no significant reduction was noted thereafter, and 10 African countries reported an increase in the incidence rate of malaria [3].

The United Nations (UN) Millennium Development Goals were adopted in September 2000 and signed by 191 UN members. Among the 8 Development Goals, three of them aimed for combating malaria along with reducing child and maternal mortality. These ambitious goals were to be achieved by 2015 [4]. The declaration has been followed by the *Global Technical Strategy for Malaria 2016–2030* and *Action and Investment to defeat Malaria 2016–2030 — for a malaria-free world* [5].

## KEY INTERVENTIONS

The success in the reduction of number of malaria cases has been attributed to the application of the so-called key interventions. In many African countries, the implemented malaria control programmes of proven efficacy have relied on:

— LLINs — use of long-lasting insecticidal bed nets;
— IRS — indoor residual spraying;
— RDTs — rapid diagnostic tests;
— ACTs — artemisinin combination therapies [2].

In some African settings, a fifth strategy has been involved, SMC — seasonal malaria chemoprevention with the administration of full course of malaria treatment to young children at monthly intervals during malaria season [6]. Although individual protective measures against mosquito bites the improvement in diagnosis and treatment of malaria

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prove to be very efficient, the eradication of the disease seems to be unachievable without a vaccine [7].

## MALARIA VACCINE CANDIDATES

*Plasmodium* parasite is a complex eukaryotic organism and has a complicated life cycle involving two hosts: mosquito and human. More than 30 *Plasmodium falciparum* vaccines are in development [8] and one has completed Phase III clinical testing. *Plasmodium vivax* is only distantly related to *P. falciparum* and has a different biology; only two subunit vaccines have reached clinical trials [1].

Currently investigated malaria vaccine candidates are designed as pre-erythrocytic vaccines: whole sporozoite and liver-stage subunit, blood-stage vaccines and transmission-blocking vaccines.

The whole sporozoite vaccine (WSV) strategy has demonstrated high level of protection and includes administration of live-attenuated sporozoites or live sporozoites accompanied with antimalarial drugs. This approach aims to prevent the blood-stage infection. The first whole sporozoite vaccine contained radiation-attenuated parasites (PfSPZ Vaccine) and relied on intravenous administration with subsequent eliciting of potent immunity in humans. Cytotoxic CD8+ T cells response is the main immune mechanism responsible for sterile protection after WSV administration [9]. The first clinical trial using genetically modified *Plasmodium* (GAP) is promising; the parasite used lacks two genes required for breakthrough infection [9].

Liver-stage subunit vaccine focuses on identifying antigens on parasitized hepatocytes resulting in their destruction. Vaccination should generate strong CD8 + T cell response against infected liver cells. Phase 2b field trial provided 20–25% sterile protection against controlled human malaria infection [10].

Blood-stage vaccines are based on merozoite antigens and inducing antibodies that block erythrocyte invasion. Production of a broad spectrum of antibodies against merozoites and infected erythrocytes induces naturally acquired immunity to malaria infection [9].

Transmission-blocking vaccines are designed to impact the parasite's life cycle in the mosquito and not in the human body to prevent its further transmission [9]. These approaches focus on protection of the community and impact on public health than on individuals herd immunity.

## THE RTS,S/AS01 VACCINE

The most advanced vaccine is composed of the repeat region of circumsporozoite protein (CSP) added to the hepatitis B virus surface antigen (HBsAg) and AS01 adjuvant, leading to the induction of high level of human immunity (antibody titres) [7, 9]. In July 2015, the RTS,S/AS01 vaccine marketed by GlaxoSmithKline under the brand Mosquirix was the first and so far the only one to receive a positive regulatory assessment issued by the European Medicines Agency [11]. The vaccine belongs to the sporozoite subunit vaccine (pre-erythrocytic) group.

A phase 3 trial involved 15,460 children in 7 sub-Saharan countries. All children received three doses of immunisation at 1-month intervals and were divided in two age groups: infants aged 6–12 weeks and young children aged 5–17 months. The fourth dose was administered after 18–20 months. The RTS,S/AS01 trial began in 2009 and has recently been completed [2].

During over 48 months of follow-up, the efficacy of RTS,S/AS01 was estimated to be 36.3% in older group after four doses of immunisation and 28.3% after three doses. The observation period for infants was shorter; during over 38 months of follow-up, the protection against clinical malaria was assessed to be 25.9% after four doses and 18.3% after three doses [12]. Thus, the efficacy is moderate in the group of older children, but it is not sufficient in infants to encourage further studies.

The RTS,S/AS01 was generally well tolerated in the trials, with typical side effects similar to other established childhood vaccines. Among older children, an increased risk of febrile seizures was identified, albeit without any serious consequences of these episodes [2]. There were also 16 cases of meningitis with 8 deaths and cerebral malaria cases, only in the older children group. A clear link between meningitis or cerebral malaria and administration of the RTS,S/AS01 remains unconfirmed and needs to be evaluated in pilot study that has begun in Africa [2].

The level of protection depends on the antibody titre against sporozoite surface and wanes over time [12, 13].

The major limitations of the RTS,S/AS01 vaccine include only moderate level of protection, the number of doses to maintain the efficacy (high antibody titres), the delivery system in the African countries, the cost of vaccine, the probable interference with the maternally acquired antibodies against *Plasmodium*, the side effects and safety issues of the vaccine.

## A MALARIA VACCINE FOR TRAVELLERS?

There is currently no commercially available malaria vaccine for travellers. The efficacy of the RTS,S/AS01 vaccine is limited and differs dramatically from the effects of other vaccines administered in travel medicine. For example, the vaccine against yellow fever results in nearly-total immunity within 1 month for 99% of people vaccinated [14]. Other candidates for vaccines against malaria are not similarly advanced in development and clinical trials.

What is the correct prevention for travellers? Currently, the principles of malaria prophylaxis rely on the key interventions, the same ones, as successfully implemented in

the endemic regions. The vaccine RTS,S/AS01 has not been designed for and tried in non-immune and adult population. In the current recommendations, the use of repellents has been singled out as the most important measure to prevent malaria infection, and in the high-risk destination, chemoprophylaxis is strongly advised [15].

The vaccine RTS,S/AS01 is only one of the key intervention in malaria endemic countries to preserve health and life of young children. As the sole prophylactic measure, it would not eradicate malaria disease to the year 2030, as it has been planned. Furthermore, without improving the vaccine efficacy, the 2030 goal will be difficult to achieve even with intensive implementation of well-established key interventions.

## CONCLUSIONS

Many questions in malaria vaccinology remain unanswered: When will we receive the next-generation vaccine? Can whole sporozoite vaccines be improved or should we rather search for another adjuvants or components? What is the optimal schedule, doses, intervals and timing of booster? Should we include any additional antigens or genes along with the ones currently used or investigated? And should we maybe eliminate any of them? What do we know about human immunity against malaria infection? Does the level of anti-CSP truly correspond to the efficacy of vaccine RTS,S/AS01? Will there be anything in the future that we could offer for the travellers wishing to be immunised? Does immunity maternally acquired confer with antibodies induced by vaccination? Should we expect a rebound in malaria morbidity as a result of key interventions failures (resistance of mosquitoes to repellents and insecticides, spreading of resistance to artemisinin in the parasite's populations)?

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