Vaccines Against Malaria

Amed Ouattara¹ and Matthew B. Laurens²

¹Department of Medicine, Center for Vaccine Development, and ²Departments of Pediatrics and of Medicine, Howard Hughes Medical Institute / Center for Vaccine Development, University of Maryland School of Medicine, Baltimore

Despite global efforts to control malaria, the illness remains a significant public health threat. Currently, there is no licensed vaccine against malaria, but an efficacious vaccine would represent an important public health tool for successful malaria elimination. Malaria vaccine development continues to be hindered by a poor understanding of antimalarial immunity, a lack of an immune correlate of protection, and the genetic diversity of malaria parasites. Current vaccine development efforts largely target Plasmodium falciparum parasites in the pre-erythrocytic and erythrocytic stages, with some research on transmission-blocking vaccines against asexual stages and vaccines against pregnancy-associated malaria. The leading pre-erythrocytic vaccine candidate is RTS,S, and early results of ongoing Phase 3 testing show overall efficacy of 46% against clinical malaria. The next steps for malaria vaccine development will focus on the design of a product that is efficacious against the highly diverse strains of malaria and the identification of a correlate of protection against disease.

**Keywords.** malaria; vaccine; P. falciparum; P. vivax.

Malaria remains a significant public health threat, with approximately half of the world’s population at risk of infection. The disease is caused by parasites transmitted to humans by the bite of an infected mosquito. Those residing in the poorest countries are particularly vulnerable to death from malaria illness, especially children aged < 5 years in sub-Saharan African [1]. From 2000 to 2012, malaria mortality rates dropped by 45%, due in part to expanded funding for malaria control interventions including long-lasting insecticidal nets, indoor residual spraying programs, and access to artemisinin combination therapy [1].

Currently, there is no licensed vaccine against malaria. A malaria vaccine would represent a public health tool that is viewed by some experts to be necessary for successful malaria elimination. The World Health Organization (WHO) recently published strategic goals to license malaria vaccines by 2030 that target Plasmodium falciparum and Plasmodium vivax, have at least 75% protective efficacy against clinical malaria, and that reduce transmission to enable elimination [2]. The most advanced candidate vaccine to date, RTS,S/AS01, is currently in phase 3 testing in 7 African countries; final results are expected by 2015. Efforts to improve on the modest efficacy of RTS,S/AS01 include more than 20 malaria vaccine strategies currently in clinical testing; these include the use of candidate antigens (Table 1) in monovalent and multivalent formulations either alone or with other agents, viral vectors, and/or vaccine adjuvants. Here, we review the history of malaria vaccine development, then explain the malaria life cycle as a backdrop to our description of the challenges, approaches, and focus of current malaria vaccine development efforts.

**ADVANCES IN MALARIA VACCINE DEVELOPMENT**

Early malaria vaccine research began in the 1930s with a focus on inactivated or killed parasites that failed to generate a protective immune response. The addition of adjuvant systems demonstrated immunogenicity of malaria vaccine candidates in animal models; Jules Freund and colleagues demonstrated partial protection...
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in ducklings [4]. Subsequent vaccine development efforts used rodent malaria models. This led to the first human malaria vaccine trial with demonstrated efficacy, a study that delivered irradiated *P. falciparum* sporozoites to vaccinees by mosquito bite [5]. This breakthrough was regarded as impractical for mass vaccination campaigns, and synthetic peptide vaccines based on immunogenic parasite proteins began to be developed in the 1980s. As there is no biological correlate of protection for malaria, continued efforts in vaccine development were painstakingly time consuming. A series of steps needed to be taken before phase 2 field testing in the target population of children in malaria-endemic areas could finally be performed to determine vaccine efficacy. These steps included initial development of a candidate vaccine in the laboratory, testing for safety and proof-of-concept in animal models, and age de-escalation phase 1 testing in adults and then in children for safety and reactogenicity. These multiple steps represent an arduous process, require significant funding support due to the lengthy product development timeline, and carry the risk of a negative end result. To abrogate this risk, controlled human malaria infection (CHMI), where participants are inoculated with sporozoites via the bite of infected female *Anopheles* mosquitoes in well-controlled settings, was used to obtain data on vaccine and drug efficacy in order to support or refute further clinical testing in malaria-endemic areas [6]. Early testing of the RTS,S vaccine using CHMI not only predicted efficacy in field studies, it also helped to refine the choice of adjuvant and support reformulation to a lyophilized form [7].

The first malaria immunization trials to use experimental challenge by infected mosquitoes were conducted in the mid-1970s [5,8]. Field trials in which efficacy against clinical malaria was measured were conducted in the 1990s with the SPf66 vaccine, a subunit vaccine developed in Columbia that contained sequences from 3 *P. falciparum* blood-stage antigens and the circumsporozoite protein (CSP). These studies showed a modest reduction of *P. falciparum* parasitemia in South America but no protection in Africa [9]. Advances such as parasite cultivation methods and sequencing of the *P. falciparum* genome have increased hope for the development of a malaria vaccine [10]. However, after more than 35 years of laboratory research and field trials, the only vaccine that has progressed to phase 3 testing is the RTS,S vaccine, which showed efficacy of 30% in newborns and 50% in children aged 5–17 months in interim analyses from the ongoing phase 3 trial [11]. This limited success has called into question the likelihood of having a highly efficacious malaria vaccine available within the next few years. However, with funding agencies, the private sector, and international organizations joining forces to contain or even eradicate malaria, strategies are being scaled up in order to control the disease burden. In addition to effective treatment of clinical malaria and use of insecticide-impregnated barriers, malaria vaccines could play an important role in this initiative. Malaria vaccines can be divided into the following 3 groups based on the parasite developmental stages: pre-erythrocytic vaccines, blood-stage vaccines, and “other” vaccines including transmission-blocking vaccines and vaccines against pregnancy-associated malaria.

**THE MALARIA LIFE CYCLE**

Malaria is caused by a unicellular eukaryotic parasite of the genus *Plasmodium*; 5 species including *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi* cause human disease. Sporozoite-stage parasites are transmitted to humans by female *Anopheline* mosquitoes during a blood meal. These sporozoites invade hepatocytes and produce 30–40 000 progeny over a 6-day period. Those in the sporozoite and liver stages are collectively referred to as pre-erythrocytic parasites. When infected hepatocytes rupture and release progeny merozoites into the venous circulation, each merozoite will potentially invade a red blood cell and then propagate within 48–72 hours to produce 8–24 merozoites. When the infected erythrocyte ruptures, clinical symptoms present, including fever, headache, chills, and malaise. The severity of these symptoms has been correlated with parasite load [12]. Merozoites released during erythrocyte rupture will each potentially invade a new erythrocyte to continue the cycle, also known as the stage of erythrocyte parasite development. In the early stage of clinical manifestation, the fever attacks are periodic (24 hours for *P. knowlesi*; 48 hours for *P. vivax*, *P. ovale*, and *P. falciparum*; and 72 hours for *P. malariae*), corresponding with the release of a new generation of merozoites into the bloodstream (Figure 1).

Factors that affect the severity of human malaria infection include host immune status and the general health and nutritional condition of the infected individual as well as the *Plasmodium* species [13]. Uncomplicated malaria is generally observed in adolescents and adults in high-transmission areas, whereas severe (complicated) malaria is seen in young children and primigravida and malaria-naive patients who travel to areas of malaria transmission. Severe and lethal malaria are primarily seen in infections due to *P. falciparum*. Other species are less commonly fatal. The ability of *P. falciparum* to produce high parasite loads, invade all stages of red blood cells, and sequester in end organ vasculature help to explain this extensive morbidity and mortality. Cytadherence plays an important role in the pathogenesis of severe malaria due to *P. falciparum* [12] in that parasitized erythrocytes express surface cellular adhesion molecules that localize to end organs where pathologic effects manifest. Sequestration of infected red blood cells in the brain may result in cerebral malaria with convulsions, potentially followed by prostration, coma, and death. When sequestration occurs in the placenta during pregnancy, miscarriage or low birth weight may result.
Antimalarial immunity is poorly understood, and identification of an immune correlate of protection continues to elude malaria researchers, hindering vaccine development. In endemic areas, antimalarial immunity develops over a prolonged period but is incomplete. Even the most malaria-experienced persons remain susceptible to malaria infection (asymptomatic parasitemia) but not clinical illness. During infection, both humoral and cell-mediated immune responses initiate antibody production, cytokine release, regulatory and effector T-cell stimulation, and neutrophil and monocyte activation to control parasitemia [14–16]. This complex response does not permit results from a single immune assay to represent a threshold of protection, as is done for other vaccine-preventable illnesses.

**PRE-ERYTHROCYTIC MALARIA VACCINES**

An effective immune response must act quickly in order to thwart *P. falciparum* sporozoites in their minutes-long journey from the skin to the liver. Both humoral and T-cell responses are required to prevent hepatocyte invasion, which is the goal of pre-erythrocytic vaccines. Pre-erythrocytic vaccine targets include CSP that is expressed on the surface of sporozoites; the protein is composed of 412 amino acids [17] with 37 tetrapeptide repeats and a conserved central domain [18]. Anti-CSP antibodies inhibit sporozoite invasion in vitro, and anti-CSP monoclonal antibodies block experimental infection in animals [19].

RTS,S is the leading pre-erythrocytic malaria vaccine. It is comprised of hepatitis B surface antigen (HBsAg) particles fused to *P. falciparum* CSP central repeat and thrombospondin domains formulated in the adjuvant AS01, a liposome formulation that contains immunostimulants 3-O-desacyl-4′-monophosphoryl lipid A and the saponin QS-21 from *Quillaja saponaria* extract. RTS,S is a recombinant antigen comprised of conserved sequences from the 3D7 standard laboratory strain of *P. falciparum*. It includes the “R” (repeat) portion, which is a single polypeptide chain that corresponds to a highly conserved tandem repeat tetrapeptide sequence from CSP (N-acetyleneuraminic acid phosphatase [NANP] amino acid sequence repeats), and the “T” (T-cell epitope) portion, which includes T-lymphocyte epitopes separated by immunodominant CD4+ and CD8+ epitopes (Th2R and Th3R). This combined RT peptide is fused to the N-terminal of HBsAg, the “S” (surface) portion. A second “S” portion is an unfused HBsAg, hence, the name RTS,S.

In the first phase 3 clinical trial of a malaria vaccine, efficacy against clinical malaria in children during the 18 months following dose 3 was 46% overall, waned over time, was higher in older children than in infants, and showed the highest impact in areas with the greatest malaria prevalence [20]. This study is ongoing, with plans to submit the final phase 3 data in 2014/2015 to the European Medicines Agency and the WHO. Vaccine effectiveness models that simulate varying malaria transmission intensity and seasonality are being used to determine the epidemiological settings and age groups that would benefit most from RTS,S vaccination. In parallel, efforts to increase RTS,S efficacy are ongoing. These efforts include combining RTS,S with other antigens [21] and prime-boost strategies [22] where subsequent doses of vaccine antigen are delivered with a vector that is different from the initial vector in order.
to avoid immune recognition and senescence and to maximize response to the vaccine antigen. Continued challenges to the RTS,S vaccine developers include inducing a protective immune response to the genetically different strains found in nature and establishing a vaccine correlate of protection, obstacles considered central to all malaria vaccine development efforts. Field studies of RTS,S vaccine demonstrate mixed evidence of decreased malaria infections with vaccine-type CSP in vaccinees vs controls [23–25] and leave room for the rationale that RTS,S may provide protection against homologous strains with respect to key amino acid sequences, as has been shown with other malaria vaccine candidates [26]. However, difficulties in contiguous sequencing of the CSP protein through the central NANP repeat region limit the ability to test this hypothesis [27]. While anti-CSP antibody and CSP-specific CD4+ T-cell levels both increase after RTS,S vaccination, a threshold response that separates the protected from the unprotected cannot be defined, leaving refinements in vaccine formulation and adjuvant choice to be tested in CHMI studies or in field efficacy trials.

Other pre-erythrocytic vaccine strategies in development include the multiple epitope (ME) thrombospandin-related adhesion protein (TRAP) and whole-organism sporozoite strategies. ME-TRAP consists of fused B-cell and CD4 and CD8 T-cell epitopes of *P.falciparum* liver-stage antigens. This vaccine failed to show protection in phase 2b trials conducted in Kenya [28]; however, other variants are now under development [29]. In a return to the scientific principles that guided the first malaria vaccine trial showing efficacy in humans, researchers at the National Institutes of Health Vaccine Research Center demonstrated 100% efficacy against CHMI in 6 of 6 North American volunteers who received the highest dose of a whole-organism radiation-attenuated sporozoite vaccine [30]. Follow-up safety testing of this highly promising candidate vaccine is underway, including a trial in Malian adults to evaluate vaccine efficacy against diverse strains of naturally occurring malaria. Because this vaccine is currently administered intravenously, some malaria vaccine experts are skeptical that intravenous delivery is practical for mass administration, especially to infants and young children. Studies to test alternative routes of delivery are ongoing.

**ERYTHROCYTIC MALARIA VACCINES**

Clinical manifestations of malaria result from parasite blood-stage infection. Blood-stage vaccines are therefore intended to prevent disease and death without necessarily preventing infection. The gradual acquisition of natural protection against clinical disease following repeated infections in areas of malaria transmission indicates that a blood-stage malaria vaccine strategy is feasible, provided that it mimics acquired immunity to malaria in endemic areas. Immune protection during the erythrocytic stage is essentially mediated through neutralizing antibodies, as confirmed by studies of passive antibody transfer that protect against blood-stage infection [31, 32]. Antigens expressed on the surface of the merozoite and infected red blood cells are considered erythrocytic malaria vaccine candidates and include merozoite surface proteins 1, 2, and 3 (MSP1, MSP2, and MSP3); serine-repeat antigen; erythrocyte-binding antigen; ring-infected erythrocyte surface antigen (RESA); glutamate-rich protein (GLURP); and apical membrane antigen 1 (AMA1).

In malaria-endemic areas, protective immune responses are acquired over time following repeated infections by multiple alleles of multiple antigens of the malaria parasite. This suggests that the immune response may be specific to the genetic sequence of the infecting strain. Because of this specific immune response, an infecting parasite with a genetic sequence that is different from the vaccine antigen may result in malaria disease. In a field study in the Gambia, the protective effect of antibodies to genetically diverse regions of MSP3 was stronger than that of antibodies targeted to conserved regions [33]. Furthermore, a vaccine trial conducted in Papua New Guinea using combination B vaccine, a mixture of MSP1, MSP2, and RESA protein, showed an increased incidence of clinical infections with nonvaccine-type parasites with respect to MSP2 in vaccinated individuals compared with patients who received the control vaccine [34].

In recent years, only 4 blood-stage antigens (AMA1, MSP1, MSP3, and GLURP) have been tested in phase 2 vaccine trials. None of the vaccines based on the 4 antigens tested were efficacious based on the primary endpoint of clinical malaria. However, 1 AMA1-based vaccine tested in Mali demonstrated significant efficacy against clinical malaria infections that shared the identical genetic sequence with the vaccine strain with respect to key immunologically relevant amino acid positions [35]. The strain-specific efficacy and genetic diversity analyses of these malaria vaccine candidates demonstrate that in the likely event that there is too much diversity to be covered by a manageable number of allelic variants, specific amino acid residues and clusters of residues that are associated with immune protection against clinical disease can be identified, narrowing the diversity that must be considered in multivalent vaccine formulations. These analyses give insight into how current and potential vaccine candidate antigens can be designed to provide broad protection against diverse parasites.

**TRANSMISSION-BLOCKING VACCINES**

Recent increased interest in halting parasite spread to other persons has led to advances in transmission-blocking vaccines. These are sometimes called altruistic vaccines as there is no direct benefit to vaccinees. A successful transmission-blocking vaccine would induce neutralizing antibody responses against the malaria parasite’s gametocyte and/or ookinete sexual stages.
thereby blocking fertilization and halting reproduction [36]. Targeted antigens currently in early development include ookinet surface proteins P25 and P28, with phase 1 testing of *P. falciparum* and *P. vivax* P25 antigens completed [37, 38]. Efficacy testing of transmission-blocking vaccines can be measured by assays of *Anopheles* mosquito feeding directly on humans or on human blood via a membrane-feeding assay. Compared with control sera, plasma from participants immunized with a P25-based vaccine mixed with *P. falciparum*-infected blood reduced oocyte density of geographically distinct parasites in membrane-feeding assay testing [39]. The limited genetic polymorphism of the P25 encoding gene [40] may explain this cross-protective efficacy. A P25-based candidate vaccine is currently being evaluated in a phase 2 trial in Malian adults.

### VACCINES AGAINST PREGNANCY-ASSOCIATED MALARIA

Pregnancy-associated malaria occurs when erythrocytes sequester to placental endothelial cells. Binding of infected erythrocytes to placental endothelium is mediated by the interaction between *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), a ligand expressed on the surface of the infected erythrocyte, and receptors on the placental matrix, mainly, chondroitin sulfate antigen. This binding results in reduced placental blood supply and subsequent increased risk for both low-birth-weight babies and preterm delivery. The condition disproportionately affects primigravid women who have not yet developed an immune response to PfEMP1 proteins that presumably provide protection in subsequent pregnancies. Women with high anti-PfEMP1 antibody titers demonstrate reduced risk of delivering low-birth-weight babies than women with low antibody titers [41]. The durability of B-cell immunity generated to PfEMP1 antigens without reexposure lends promise to PfEMP1 as a vaccine candidate that targets females of prereproductive age with the aim to prevent pregnancy-associated malaria. The first PfEMP1-based vaccine is currently in preclinical development [42].

### CONCLUSION

The renewed worldwide effort to eliminate malaria is underway, and experts agree that this goal cannot be achieved without new tools such as a malaria vaccine that can interrupt malaria transmission (VIMT) [43]. This concept of VIMT is described as any malaria vaccine that can impact transmission, including vaccines that target the sexual and oocyte stages, but also pre-erythrocytic and erythrocytic vaccines that reduce transmission. To show promise, candidate malaria vaccines must demonstrate reduced transmission of malaria as a result of vaccination, a new challenge for malaria vaccine clinical trial design.

What are the next steps for malaria vaccine development? A vaccine with at least 75% efficacy against clinical malaria, as outlined in the malaria vaccine technology road map [2], must be efficacious against the highly diverse strains of malaria that circulate in endemic areas. A multiantigen vaccine, similar to the approach used for vaccines against *Streptococcus pneumoniae*, may be necessary. Antigens selected for inclusion should also be highly immunogenic and provide immunity that lasts at least 2 years [2]. Alternatively, a highly efficacious, whole organism approach can potentially transcend strain-specific diversity constraints, and is currently being tested in malaria-endemic areas. Novel vaccine delivery systems and adjuvants that increase vaccine immunogenicity should continue to be developed and evaluated. Concurrent with the clinical trials that evaluate vaccine efficacy, studies of transmission reduction and cross-protection against endemic malaria that attempt to determine correlates of protection against malaria, especially vaccine-induced protection, should be performed. Research and development of a laboratory-based correlate using screening tools such as microarray-based methods would propel malaria vaccine development efforts and facilitate refinements in dosing and adjuvant formulation.

If scientific and donor interest in malaria vaccine development continues at or above current levels, the difficult task to develop a highly efficacious malaria vaccine is achievable. Modeling studies that take cost, malaria transmission, overall malaria burden of disease, and other relevant scientific evidence into account will help to determine where vaccine is deployed based on public health priorities at the local and national levels. Ongoing research and evaluation will help to overcome challenges of vaccine delivery and integrate insecticide-treated bed net use and other malaria control initiatives to reduce and eventually eliminate malaria burden.

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