Malaria vaccine: Latest update and challenges ahead

Rana Chattopadhyay & Sanjai Kumar*
Malaria Research Program, Division of Emerging and Transfusion Transmitted Diseases, Office of Blood & Research Review, Center for Biologics Evaluation & Research, Food & Drug Administration, 5516 Nicholson Lane, Kensington, MD 20895, USA

Development of an effective malaria vaccine remains one of the biggest challenges faced by modern science. Although in the last decade tremendous advances have taken place in the design, construction and testing of malaria vaccines, many questions still remained unanswered. This review highlights exclusively some of the exciting and most recent progress in the development and clinical testing of candidate malaria vaccines and points out some of the outstanding scientific issues and technological challenges that must be met to develop a successful vaccine.

Keywords: Malaria, Plasmodium spp, Vaccine

A Global Malaria Action Plan (GMAP), announced at the UN Millennium Development Goals Malaria Summit in New York on September 25, 2008, has the aims of both reducing the malaria burden and eradicating the disease entirely. The plan calls for scaling up the use of existing tools such as bed nets, anti-malarial drugs, and insecticide spraying and then sustaining this effort for a long time in order to eradicate malaria. Thus, the newly adopted goal is not only for the reduction of malaria burden, but also for its ultimate eradication. There is a sense of priority among malaria researchers that in order to restrain the burden of malaria to its lowest incidence or to achieve complete eradication, along with the above mentioned tools, an effective vaccine is an absolute requirement. Although at present the term ‘malaria eradication’ may appear a bit unrealistic, this perception can dramatically change with the availability of an effective vaccine. Many scientists believe that the development of an effective malaria vaccine is one of the hardest challenges faced by modern biomedical researchers. Some of the major factors that have hindered malaria vaccine development include the complex life cycle, the genetic structure and polymorphism present in Plasmodium genome, the limited number of antigens being developed for clinical studies, and the lack of non-proprietary, effective adjuvants. Other major issues are the non-availability of in vitro assays and in vivo challenge models that could be used to measure the pre-clinical safety and efficacy of vaccines. These are important decision criteria for testing vaccines in clinical studies and for evaluating outstanding scientific and ethical questions such as determining the degree of vaccine efficacy that would be acceptable in adults before their testing is allowed in young children. Another important point to note is that the greatly anticipated availability of genome information for Plasmodium falciparum and Plasmodium vivax (the two most common human malaria species) has to this date failed to have a significant impact on the number of vaccine antigens that are undergoing development for clinical testing.

As the life cycle of malaria parasites (Plasmodium spp.) involves the female Anopheline mosquito as the definitive host and includes humans as a secondary host, efforts to contain the progression of development in either host have been attempted. In the mammalian host, malaria infection commences with the inoculation of infective sporozoites by the female Anopheles mosquitoes during their blood meal. Sporozoites invade the liver cells and thus initiate the pre-erythrocytic (PE) stage of parasite development in the hepatocytes. Within the infected hepatocytes, parasites undergo rapid multiplication and depending on Plasmodium species, within 2-14 days, expand from a single sporozoite up to 10,000-40,000 liver form merozoites. Upon their release, liver form merozoites invade erythrocytes and initiate blood-stage (BS) infection, the stage that is responsible for the

*Correspondent author
Telephone: +1 301 827 75 33
Fax: +1 301 827 4622
E-Mail: sanjai.kumar@fda.hhs.gov
pathogenesis of malaria disease. Inside the erythrocytes, within 24-72 hr, the merozoites transform to ring, trophozoite and schizont stages. Mature schizonts are comprised of 6-36 merozoites depending on the species of \textit{Plasmodium} that are liberated after rupture of the schizont-infected erythrocyte, and the free merozoites further infect fresh erythrocytes to continue the cycle. Through a mechanism that is yet not fully understood, some of the blood form merozoites develop into male and female gametes that are picked up by female mosquitoes during their blood meal. This begins the mosquito stage (MS) of the parasite development. Gametocytes within the mosquito gut undergo the fertilization and subsequent sporogonic development and finally sporozoites emerge and invade the salivary glands of the mosquitoes. During the next blood meal, sporozoites are inoculated into the mammalian host. Several laboratories are working to develop malaria vaccines that are based on targeting antigens on one or multiple parasite developmental stages described above. These different vaccine development strategies have certain advantages and pitfalls that are largely determined by the age, area of residence, and status of prior malaria exposure in the vaccine recipients.

In the face of the multiple challenges that include biological (both host and parasite) factors and technological limitations, the scientific rationale behind the possibility of a successful malaria vaccine is based on two key models of malaria immunity. The first model is the irradiated sporozoite vaccine which has proven to be effective in all tested experimental models (including humans). The second model is the natural clinical immunity that is commonly observed in adults living in endemic areas. All of the technological tools and vaccine delivery methods that are available to modern science have been applied to replicate the above described models of malaria immunity. These approaches can be broadly divided into the whole organism based vaccines (mostly live attenuated malaria sporozoites) and the subunit based vaccines (recombinant proteins, synthetic peptides, DNA plasmids, pox virus and adenovirus constructs) which can be delivered with or without adjuvant formulations in homologous immunization or applied in complex prime boost immunization regimens.

The aim of this article is to review some of the most recent advancements and achievements in malaria vaccine development and discuss the challenges and road blocks that remain towards the development of a successful vaccine against malaria.

**Pre-erythrocytic (PE) stage vaccines**

As the malaria infection commences with the inoculation of sporozoites into a human host, an ideal vaccine could be one that can either prevents the invasion of sporozoites into liver cells or, if invasion does take place, blocks the formation of liver form merozoites. From that perspective, the PE stage is most ideal for the development of an ‘anti-infection’ vaccine for malaria that would also block further transmission, at least in and from vaccinees. The concept for the feasibility of such a vaccine comes from data that attenuated \textit{Plasmodium} sporozoites can confer sterile protection against malaria. In fact, the use of attenuated \textit{Plasmodium} sporozoites is the only experimental vaccine that has been shown to confer sterile protection against malaria in several host-parasite systems including chickens with UV irradiated \textit{P. gallinaceum} sporozoites\(^6\), mice with X-ray irradiated \textit{P. berghei} and \textit{P. yoelii}\(^5\) sporozoites, and humans with X-ray and gamma irradiated \textit{P. vivax}\(^6\) and \textit{P. falciparum} sporozoites \(^6\)\(^{11}\). These studies have demonstrated that similar to several bacterial and viral infections, whole malaria parasites are highly effective in inducing protective immunity. Currently, both radiation-attenuation\(^12\) and genetic deletion methods\(^13\)\(^{16}\) are being pursued to develop the candidate live, attenuated \textit{P. falciparum} sporozoite vaccines.

Although the first demonstration of the ability of an irradiated sporozoite vaccine to protect humans against malaria was in the 1970s\(^6\)\(^{10}\), the feasibility of developing such a vaccine for general use was deemed impractical until recently. Some of the challenges that had hindered serious efforts to develop live, attenuated sporozoite vaccines included limitations related to large scale production of sufficient doses of sporozoites for clinical testing, logistical hurdles related to \textit{en masse} vaccination, and safety concerns due to residual contamination with mosquito tissue materials. In human studies, induction of protective immunity required that irradiated sporozoites were delivered by more than 1000 bites by infected mosquitoes. Whether a needle-based delivery method will be able to mimic the degree of protective immunity that was induced by mosquito-based sporozoite delivery remains to be seen. The other formidable challenge is the storage and shipping conditions that may be needed to maintain the efficacy of live, attenuated sporozoite based vaccines, especially for administration in African villages and
other remote parts of the world. Recently, spurred by large investments made by the Malaria Vaccine Initiative (MVI)/PATH of the Bill & Melinda Gates Foundation and other funding agencies, serious efforts are being made to systemically address the outstanding scientific issues related to the development of live attenuated malaria sporozoite vaccines.

Circumsporozoite protein (CSP), the major surface protein of the sporozoite, was the first malaria protein for which the corresponding gene was isolated and its DNA sequence was determined in 1983. This remarkable achievement paved the way to produce and test candidate sub-unit malaria vaccines. Since then, CSP based constructs have remained the primary focus for targeting the pre-erythrocytic stage parasites. Numerous trials based on a variety of peptides, recombinant proteins, modified virus vectors, DNA plasmids and a large array of adjuvants and immunization protocols have been conducted with CSP. All of these efforts have led to only limited success in clinical studies. Nonetheless, so far the most successful malaria vaccine, in terms of advanced stage of development and clinical testing is RTS,S, which is CSP based. RTS,S is a particulate formulation of recombinant CSP fused with the Hepatitis B surface antigen. RTS,S is the only malaria vaccine currently in Phase III clinical studies. In many trials in Africa, including children and adults, RTS,S showed efficacy between 30% and 50% for an average duration of approximately 18 months. A 49% reduction in severe malaria cases in the 18 month follow up of the vaccinated Mozambican children is encouraging for testing the vaccine in larger clinical trials in Africa. In the latest phase IIIB, single center, double blinded, controlled trial involving 340 infants in Tanzania, RTS,S vaccine has been delivered with other vaccines as a part of the Expanded Program on Immunization (EPI). RTS,S didn’t interfere with the immunologic responses to co-administered EPI antigens and during the six month period follow-up after the third dose of RTS,S vaccine, a 65% reduction in incidence of malaria infection was observed in the vaccinated infants. Further larger trials of RTS,S in Africa involving infants, children and pregnant women in different endemic settings will be necessary to determine the true efficacy and its effect on long term malaria transmission in the study areas.

**Blood stage (BS) vaccine**

The blood stage of the malaria life cycle begins with the release of liver form merozoites from the infected hepatocytes and the invasion of erythrocytes (1st cycle of BS infection), or when merozoites come out of infected erythrocytes from a previous BS cycle and infect fresh erythrocytes. This is the only stage of parasite development that causes the clinical symptoms of malaria and associated deaths. A vaccine based on BS parasites is expected to function by either causing a total elimination or a significant reduction in parasite burden in the vaccinated host. It is generally believed that reduced parasitemia in young African children may result in less severe disease and reduction in mortality. Thus, a BS vaccine, even if only partially effective may have a significant impact on malaria morbidity and mortality in endemic areas. Furthermore, a combination of PE and BS vaccines may produce synergistic effects and can serve as an important tool to contain and eventually eradicate malaria. Some of the prominent antigens of BS which have been pursued as vaccine candidates for a number of years are merozoite surface protein 1 (MSP-1), apical membrane protein 1(AMA-1), and erythrocyte binding antigen 175 region II (EBA-RII). These candidates are tried as vaccines in various antigenic forms (partial or full length recombinant proteins, peptides, etc.), delivered in different adjuvant formulations or as vectored vaccines (DNA plasmid, modified pox and adenovirus constructs). All these formulations are in early phases of clinical trials, but so far none has shown substantial protective efficacy. Details of these trials are available at http://www.ClinicalTrials.gov.

In a recent review, Graves and Gelband, have highlighted vaccines of promise in clinical trials. In a study of the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library 2006, Issue 1), MEDLINE, EMBASE, LILACS, and the Science Citation Index, it has been found that although several blood-stage vaccines are currently under development, only a combination of merozoite surface protein-1 (MSP-1) and merozoite surface protein 2 (MSP-2) with Ring-infected Erythrocyte Surface Antigen (RESA), known as Combination B, has been tested in randomized controlled trials to assess its effect in preventing infection, disease and death. Five clinical trials of the Combination B vaccine with a total of
217 participants have been reported on safety and two trials on efficacy. No severe or systemic adverse effects have been reported at doses of 13 to 15 μg of each antigen (39 to 45 μg total). One small efficacy trial with 17 non-immune participants with the BS parasites showed no reduction or delay in parasite growth rates after an artificial challenge. In the second efficacy trial with 120 children aged five to nine years in Papua New Guinea, episodes of clinical malaria were not reduced, but Combination B significantly reduced parasite density. However, this reduction in parasite density occurred only in children who had not been pre-treated with sulfadoxine-pyrimethamine. Overall, the Combination B vaccine shows some promise in reducing the severity of malaria episodes, but not in the protection from malaria.

In line with a whole sporozoite vaccine, a study conducted at the Queensland Institute for Medical Research (QIMR), Australia, observed protection against \textit{P. falciparum} blood-stage challenge in healthy adult volunteers who received several ultra-low subclinical doses of \textit{P. falciparum} infected human erythrocytes followed by drug cure using atovaquone-poguanil\textsuperscript{27}. This study demonstrated that immunity was induced by both CD4\textsuperscript{+} and CD8\textsuperscript{+} T-cells with induction of IFN-\( \gamma \) and nitric oxide production and an absence of detectable antibodies. But the main drawback of this study was that it was not clear whether the residual presence of atovaquone-poguanil in the volunteers actually suppressed the development of parasites upon challenge\textsuperscript{28}.

**Transmission blocking vaccine (TBV)**

The concept of a malaria TBV came into existence from a study in 1958 that demonstrated that transmission blocking immunity could be induced in chickens immunized with a mixture of \textit{P. gallinaceum} asexual and sexual stage parasites\textsuperscript{29}. TBVs are based on the antigens expressed either on the surface of the sexual gamete forms and/or in mosquito mid-gut stages of malaria parasites. These antigens are the targets of antibodies induced by vaccination of the host and ingested with the parasites in a mosquito blood meal. The antibodies act by either preventing the fertilization or by inhibiting the parasite development within the mosquito, and this may lead to a reduction or complete failure in sporozoite production. Thus, if effective, TBVs may contribute to a reduction or total interruption of the malaria cycle in relatively low transmission areas, mostly outside sub-Saharan Africa. Promising recombinant TBV candidate antigens for the two main human malaria parasite species, \textit{P. falciparum} and \textit{P. vivax}, have been produced and tested in the laboratory\textsuperscript{30}. In a recent report, in a Phase I trial involving PfBs 25 and PvBs 25 candidate transmission blocking antigens of \textit{P. falciparum} and \textit{P. vivax}, respectively formulated with Montanide ISA 51 systemic adverse events occurred in the human volunteers\textsuperscript{31}. Although, other TBV vaccines are under preclinical development, no TBV is currently in clinical trial.

In recent years, the mosquito-based TBV(MTBV) concept has been put forward as another class of TBVs. These vaccines will be designed to target mosquito midgut or salivary gland determinants (immunogens) like trypsin, CarboxyPeptidase B \textit{Anopheles gambiae} 1 (CPBAg1), \textit{Anopheles gambiae} AminoPeptidase N1 (AgAPN1), saglin, and few others. A recent review has provided detail of each of these mosquito molecules and the reasons they are being considered as MTBVs\textsuperscript{32}.

**Challenges ahead for a successful malaria vaccine production and deployment**

There is no licensed malaria vaccine till date. Some of the well recognized factors that have hindered the development of an effective vaccine include lack of understanding of the host mediators of natural immunity; lack of appropriate assays and surrogates for vaccine safety and efficacy; a limited number of antigens being pursued as vaccine candidates; a limited number of immune-enhancing adjuvants and the vaccine delivery platforms available for use in humans. Some of these issues are discussed below.

**Choice of vaccine candidates and their clinical grade production** — During the last two decades, several antigenic targets of malaria parasites have been identified for development as candidate vaccines. A majority of these target immunogens did not progress beyond the pre-clinical development or early phase of clinical trials. Efforts to improve the track record of candidate malaria vaccine antigens in clinical studies would require a more rationale approach for the selection of malaria antigens that are chosen for pre-clinical development. These considerations should include the role of the candidate antigen in natural immunity and whether the target antigenic domains are polymorphic and amenable to immune pressure that could be intensified by vaccination induced immune responses. In addition,
the concept of single antigen vaccines versus multi-stage, multi-antigen vaccines must be validated in carefully designed clinical studies. The ability to express the target antigens as highly purified recombinant molecules that closely mimic native conformations is also an important criterion for consideration.

Several of these issues have been actively addressed over the years with varying degrees of success. For example, in *E. coli*, expression of several malarial antigens has been achieved successfully, and the conformation and structure of these expressed proteins closely resemble their native forms. Furthermore, codon optimization and codon harmonization of malarial gene sequences have led to higher levels of recombinant expression and conformational folding in heterologous systems. The codon harmonization approach has been remarkably successful in the heterologous production of two of the malaria vaccine antigens, a liver-stage antigen of *P. falciparum* (LSA-1) and MSP-1 FVO allele, that had previously been refractory to recombinant expression even with codon-optimization as well as co-expression with a rare frequency tRNA plasmid.

**Biological assays that could serve as surrogates of efficacy of candidate malaria vaccine** — This is one of the most challenging and difficult areas in malaria vaccine development efforts. There are no validated assays which could be used reliably to predict the safety profile and adverse events that may result from vaccinations with candidate malaria vaccines. In particular, biomarkers/assays that could predict the virulence and long term safety of malaria vaccines are greatly needed. For example, there is no reliable and easily accessible non-human model to measure the efficacy or virulence profile of live, attenuated sporozoite vaccines. The commonly used *in vitro* liver cell assay to measure the progression of liver stage parasites as a marker for attenuation is highly limited due to the low sporozoite infectivity rates seen in the available cell lines.

Significant investments have been made to define the mechanism of protection conferred by natural immunity and vaccination-induced immunity. Natural immunity against the pre-erythrocytic stage is at best only partial as evidenced by the fact that after radical drug cure, clinically immune adults become parasitemic after a brief duration. Irradiated sporozoite induced immunity, as defined in *P. berghei* and *P. yoelii* murine malarias, is shown to be multifactorial involving antibody, CD8+ T-cells, and CD8+ T-cell derived IFN-γ, CD4+ T-cells, non-IFN-γ cytokines like IL-12, TNF-α, inducible nitric oxide synthase (iNOS) and the L-arginine dependent nitric oxide pathway. Immune mechanisms against PE stages in human malarias is not clearly defined, although CD8+ and CD4+ T cell responses to several antigens including CSP, SSP2/TRAP, LSA-1 and EXP-1, have been detected in humans immunized with irradiated *P. falciparum* sporozoites. RTS,S vaccine induces strong humoral and also cell mediated immune (CMI) responses in malaria-naive and semi-immune individuals as tested by ELISA, ELISPOT and IFA assays, but the correlation of vaccine induced protection with these humoral and/or CMI response has not been defined.

The currently available assays that are used to measure the efficacy of BS vaccines are also less than satisfactory. Extensive efforts have been made to associate antigen-specific ELISA titers against recombinant proteins and IFAT antibody levels against whole parasite with protective immunity with very limited success. Immunizations with several blood stage antigens in Phase I clinical trials induced high levels of antibody responses in ELISA. The question remains whether antibody levels detected during natural infection or in vaccinated individuals are directly related to the degree of immunity against BS parasites. Antibodies are generally thought to render their protective effect by neutralizing the merozoites and thus either completely block or reduce their entry and growth in red cells.

Accordingly, a growth inhibition assay (GIA) that measures the effect of anti-malarial antibodies on the replication of blood stage *P. falciparum* parasites in culture is commonly used (a) to measure pre-clinical efficacy of candidate BS vaccines and (b) to determine whether in clinical studies, vaccine antigen-specific antibodies have any effect on *in vitro* parasite growth. However, it is not clear whether the detected ELISA titers and antibodies that exhibited the growth inhibitory effects are the same ones that are associated with protective immunity. The correlation of these antibodies to immunity or clinical protection is also uncertain. Thus, the relevance of GIA in determining the efficacy of BS candidate vaccine remains to be established.

**Trial endpoint(s) and determination of vaccine efficacy** — Selection of trial endpoints for a malaria
vaccine is highly complex and relies on many factors. The endpoints that can be assessed in field trials of malaria vaccines are dependent on the developmental stage that is targeted and the intended population. To be effective, pre-erythrocytic stage vaccines, by definition, should induce sterilizing immunity as measured by the absence of blood stage parasites. On the other hand, measuring the efficacy of BS vaccines is far more complex and is dependent on the age, prior immune status and transmission intensity in the study area. The efficacy criteria for a BS vaccine include a significant reduction in parasite burden and protection from severe disease (cerebral malaria and severe anemia). Thus, a BS vaccine may have a severe reduction in malaria mortality and morbidity in young African children or in children and adults in low-transmission areas without inducing sterilizing immunity. Carefully establishing case definitions for each of these endpoints to be measured is of paramount importance in analyzing the overall efficacy and effectiveness of the vaccines. Unfortunately, the range, limits and standard definitions for these endpoints are not clearly defined. For example, it is important to calculate the number of fever cases exclusively resulting from malaria infection in different age groups in an endemic area. The definition of severe malaria is also not fully established and often severe malaria cases are misclassified. In one study in Malawi, where 31 children were claimed to have died of cerebral malaria, autopsy results indicated that 23% had actually died of other causes including bacterial meningitis. This study, along with a few other reports, indicates that malaria-specific mortality is not very stringently defined and that autopsies used to define them have a low specificity.

Co-infection with other tropical infectious agents— People living in malaria endemic regions are often exposed and infected with other pathogens as well. The presence of co-infections makes it difficult to define complications exclusively attributed to malaria. For example, the features of anemia caused by hook worm infections closely resemble the features of malaria-induced anemia in children of endemic areas. In order to define exclusively malaria related anemia, the possibility of hook worm infection must be considered. People living in malaria endemic areas are reported to be frequently exposed to fourteen major neglected tropical diseases (NTD), namely Buruli ulcer, Chagas disease, cholera/epidemic diarrheal diseases, dengue, guinea worm infection, endemic treponematoses (yaws, pinta, syphilis), African trypanosomiasis, leishmaniasis, leprosy, filariasis, onchocerciasis, schistosomiasis, soil-transmitted helminthiasis, and trachoma. Hook worm infections and schistosomiasis are frequently the most prevalent co-infections with malaria, HIV/AIDS and tuberculosis. Co-infections can elicit an array of synergistic as well as antagonistic immune interactions, which may play an important role in defining clinical malaria and the outcomes of vaccine trials as well. Immune interactions between malaria and helminthes, ubiquitous viruses like Epstein-Barr virus (EBV) and HIV, bacteria like Mycobacterium sp., other protozoan parasite like Leishmania sp and Trypanosoma sp. have not been studied to a great extent. There is an urgent need to understand how multiple pathogens modulate immune responses in infants, children and adults of malaria endemic areas in order to have a system of better case definition and also to define vaccine efficacy and safety. It is not known yet, what is the safety profile of any of the malaria vaccine formulations in immunocompromised individuals infected with HIV or EBV. In a recent report, however, it has been shown that infection of immunocompromised SCID mice with $1 \times 10^6$ radiation attenuated P. yoelii sporozoites does not produce breakthrough malaria infection even when administered through an intravenous route. This type of data is not yet available from human malaria vaccines.

Research funding — Historically, malaria vaccine development efforts have progressed at a slow pace due to lack of interest by large funding agencies, both public and private. However, recent years have seen a great surge in funding for malaria vaccine research. This change in funding scenario has largely occurred due to keen interest and investments made by the Bill and Melinda Gates Foundation to support malaria eradication efforts including vaccine development. According to a recent estimate by the Global Malaria Action Plan (GMAP)/Roll Back Malaria (RBM) (http://www.rollbackmalaria.org/gmap/3-1.html), in order to eradicate malaria by 2020, $5.3$ billion is required in 2009, $6.2$ billion is required in 2010, and between 2011 and 2020 $5.1$ billion is required. WHO has reported in its most recent World Malaria Report 2008 that an estimated 3.3 billion people are at risk of malaria, that almost 247 million episodes of
malaria occurred, and these episodes resulted in an estimated 881,000 malaria deaths in 2006 globally. In comparison, as per the latest report in AIDS Epidemic Update of UNAIDS/WHO in December 2007, 33.2 million people were living with HIV globally in 2007 and the number of deaths from AIDS in 2007 was 2.1 million. These reports highlight that there are more people globally who are infected with malaria or who are at risk of getting malaria infection than there are people who are infected with HIV/AIDS or at risk of infection. However, the R&D funding for HIV/AIDS in 2007 was US$ 1.08 billion in comparison to US$ 468.5 million for malaria. In 2007, out of US$1.08 billion funding for HIV/AIDS, US$ 692 million (63.9%) was directed to vaccines, whereas, out of US$ 468.5 million funding for malaria, vaccine development efforts received only US$88.4 million (18.9%). It is critical that current or higher level of funding through global governments and private agencies must be made available in the coming years to maintain and accelerate the ongoing malaria eradication and vaccine developing efforts.

Conclusion

Development of a successful malaria vaccine is an important component of the global efforts for malaria eradication as well as a major challenge to the scientific community and funding agencies. Recent reports of limited protection form severe malaria in young African children vaccinated with RTS,S, a recombinant subunit malaria vaccine and renewed interest in the production and testing of live attenuated sporozoite based candidate vaccines have sparked the prospects of an effective malaria vaccine in the near future. While the development and testing of the current candidates in pipeline are ongoing, there is an urgent need to develop and test the next generation malaria vaccines that are based on the most recent technological advances in vaccine design and delivery platforms including their delivery in novel adjuvant formulations. Simultaneously, genomics based antigen discovery efforts must continue in order to find more effective candidate vaccine antigens. The other areas that will require a significant amount of investment include building infrastructures in malaria endemic countries where the trials can be conducted, identification and validation of surrogate markers to measure the vaccine safety and efficacy, standardization of assays to measure the potency, safety and stability of vaccines, and clear strategies for case definition and severe malaria definition. Finally, it is of great importance to evaluate the efficacy of candidate vaccines at multiple clinical sites that offer varied endemicity and transmission rates. It is also important to test candidate vaccines in combination with other malaria control measures like insecticide treated mosquito nets (ITNs) and intermittent preventive treatment in infants (IPTi) with antimalarial drugs through the expanded program on immunization (EPI).

Acknowledgement

We thank NJ Gerald for critical reading of the manuscript. The views and opinions expressed in this article are those of the authors and do not represent the official position of the US Food and Drug Administration.

References


34 Pandey K C, Singh S, Pattnaik P, Pillai C R, Pillai U, Lynn A, Jain S K & Chitnis C E, Bacterially expressed and


