DOI: 10.7860/JCDR/2019/19314.13091

Editorial

Immunology and Infectious Diseases Section

Malaria Vaccine Development: Challenges and Prospects

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Malaria is a vector-borne, infectious, parasitic disease caused by *Plasmodium* and transmitted through the bites of infected female *Anopheles* mosquitoes. The term 'malaria' originated from the Italian *'mal'* (bad) and *'aria'* (air). Before the advent of the 'Germ Theory' propounded by Louis Pasteur, it was thought that malaria was transmitted via miasmas or foul-smelling air found near swamps, marshland and bogs. The term 'malaria' first appeared in English medical literature in 1829.

There are primarily four species of *Plasmodium*- *P. falciparum, P. vivax, P. malariae,* and *P. ovale,* although *P. knowlesi*, which normally infects animals, has also been known to occasionally infect humans. In the Indian context, *P. falciparum* and *P. vivax* are the most important.

There are over 400 species of *Anopheles* mosquitoes, of which 30 are of major importance with regard to malaria transmission. Climatic factors such as temperature, humidity, and rainfall impact transmission patterns, which often peaks after the monsoon season.

GLOBAL BURDEN OF MALARIA [1]

As per the World Malaria Report 2018, published by the World Health Organisation (WHO), there are 219 million cases and 435,000 deaths worldwide due to malaria. Africa continues to bear the brunt of the global malaria burden, with 92% of malaria cases and 93% of malaria deaths. Notably, nearly 50% of all malaria cases worldwide are borne by just 5 countries, of which four are in Africa and the other is India, which accounts for 4% of the global burden. The most vulnerable group are children below 5 years, which accounts for 61% (266,000) of all malaria deaths (killing one child every 2 minutes) globally. Other vulnerable groups include pregnant women, HIV/AIDS patients, and non-immune migrant populations.

ELIMINATION OF MALARIA [2]

The global target set by WHO is to reduce malaria incidence and deaths by 90% by 2030. Although the goal may seem ambitious, it is nevertheless achievable. Malaria is considered to be eliminated if there are no cases for at least three consecutive years. It is very encouraging that in recent years 9 countries have eliminated malaria, most recently being Sri Lanka (2016), Kyrgyzstan (2016), Paraguay (2018), and Uzbekistan (2018).

MALARIA: THE INDIAN SCENARIO [1]

As per the World Malaria Report 2018, India reported a reduction in malaria cases between 2016 and 2017, with 3 million fewer malaria cases during this period, which translates into a 24% reduction in cases.

The WHO's Global Technical Strategy (GTS) for Malaria 2016-2030 measures the performance of various countries in reaching the GTS targets. It is encouraging to see that India has made impressive progress and is on track for achieving the 2030 GTS targets. Moreover, India's estimated change in malaria case incidence for reaching the 2020 GTS milestone is a staggering 64.4%. Importantly, India has received the highest funding for malaria control in South-East Asia from the Global Fund between 2015 and 2017.

However, despite the progress, India still accounts for 4% of all malaria deaths worldwide. Also, India is one of 7 countries that failed to reach the operational universal coverage target of one insecticide-treated bed net (ITN) per two persons at risk by 2017. Also, expenditure per person at risk of malaria in India is only a few cents- the lowest in South-East Asia. Approximately 82% of all *P. vivax* cases occur in just 5 countries, of which India has the highest number of cases, accounting for 48% of all *P. vivax* cases in these 5 countries. In India, the treatment failure rate for the antimalarial drugs, artesunate+sulfadoxine-pyrimethamine, was 12.1% in 2012, primarily in the north-eastern states. Since then, India has changed its malaria treatment policy.

CHALLENGES IN DEVELOPING A MALARIA VACCINE [3]

Vaccines are the ideal tools for preventing malaria. However, development of a malaria vaccine is technically very challenging, compared to that of bacterial and viral vaccines. This arises from the fact that the genome of the malarial parasite (*Plasmodium*) is much larger and more complex than bacterial and viral genomes. Moreover, *Plasmodium* has three stages in its life cycle and undergoes both asexual and sexual reproduction within two different hosts. The first two stages, namely, pre-erythrocytic and erythrocytic stages, involve asexual reproduction within the human host, while the third stage involves sexual reproduction within the mosquito gut. This makes it a huge challenge for researchers to design an ideal malaria vaccine.

Another challenge for malaria vaccine development is the lack of a traditional vaccine market. Since malaria disproportionately affects the poorest countries, which lack purchasing power, the vaccine manufacturers have little incentive for developing vaccines for this disease.

TYPES OF MALARIA VACCINES [3,4,5]

Malaria vaccines are designed in such a way that they target one of the three stages in the life cycle of the malarial parasite. Hence, there are three types of malaria vaccines, which are briefly discussed below:

- **Pre-erythrocytic vaccines:** Sporozoites are infectious agents injected into humans during the bite of an infected *Anopheles* mosquito. Sporozoites target the liver, causing infection. The pre-erythrocytic vaccines produce antibody-mediated inhibition of sporozoite infection of the liver by blocking their entry into the hepatocytes, thereby stopping progression of the liver stage. During the liver stage, the malarial parasite rapidly multiplies, producing thousands of merozoites. These vaccines can induce T-cells that target and kill infected hepatocytes, thereby preventing release of merozoites and halting further parasite development. There are currently 12 pre-erythrocytic

vaccine candidates under development, of which the RTS,S malaria vaccine is the most advanced.

- **Erythrocytic vaccines:** After completion of the pre-erythrocytic stage, the merozoites are released from the liver and enter the blood to infect erythrocytes. This is why these vaccines are also known as blood stage vaccines, which aim to stop the invasion of red blood cells (RBCs), thereby preventing asexual reproduction of the parasite. The mechanism of action of erythrocytic vaccines is mediated through antibodies that target the merozoite surface proteins (MSP), such as MSP-1, thereby halting invasion of RBCs. There are currently 15 erythrocytic or blood stage vaccine candidates under development.
- **Transmission blocking vaccines:** At the end of the erythocytic stage, a proportion of the merozoites differentiate into sexual stages, which are taken-up by an *Anopheles* mosquito when it bites an infected person. The parasite completes its life cycle within the gut of the mosquito. The transmission blocking vaccines target the mosquito gut to stop sexual reproduction of the parasite. They are so called because they aim to kill the mosquito to block further transmission of the parasite. These vaccines generate antibodies that either prevent fertilisation of the gametes in the mosquito gut or stop the development of the zygote into sporozoites. They do not confer direct protection to the immunised individual but produce herd immunity. There are currently 6 transmission blocking vaccine candidates under development.

MAJOR MALARIA VACCINES CURRENTLY UNDER DEVELOPMENT [5,6,7]

There are over 30 malaria vaccine candidates that are undergoing clinical trials or in advanced preclinical development. The major vaccine candidates targeted against *P. falciparum* are highlighted below with reference to the stage of development:

- **Lead identification/optimisation stage:** There are a total of five vaccine candidates in this stage of development. These include a B-cell target vaccine (pre-erythrocytic), a virus-like particle (VLP) based RH5 protein vaccine (erythrocytic), and three transmission blocking vaccine candidates (*Pfs*48/45; *Pfs*230 fragments; and *Pfs*25 VLP/*Pfs*230 VLP).
- **Translational stage:** There are a total of six vaccine candidates in this stage of development. Four of these are pre-erythrocytic- one in pre-clinical development (CSP mAb), three in Phase 1/2a (RTS,S-AS01 delayed fractional dose CHMI study; RTS,S-AS01 fractional dose co-administered with DHA-PIP+PQ field study; Transgenic *P. berghei*) and one in Phase 2b (RTS,S-AS01 delayed fractional dose field study). There is also a transmission blocking vaccine candidate in Phase 1/2a (*Pfs*25-EPA and/or *Pfs*230-EPA formulated with AS01).

Besides the above vaccine candidates, the most advanced malaria vaccine, which has passed all clinical trials and has been approved as the world's first malaria vaccine is RTS,S-AS01$_E$ (for paediatic use), also known as Mosquirix™.

RTS,S (MOSQUIRIX™)- THE WORLD'S FIRST MALARIA VACCINE [8,9]

The RTS,S malaria vaccine, also known as Mosquirix™ is the world's first approved malaria vaccine. It is a recombinant vaccine, consisting of VLPs made by expression of the hepatitis B surface (S) antigen (HBsAg) in the yeast *Saccharomyces cerevisiae*. The S antigen is fused to the circumsporozoite protein (CSP) of *P. falciparum*, containing the repeat region (R) and a T-cell epitope (T). The vaccine is formulated with AS01, which is a liposome-based vaccine adjuvant that boosts the immunogenicity of the vaccine.

The RTS,S malaria vaccine development began in 1984 at the Walter Reed Army Institute of Research (WRAIR), Silver Springs, Maryland, USA. Over the next 30 years, the vaccine was taken forward by GlaxoSmithKline (GSK) with collaboration from PATH's Malaria Vaccine Initiative (MVI). The total expenditure incurred for developing the vaccine was over USD 700 million.

RTS,S MALARIA VACCINE CLINICAL TRIAL [10, 11]

A large-scale Phase III clinical trial was conducted in 7 African countries over a span of 5 years (2009-2014) by GSK and MVI, with funding from the Bill & Melinda Gates Foundation (BMGF). The trial involved a large network of research centres at 11 sites in the 7 countries in Africa. The vaccine for the trial was manufactured and supplied by GSK.

Clinical Trial Design

This Phase III clinical trial included a total of 15,460 participants, including 6,537 infants and 8,923 children, aged 5-17 months. These infants and children were vaccinated either 3-times or 4-times with the RTS,S malaria vaccine or a control vaccine (meningococcal C vaccine for infants and rabies vaccine for children). Vaccine efficacy was based on the reduction of the number of clinical malaria cases, severe malaria cases, and malaria hospitalisations. The immunogenicity of the vaccine was determined by its antibody-inductive capacity against CSP. The impact of the vaccine on disease burden was estimated on the basis of the number of clinical and severe malaria cases averted per 1,000 immunised children. The follow-up period, post-vaccination was 4 years.

Clinical Trial Findings

After 4 years of follow-up, it was found that the protection conferred by the RTS,S malaria vaccine against clinical malaria was 36.3% (95% CI: 31.8-40.5) among children 5-17 months of age who had received all 4 doses of the vaccine. In case of children who received 3 doses of the vaccine, protection against clinical malaria was 28.3% (95% CI: 23.3-32.9). In case of young infants, who were aged 6-12 weeks at the time of first vaccination, protection against clinical malaria was 25.9% (95% CI: 19.9-31.5) in those who received 4 doses and 18.3% (95% CI: 11.7-24.4) in those who received 3 doses. Therefore, protection was lower in the 6-12 week group, compared to the 5-17 months group.

The RTS,S vaccine also provided significant protection against severe malaria and substantially reduced the number of hospital admissions arising from malaria in case of children who received all 4 doses. In case of children who received all 4 doses, approximately 1,774 (95% CI: 1,387-2,186) clinical malaria cases were averted per 1,000 vaccinated children.

However, two negative aspects of the RTS,S vaccine were noticed in this clinical trial. The first was an increase in the incidence of meningitis cases in the vaccinated children, which was considered to be an adverse effect of the vaccine. The second was the waning of the vaccine efficacy over time, resulting in rebound malaria cases, also termed as "age shift".

Clinical Trial Implications

On the basis of the study findings, the European Medicines Agency (EMA) gave a positive opinion with regard to using the vaccine in both the younger (6-12 weeks) and older (5-17 months) age groups included in the Phase III clinical trial.

However, WHO exercised caution while making its recommendations. WHO's Strategic Advisory Group of Experts (SAGE) on Immunisation and Malaria Policy Advisory Committee recommended that the vaccine should be used only in the older age group. The experts further recommended that the vaccine should be introduced in phases in the form of pilot projects in several African countries, prior to widespread deployment of the vaccine. These pilot projects have already started in Malawi and Ghana, and will soon begin in Kenya.

INTRODUCTION OF THE RTS,S MALARIA VACCINE IN AFRICA [12,13]

The RTS,S malaria vaccine is being rolled out in a phased manner in three pilot countries in Africa, namely, Malawi, Ghana, and Kenya under the supervision of WHO. The vaccine, which will be made available for children up to 2 years of age, has already been launched in Malawi and Ghana.

It is estimated that approximately 360,000 children annually across the three pilot countries will receive the RTS,S vaccine. The vaccine has a 4-dose schedule. The 1st dose is given at 5 months of age, followed by the 2nd and 3rd doses at monthly intervals, and the 4th (booster) dose at 2 years of age.

GSK has agreed to supply 10 million doses of the vaccine free of cost for WHO's Malaria Vaccine Implementation Programme (MVIP), which is being jointly funded by Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid.

The three pilot programmes, led by WHO, will generate important evidence about several aspects that will shape WHO's future malaria vaccine policy. These include reduction in child mortality, vaccine safety, and vaccine uptake, in the context of routine immunisation.

CONCERNS REGARDING THE RTS,S MALARIA VACCINE [14]

The RTS,S malaria vaccine has recently faced some stiff opposition from the research community. Since RTS,S protects only 40% of vaccinees and requires 4 doses over a span of 18 months, some think that the pilot programmes are a waste of time and money, which could have been invested in accelerating the development of other potential malaria vaccine candidates in advanced stages of clinical testing.

Moreover, the long-term programmatic cost of implementation of this 4-dose vaccine, which will cost USD 20 per child for the full course, will be out of reach for most African countries, who are already struggling to deploy bed nets and drugs for treating malaria. This is why WHO recommended in 2015 to roll out the RTS,S vaccine in phases, so that safety and other issues could be identified at each phase to decide on the feasibility of wider applicability of the vaccine.

PREDICTIONS FOR GROWTH OF THE MALARIA VACCINE MARKET [15]

It is anticipated that the global malaria vaccine market will witness a significant growth in the coming years, especially between 2019 and 2028. This largely stems from the increased demand for malaria vaccines. The main types of malaria vaccines that are in demand are the pre-erythrocytic, erythrocytic, and multi-antigen vaccines. The key global players in the malaria vaccine market, namely, GSK, Sanaria, Nobelpharma, Sumaya Biotech, and GenVec are trying their best to capitalise on the opportunities in the vaccine market arising from the increased demand.

FUTURE PROSPECTS [16]

From the foregoing discussion, it is evident that although many promising malaria vaccines are under various stages of development, the RTS,S vaccine is the only approved malaria vaccine currently available for immunisation. The three pilot programmes being implemented in Malawi, Ghana and Kenya are expected to be completed by 2023. The evidence generated from these programmes will enable WHO to update its malaria vaccine policy and make recommendations for the broader use of RTS,S for routine immunisation of African children.

Hence, these are exciting times for the development of malaria vaccines and the future prospects, especially for RTS,S is looking good, and will improve further once the results of the pilot programmes become available in 2023.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jun 02, 2019**
Date of Peer Review: **Jul 03, 2019**
Date of Acceptance: **Jul 20, 2019**
Date of Publishing: **Aug 01, 2019**