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The Need for a Malaria Vaccine

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Introduction

Malaria is the world's largest parasitic disease, affecting more than 100 countries. The parasite species that causes the disease worldwide have been identified as *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*. Transmission of these parasites is through a bite of *Anopheline* mosquitoes [1].

In developing countries such as in Africa, malaria carries a large burden on peoples' lives, medical costs and days of labour lost. According to WHO 2017 Malaria report, in 2016, an estimated 216 million cases of malaria occurred worldwide compared with 237 million cases in 2010; Most of the cases in 2016 occurred in the WHO African Region (90%), followed by the WHO South-East Asia Region (7%) and the WHO Eastern Mediterranean Region (2%) [2]. The incidence rate of malaria is estimated to have decreased by 18% globally, from 76 to 63 cases per 1000 population at risk, between 2010 and 2016 [2]. In spite of these reductions, between the period of 2014 and 2016, there was a substantial increases in case incidence in the WHO Region of the Americas, and marginally in the WHO South-East Asia, Western Pacific and African regions [2]. Also, in 2016, an estimated 445000 deaths from malaria occurred globally, compared to 446 000 estimated deaths in 2015 [2]. Malaria has always been and continues to present a major health challenge among children and pregnant women in Africa or the sub-Saharan region [3,4]. Majority of clinical cases and deaths from malaria occur in sub-Saharan Africa affecting children under five years of age and pregnant women [4,5]. Malaria poses a serious health risk to an increasing number of individuals to this day with no vaccines being available for this parasitic disease. While Artemisinin Combination Therapies (ACTs) have been integral to the recent success of global malaria control, multidrug resistance, including artemisinin (partial) resistance and partner drug resistance, has been reported so far in five countries of the Greater Mekong sub region; also, in 2016, resistance to one or more insecticides was present in all WHO regions [2]. Malaria control with the vaccine perspective according to Birkett, involves two strategic goals; the first such goal is to target induction of immunity in order to prevent clinical disease and the second is to target induction of immunity to interrupt transmission and thereby supporting elimination and eradication efforts [1].

History of malaria vaccine

Reports showed that it has been over 50 years ago since it became feasible to develop a cost-effective malaria vaccine. However, despite this milestone the vaccine only achieved moderate efficacy in protecting against the malaria parasite. The authors claim that the slow advancement in developing a better vaccine is the strong capacity of *Plasmodium* parasite to evade the host's immune response [6]. In the course of a malaria infection, naturally acquired immunity is possible however it develops slowly [7]. Protection against malaria pathogens requires a specific approach to vaccine design, which requires a great amount of time and the outcomes less certain. In the past, vaccine technologies which have been used are outdated and ill-suited for a rapid response to the emerging outbreaks. The development of the malaria vaccine predates back to 1910s when the first attempt was made using malaria infected canaries and a vaccine with attenuated sporozoites. Following this in the 1960s researchers, using infected mice, discovered a Circumsporozoite Protein (CSP) during vaccination process. In 1967, humans' volunteers were tested on for prevention of malaria using irradiated sporozoites. However, it was not until two decades later in 1990s that

clinical trials took place to test the blood stage peptide vaccine SPf66 followed by the initiation of first trials of DNA vaccines and development of the prime boost approach using viral vectors and demonstration of the efficacy of the RTSS vaccine in volunteers from years prior, in years after 2000s. In 2010, phase 3 trial of RTSS vaccine was initiated with reported number of approximately 30 new malaria vaccines in development [6-8].

A newer approach in malaria vaccine is one that targets the blood stages of malaria and it is intended to reduce morbidity. This new approach is intended to create a multistage, multi-antigen vaccine for better immunity against the malaria parasite [9]. During the last decades, adjuvants have become increasingly important in the development and preparation of malaria vaccines. According to Mata, the uses of adjuvants are important compounds that enhance and direct a specific immune response in humans [6]. According to White, there still does not exist a very effective anti-malaria vaccine but advancements are being made; furthermore as early as 2015 a first malaria vaccine would be available for public use in some African countries. This goal is dependent upon the successful completion of a phase 3 trial by pharmaceutical companies such as GlaxoSmithKline and Program for Appropriate Technology in Health (PATH) Malaria Vaccine Initiative [10].

Malaria vaccine in development

Overview: The development of malaria vaccine has been a slow progress due to the *Plasmodium* parasite. This parasite has the capacity to elude the host's immune system; hence, the most advanced vaccine up to date has only 30% efficacy against this parasite. "This ability derives from the genetic complexity of the pathogen, which exhibits genetic diversity as well as antigenic variation during the multistage life cycle" [6]. With combination from both the humoral as well as the cellular responses to the *Plasmodium* parasite, the host's cell would be able to achieve excellent protection. Also, vaccines aimed directly at the different sexual stages would help block the transmission of the parasite. In terms of humoral response, red cell invasion can be prevented as well as eliminating infected cells directly via induction of opsonization of sporozoites. On the other hand, cellular response production of cytokines and immune mediators (T helper cells (Th)) and killing of infected hepatocytes (cytotoxic CD8+ T lymphocytes, CTLs)) can be achieved via cellular response [6].

Types of malaria vaccines: Malaria vaccines are made to stimulate the host's immune system to attack and destroy or to arrest the malaria parasite. The vaccine can manifest the desired actions at any point during the life cycle of the parasite. The only change or the challenge that most scientist face when developing the malaria vaccine is lack of understanding of the specific immune responses that comes with the protection against the parasitic disease. Due to the complexity of the malaria parasite, developers have pursued diverse approaches [11,12]. .

There are three types of malaria vaccines available. They are the Pre-erythrocyte vaccine candidates, Blood-stage vaccine candidates and Transmission-blocking vaccine candidates. "Pre-erythrocyte vaccine candidates aim to protect against the early stage of malaria infection- the stage at which the parasite enters or matures in an infected person's liver cells" [11,12]. The vaccine stimulates an immune response that either prevents infection attack or it attacks the infected liver cell if the infection does not occur [11,12]. These candidates include:

- "Recombinant or genetically engineered proteins or antigens from the surface of the parasite or from the infected liver cell".
- "DNA vaccines that contain the genetic information for producing the vaccine antigen in the vaccine recipient".
- "Live, attenuated vaccines that consist of a weakened form of the whole parasite (the sporozoite) as the vaccine's main component".

"Blood-stage vaccine candidates target the malaria parasite at its most destructive stage—the rapid replication of the organism in human red blood cells". The aim of this type of malaria vaccine is to decrease the number of parasites in the blood; hence, reducing the severity of the disease. The function of this vaccine is to help the host's cell develop natural immunity against the malaria parasite. For instance, an individual will develop natural immunity overtime once exposed to malaria. Just like being exposed to the malaria parasite, the Blood-stage vaccine acts the same way, helping the host's cell develop this immunity against the parasite [11,12].

"Transmission-blocking vaccine candidates seek to interrupt the life cycle of the parasite by inducing antibodies that prevent the parasite from maturing in the mosquito after it takes a blood meal from a vaccinated person". Unlike the other two forms of vaccines mentioned above, the Transmission-blocking vaccine does not prevent the individual from getting malaria nor reduce the symptoms but rather, minimize the spread of the infection by preventing mosquitoes that fed on an infected person from spreading the malaria to a new host. Thus, this form of vaccine would decrease deaths as well as illnesses relating to malaria within the community [11,12].

RTS, S/AS01 (RTS, S; trade name Mosquirix™) vaccine which acts against *Plasmodium falciparum* is the world's first malaria vaccine that has been reported to provide partial protection against malaria in young children in Africa [13,14]. Starting from 2018, the vaccine will be the first to be provided to young children through routine immunization programmes in selected areas of three sub-Saharan African countries (Ghana, Kenya and Malawi) as part of a large-scale pilot implementation programme [14].

General consideration, key challenges and opportunities for malaria vaccine

There is a requirement for a vaccine to prevent malaria as the disease could not be controlled with the usage of the tools that are present for controlling the disease in the endemic area. The other factor that put stress on the requirement of the anti-malaria vaccine is the growing resistance of the malaria parasite to the insecticides and the anti-malarial drugs that are being used to prevent the widespread of the disease. The mode that is being used for the delivery of the vaccine is relatively easy and times and again it has been proven that vaccine is useful in the prevention of many epidemic disease like smallpox and polio [12].

Availability of a malaria vaccine would help in protecting the individuals against the infection caused by the disease as well as the clinical consequences associated with it. It would also act beneficial in the reduction of the infections caused by malaria [12]. The challenges associated with the malaria vaccine are clear alignment with the community goal related to the development of the vaccine, the vaccine developed is able to meet the need globally, and the development of the pharmacovigilance studies in relation to the vaccine and unavailability of dual market opportunity for the vaccine. In addition, current funding is inadequate for malaria vaccine production and delivery. Hence, to achieve this goal, more donors are required to provide support; more scientists and vaccine developers are equally required to invest their political and intellectual capital [12].

Conclusion

The above description in relation to the disease specifically emphasizes on the need for a malaria vaccine. This could be attributed to the fact that the parasites are becoming more and more resistant to the drugs that are used for the prevention of the disease. Moreover it is more comfortable to use the vaccine, as it is injected to the individual's body through the intravenous passage thus making it more effective in the prevention of malaria. Due to the proven benefit that vaccines bring for the prevention and control of diseases, it is highly recommended. There are certain expectation that is associated with the vaccine which could be related both to the present and the future needs. The vaccine is expected to optimize the effect of the current and the future intervention and at the same time be able to create a strong mantle to prevent the resistance that the Malaria parasite had created for some drugs or combination of drugs. These expectations and the proven advantage that the formulation of the malaria vaccine would bring makes it more important to be a part in the treatment as well as the prevention of the disease

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