ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 13, Issue, 12(A), pp. 2470-2473, November, 2022

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

Malaria vaccine: recent updates

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DOI: http://dx.doi.org/10.24327/ijrsr.2021.1312.0505

ARTICLE INFO

Article History:

Received 3rd October, 2022
Received in revised form 16th October, 2022
Accepted 18th November, 2022
Published online 28th November, 2022

Keywords:

ABSTRACT

Malaria continues to be a global burden in spite of effective vector control and the use of preventive anti-malarial drugs, especially in African countries, mainly in young children. Hence the need for development of effective and durable vaccine against the human malaria parasite *P. falciparum* and *P. vivax* remains a key priority. Developing a vaccine to stop this deadly disease has been challenging because of complex life cycle of parasite and lack of understanding of the complex immune response to malaria infection. However, recent work in malaria vaccine research provides optimism. With first generation pre-erythrocytic vaccines in use, it is important to reflect how next generation vaccine approaches can improve on their success. We review the latest vaccine approach which aims to develop an effective vaccine against malaria.

INTRODUCTION

- Malaria, the most well-known parasitic disease of human, is a life-threatening disease caused by plasmodium parasites that are transmitted to people through the bite of an infected female Anopheles mosquito.
- It is preventable and curable

DISEASE BURDEN

- According to the latest world malaria report (1) there were 241 million cases of malaria worldwide in 2020.
- The estimated number of malaria deaths were 627000 in 2020.
- The WHO African region continues to account for a high share of the global malaria burden. In 2020 the region was home to 95% of all malaria cases and 96% of deaths. Children under 5 years of age accounted for about 80% of all malaria deaths in the region.
- More than 260000 African children under the age of five die from malaria annually.

ETIOLOGY

- Six species of the genus Plasmodium cause malaria in humans.
- These are *P. falciparum*, *P. vivax*, two morphologically identical sympatric species of *P. ovale* (curtisi and wallikeri), *P. malariae*, and in Southeast Asia—the monkey malaria parasite *P. knowlesi*.
- *P. falciparum* and *P. vivax* – pose the greatest threat
- *P. falciparum* is the deadliest malaria parasite and the most prevalent on the African continent. *P. vivax* is the dominant malaria parasite in most countries outside the sub-Saharan Africa.

PARASITE LIFE CYCLE

Plasmodium falciparum, the parasite responsible for the most severe form of malaria, spends a considerable part of its life cycle inside the human body. As parasite takes on different forms and infect different parts of the body, it presents researchers with several distinct targets for vaccines by presenting different antigens at different stages of its life cycle.

The vaccines work by breaking the life cycle of the parasite

1. The parasite life cycle starts when an infected Anopheles mosquito bites a person injecting plasmodium parasites in the form of sporozoites into the bloodstream.
2. The sporozoites quickly infiltrate liver cells and multiply
3. Tens of thousands of parasites in the form of merozoites burst from liver cells and enter the bloodstream.

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4. In the bloodstream the merozoites invade RBCs and multiply.
5. a) Merozoites burst out from RBCs and invade more RBCs, releasing toxic substances that cause many of the clinical symptoms of malaria.

   b) Some merozoites mature into sexual form of the parasite called gametocytes, that circulates in the bloodstream.
6. These gametocytes are ingested by the mosquitoes when they bite humans. In the mosquito sexual reproduction occurs and new sporozoites are formed.
7. The cycle of the human infection begins again when mosquito bites another person.

HISTORY

Modern malaria vaccine development began with seminal studies in mice using irradiated sporozoites. In 1967 Nussenzweig et al immunized mice with radiation-attenuated plasmodium berghei (a non-human form of malaria) sporozoites and observed that the mice were protected in a later challenge with infectious sporozoites [(2)]. In 2002, Hoffman et al attenuated the sporozoites inside the infected mosquitoes by gamma radiation and showed that these attenuated sporozoites did not produce disease in the human but were still able to elicit immune response in the human host[(3)]. This radiation approach was not cost effective and was not practical on a large scale.

During the 1980s, scientists at the Walter Reed Army Institute of Research in US along with scientists from Smithkleine and French, the predecessor of GSK,tried to develop a protein subunit vaccine against the sporozoites form of the parasite, by using a sporozite surface antigen called circumsporozoite protein (CSP). To increase the immune response to CSP a GSK researcher, Joe Cohen, combined CSP with Hepatatis B virus surface antigen (HBsAg). In 1997 to increase the protection provided by CSP-HBsAg construct, the team identified an adjuvant formulation (AS01) which when combined with the CSP-HBsAg construct was highly protective against malaria.This is how the final composition of first malaria vaccine RTS,S/AS01 was reached.

Over the next two decades many human trials were carried out,in 2015 the results of a large phase III trial conducted in more than 7 African countries showed that three doses of RTS,S/AS01, followed by a booster 18 months later helped to protect children and infants from clinical malaria for atleast 3 years after the first vaccination.

Following the publication of those trial results in 2015, the WHO launched pilot programmes in Ghana, Kenya and Malawi in 2019. More than 900000 children are vaccinated so far. The first result showed that hospitalizations from severe malaria have decreased by about 30%. Based on this result finally on October 6, 2021 WHO recommended the use of RTS, S/AS01 vaccine to children in moderate to high endemic areas to reduce infections with P. falciparum.

TYPES OF VACCINES

I. Pre-Erythrocytic Vaccines

1. Inhibition of sporozoite infection: These vaccines work by producing antibodies against sporozoites. They target sporozoites before they reach the liver Examples:
   i. RTS,S/AS01 (Pilot implementation)
   ii. RTS,S/AS01 'Fractional Dose' (phase IIb)
   iii. R21/AS01 (Phase I/IIa)
2. Killing of infected hepatocytes: These vaccines work by training killer T cells to find and destroy infected liver cells. Example: candidate vaccines such as PfSPZ vaccine (Phase 11b)

II. Erythrocytic Stage Vaccines

1. These vaccines aim at the merozoite stage. They work by inhibition of merozoite invasion. They are aimed at reducing parasite multiplication and growth, in order to protect against clinically severe disease.
2. They are designed to induce antibody responses against the targets on the merozoite (asexual) such as merozoite surface protein (example MSP-1) or those contained in specialized organelles associated with invasion (AMA-1)
3. The disadvantage are:
   i. Merozoite stay outside the red cell for a very short duration (less than 30 minutes)
   ii. The high degree of polymorphic variability and
   iii. Use of alternate invasion pathway by *P.faciparum.*

III. Transmission- Blocking vaccines: They target sexual stage of the parasite and aim at reducing malaria transmission by interrupting the parasite life cycle in the mosquito by inducing antibodies that prevent either fertilization of the gametes in the mosquito gut or the further development of the zygote into sporozoites. These vaccines do not protect the immunized individual but rather provide herd benefit.

All these vaccines are in the experimental phase except RTS, S/AS01 which is recommended for use by WHO in moderate to high endemic areas since October 2021.

RTS, S/AS01 (RTS,S): THE FIRST MALARIA VACCINE

- On October 2021, after more than four decades of basic research and clinical trials, the World Health Organization (WHO) has recommended the malaria vaccine RTS,S for widespread use among children living in regions with moderate to high *P. falciparum* malaria transmission.
- The recommendation is based on results from an ongoing pilot program in Ghana, Kenya and Malawi that has reached more than 900000 children since 2019.
- RTS, S/AS01 malaria vaccine should be provided in a schedule of 4 doses in children from 5 months of age for the reduction of malaria disease and burden.
- The vaccine has been shown to significantly reduce severe malaria among young children.
- Circumsporozoite protein (CSP), the sporozoite-specific molecule is the antigen incorporated in the RTS,S vaccine[(4)]. The CSP is expressed on the surface of sporozoites of different plasmodium species and contains a central domain of tandem repeats that represent approximately 30% of the entire sequence.

- The RTS, S vaccine is a hepatitis B virus-like particle that contains a genetically fused portion of the repeat domain and the C-terminal region of the *P. falciparum* CSP (5).
- Vaccination with RTS, S induces antibodies against CSP, which is expressed by sporozoites, the infective form of plasmodium that mosquito transmit. During infection in unvaccinated individuals, sporozoite travel to the liver, where they move through hepatocytes and differentiate to hepatic merozoites. CSP is expressed in the early liver stages but not by liver stage merozoites. Antibodies to CSP following RTS, S vaccination, immobilize the sporozoites, thereby preventing infection of hepatocytes. RTS, S induced protection from infection and severe disease wanes over time and correlates with the level of anti-CSP antibodies. RTS, S induced immune responses do not interfere with the infectivity of plasmodium gametocytes to mosquitoes. Even following vaccination, most children will carry parasites that will infect mosquitoes, thus transmission in the population will remain unchanged.

CLINICAL TRIALS FOR RTS, S

In 1996 the Walter Reed Army Institute of Research conducted the first human trial demonstrating protection against infection by *P.falciparum* sporozoites using RTS, S vaccine developed by Glaxo SmithKline[(6)]. Over the next two decades many phase II and III vaccine trials were conducted in endemic areas and the result consistently showed that vaccination of children 6-12 weeks and 5-7 months of age induces a protective immunity that neutralizes the sporozoite infection or decreases the clinical severity of the infection. In 2015 an extensive phase III trial that included different endemic areas of Africa using three doses of RTS,S vaccine administered with a 1-month interval, and followed by a booster 18 months later, showed that the vaccine helped to protect children and infants from clinical malaria for at least 3 years after the first vaccination. The protection was 74% in children aged 5 to 17 months a few weeks after the last vaccination and decreases to 28% after 1 year and 9% after 5 years. In children 6 to 12 weeks the protection was 63% after the last vaccination and waned to 11% after 1 year and 3% after 5 years[(7)].The protective effect of this vaccine is short-lived, and it appears to depend on the intensity of transmission in different endemic areas. This decreased efficacy correlates with reduced levels of anti-CSP antibodies(8). There is only limited information on the vaccination of adults. In Gambia, RTS,S immunization of adults induced short-lived protection from infection in 34% of vaccines[(9)], while no significant protection was observed in Kenya[(10)].

The WHO launched pilot programmesin Ghana, Kenya and Malawi in 2019, more than 900000 children vaccinated so far under this pilot programme. The first results showed that hospitalizations from severe malaria have decreased by about 30%[(11)].

NEW GENERATION MALARIA VACCINE

There is consensus that major improvements are necessary to develop a vaccine that is likely to have a greater epidemiological impact in endemic areas. Since the development of RTS, S in the late 1980s, continuing research has greatly increased the understanding of the protective immune mechanisms that neutralize parasite infectivity and of factors influencing vaccine-induced immune responses. New vaccine candidates have been developed that consist of antigenic domains similar to RTS, Sexpressed in different platforms such as nanoparticles, mRNA and others. Recently human trials using a nanoparticle, R21 were conducted with children in Burkina Faso and the initial results indicate that 1 year after 3 immunizations, this vaccine conferred a 77% protection from severe disease[(12)]. Another vaccine candidate, attenuated *P. falciparum* sporozoites were also evaluated in adults living in Mali and the estimated protective efficacy was 29%[(13)]. A recent trial of this attenuated sporozoite vaccine in Kenya failed to demonstrate significant efficacy in 5-12 months old children[(14)]. Most malariologists believe that a vaccine capable of inducing protective immunity against all the stages of parasite infection is most likely to have the highest impact on infection, morbidity, and transmission of malaria. The anti-sporozoite vaccines like RTS,S are an important first step in the development of multi-stage vaccines that will one day become a powerful tool to help with malaria eradication.

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