

Review Article

## Killer of Generations: Malaria Combat and Challenges

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**Abstract:** Malaria is a devastating disease affecting millions of lives in tropical and subtropical countries since ages. Despite significant reduction in malaria cases since 2010, malaria continues to be one of the major infectious diseases. Malaria elimination efforts are hampered with the emergence of multidrug resistant strains. The most promising vaccine candidate against malaria is RTS,S that showed an efficacy of 39-50%. The development of efficient vaccine remains elusive because of parasite multistage life cycle and antigenic variation. Global efforts are underway to eradicate malaria and there is significant progress in fight against malaria with many countries certified malaria free during last five years. The recent addition to this list is Algeria and Argentina and China is heading forward to be malaria free with no indigenous malaria case. However, rapid development of drug resistance strains highlights requirements of more efforts to defeat the pathogen.

**Keywords:** Anopheles, Antimalarials, Malaria, Malaria elimination, Plasmodium.

### INTRODUCTION

Malaria is a life threatening disease, responsible for 219 million cases and 4, 35,000 deaths in tropical and subtropical regions each year [1]. As per WHO report 2018, 92% of the malaria cases belong to WHO African region, 5% cases reported in South-East Asia and 2% in Eastern Mediterranean region. Malaria is considered to be one of the top ten diseases affecting 80% population in India and Sub Saharan Africa [1]. There were about 20 million less cases of malaria worldwide in 2017 than 2010 marking significant reduction in the disease in the last 7 years. In India, 16,733 deaths and 9.5 million malaria cases were reported in 2017. India marked a significant reduction in malaria cases in 2017 i.e. 24% less cases than 2016 [1]. Many countries have been certified as malaria free in the last 5 years such as Armenia, Morocco, Turkmenistan, Algeria, Argentina and the United Arab Emirates [1, 2].

The causative agent of malaria is an intracellular apicomplexan parasite of the genus *Plasmodium*. Malaria in humans is caused by the five species of *Plasmodium*:

*P. malariae* (Laveran, 1880),

*P. vivax* (Grassi and Feletti 1890),

*P. falciparum* (Welch, 1897),

*P. ovale* (Stephens, 1922)

*P. knowlesi* (Sinton & Mulligan, 1933)

*P. falciparum* is the descendent of chimpanzee parasite *Plasmodium reichenowi* while other species evolved from monkey parasites [3]. *P. falciparum* in humans causes most extreme form of malaria and accounts for approximately 99.7% cases in WHO African region followed by 62.8% cases in South-East Asia, 69% in Eastern Mediterranean and 71.9% in Western Pacific region in 2017 [1]. It is usually associated with cerebral and placental malaria. The distinctive feature of *P. falciparum* infection is the aggregation of parasite infected RBCs in lung, liver, intestine, skin, brain and placenta that leads to severe form of malaria [4-9].

### The parasite life cycle

The life cycle of malaria parasite requires two different hosts, one is invertebrate (mosquito) and other is vertebrate (human) [10]. The *Plasmodium* life cycle is depicted in figure 1. The cycle starts with the *Anopheles* mosquito bite releasing a number of sporozoites from salivary glands into the blood of human host. From bloodstream, sporozoites enter the liver and invade the liver cells (hepatocytes). Here, the parasite undergoes asexual replication known as exoerythrocytic schizogony. The thrombospondin domain

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on circumsporozoite protein and thrombospondin related binding protein act as a receptors that mediate hepatocyte invasion. These domains specifically interact with the heparin sulfate proteoglycans on hepatocytes [11]. Each sporozoite results in the assembly of thousands of merozoites. These merozoites are additionally discharged into the blood where they invade and replicate inside red blood cells (RBCs). Merozoites from the hepatocytes are released in membrane bound vesicles called merozoites that protect the parasite from host immune system [12].

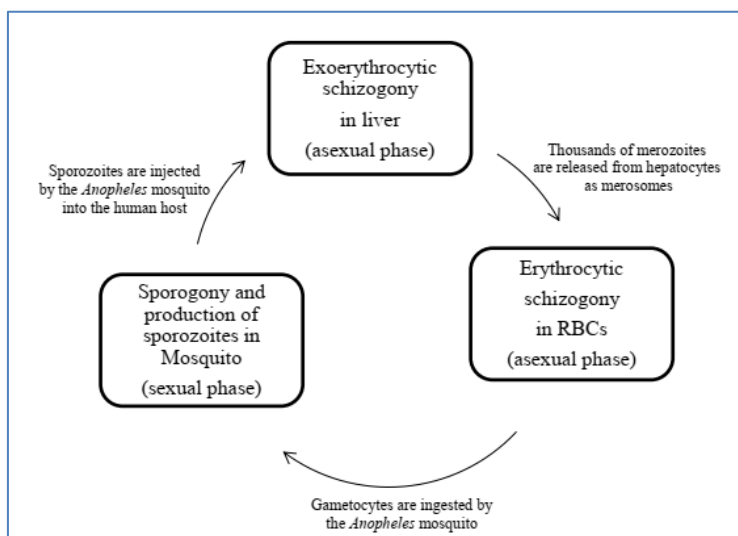


Fig-1: Schematic representation of Human malaria parasite *Plasmodium* Life Cycle.

In erythrocytes, *Plasmodium* goes through asexual replication and form mature schizonts. These schizonts burst through the layer and discharge 8-36 merozoites that further attack new erythrocytes. Two parasite proteins i.e. rhoptry neck protein (RON2) and Apical membrane antigen 1 (AMA1) play essential role in merozoite invasion by interacting with each other that triggers the formation of junction between merozoites and the RBCs [13]. Some of blood stage parasite differentiates into gametocytes- the sexual stage of the *Plasmodium*. The gametocytes are infectious to the female *Anopheles* mosquito that are ingested while taking meal and generate male and female gametes. Gametes fertilize to form zygote in the insect midgut that further changes into ookinete. The motile ookinete develops into an oocyst that undergoes sporogony to deliver numerous sporozoites. The sporozoites released from oocyst rupture move to the mosquito's salivary gland that can infect the new host.

## Control measures

### Vaccines

To create potential malaria vaccine, three stages are focused on. The principal target stage is pre-erythrocytic stage where hepatocyte infections are restrained through antibodies that prevent sporozoites from invading hepatocytes [14-16]. RTS, S/AS01 is the most developed pre-erythrocytic vaccine that has been authorized for pilot implementation in three African countries- Kenya, Malawi and Ghana [17]. Malawi is the first country to start malaria vaccination program [18]. RTS, S/AS01 comprises of the recombinant protein of *P. falciparum* circumsporozoite protein (CSP) C-terminal region conjugated to the surface antigen of the hepatitis B virus [15]. The vaccine was developed in collaboration by PATH Malaria Vaccine Initiative, GlaxoSmithKline and academic institutions. To identify the challenges facing malaria vaccine development and to establish a goal and plan to accelerate malaria vaccine development, the Malaria Vaccine Technology Roadmap was established in 2006. Later on, in 2013 this roadmap was subsequently updated and introduced two new goals i.e. to develop the vaccine to control malaria in multiple settings and the vaccines that are highly efficacious against clinical malaria [19]. Despite the fact that the immunization was observed to be protected in RTS, S/AS01 vaccine with an efficacy of 39–50% against all episodes of clinical malaria [20] and has no antagonistic effects yet it neglects to meet the necessity of Malaria Vaccine Technology Roadmap that goals of a next generation vaccine to give 75% efficacy for more than 2 years. Therefore, other vaccination regimens are being assessed. Another vaccine the R21 is the improved version of RTS, S as it comprises of CSP conjugated to a single hepatitis B surface antigen making CSP portion more than earlier one RTS, S vaccine [21]. The subsequent stage vaccines target erythrocytic-phase of the parasite blocking the invasion of merozoites into the RBCs. The blood stage invasion blocking vaccines target parasite surface proteins, for example, reticulocyte homolog (Rh), proteins, apical membrane antigen 1 (AMA1) and merozoite surface proteins [22, 23, 24, 25]. The blood stage vaccines that target parasite antigen on the infected RBCs surface are *P. falciparum* Erythrocyte Membrane Protein-1 (PEMP-1) [26].

The third stage of the parasite vaccines target parasite sexual stage- gametocytes. These are the vaccines that intrude the malaria transmission from human and mosquito vector, thus are called Transmission Blocking Vaccines (TBV) [27]. They are of two kinds- sexual sporogonic or mosquito stage vaccine that interferes with human to mosquito transmission and others are pre-erythrocytic that intrude on mosquito to-human transmission. Instances of transmission blocking vaccines are Pfs25, Pfs230 and Pfs48/45 [28, 29]

## Antimalarials

Antimalarial drugs are commonly used to treat malaria. They principally target the erythrocytic stages of the malaria that causes illness in human. In 1940s, chloroquine was utilized for treatment of malaria [30]. Later on in 1980s, resistance against the chloroquine was seen in Africa, Southeast Asia, Oceania, and South America pursued by the resistance against different antimalarials, for example, sulfadoxine/pyrimethamine, mefloquine, halofantrine and quinine [31-34]. Subsequently, in 1972, Tu Youyou, discovered artemisinin, a sesquiterpene lactone used to treat malaria caused by *P. falciparum*. In comparison to quinine, pregnant women with severe malaria in any trimester can be efficiently treated with artemisinin derivatives [35]. As of late in 2008, resistance against artemisinin-based combination therapies was first seen in Western Cambodia [36] followed by certain places of South East Asia [37-40] and recently in Brazil [41] and India [42]. Between 2008 and 2013, rapid spread of KEL1/PLA1 a multidrug-resistant co-lineage was reported in Cambodia. This co-lineage of *P. falciparum* results in failure of dihydroartemisinin-piperaquine treatment [43]. The non-stop spread of resistance against artemisinin-based therapies and antimalarials requires the disclosure of novel antimalarials agents. At the cutting edge of antimalarial improvement are the Medicines for Malaria Venture (MMV), which was set up in 1999 as a not-for-profit, public-private partnership. The current MMV portfolio has numerous antimalarials at different stages of development like Artefenomel, Cipargamin, DSM265, Ferroquine, KAF156, MMV048, SJ733 and Tafenoquine. Artefenomel, Cipargamin, Ferroquine, KAF156, MMV048 and SJ733 hinders the transmission by targeting asexual stage of the parasite while DSM265 focuses on the liver schizonts and Tafenoquine targets *Plasmodium* hypnozoites [44].

## CONCLUSION

Despite significant reduction in malaria cases from 2010 to 2017, malaria stays a serious threat to the lives of a large number of individuals. Rapid emergence of antimalarial drug resistance is the biggest challenge confronting malaria control and compels us to identify new targets in the parasite.

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