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Mini-Review Article

Recent advances in the fight against malaria

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Malaria is an infectious disease that dates as early as 2700 B.C., and is caused by a unicellular eukaryotic parasite '*Plasmodium*'. The word '*malaria*' originates from the Italian phrase '*mala aria*' meaning 'bad air'. British physician Sir Ronald Ross identified genus Anopheles mosquitoes as vectors for transmission of this disease in 1897. There are more than 60 different species of Anopheles mosquitoes which are now known to be vectors of malaria parasite. Malaria is most widespread in the tropical countries with the African, South East Asian, Eastern Mediterranean and Western Pacific being defined as the endemic regions by World Health Organization (WHO). Spread of this disease in humans occurs through the bite of female anopheles mosquito infected with species *Plasmodium falciparum* (Pf), *P. vivax*(Pv), *P. ovale*(Po), *P. malariae*(Pm)or *P. knowlesi*(Pk). Of these, Pf causes the most lethal form of malaria which is responsible for most associated deaths especially in the Sub-Saharan African region. While Pf infections predominate the African continent, Pv and Pf-Pv mixed infections are more common in South-East Asia, including India. Globally, malaria accounts for nearly 0.4 million deaths annually with most victims being children less than 5 years of age. Common manifestations of the disease include high fever, shaking chills, anemia, respiratory distress etc. Though uncomplicated malaria is considered easily treatable with drugs, a large fraction of Pf infected patients develop severe complicated malaria. This may present itself as cerebral malaria causing seizures and coma. Neurological sequelaeresulting from cerebral malaria include cognitive defects, cortical blindness, deafness, epilepsy etc. leading to prolonged or permanent debilitation of the patients. Cerebral malaria is a form of malaria that results from cytoadherence of *Plasmodium* infected red blood cells on brain endothelium obstructing blood flow to the brain. Pregnant women residing in endemic areas are considered susceptible to placental malaria in which blood blow to the placental tissue is blocked by cytoadherence, leading to fetal mortality. While Pf is responsible for severe disease, Pv infection can cause recurrent malaria due to the formation of hypnozoites that lie dormant in the liver for long periods. These can be activated to show disease symptoms when favorable conditions occur.

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Drugs against malaria

Efforts by the WHO to curb malaria by providing insecticide treated bed nets and better sanitation in endemic areas along with advanced drugs has significantly reduced the disease load in the past few years, though occurrences are still fairly common. Treatment of malaria patients was historically done by using quinine obtained from the bark of cinchona tree. Monotherapy using drugs like chloroquine, proguanil, sulfadoxine, mefloquine etc. against parasite led to rise of resistance against theseanti-malarial drugs (2).Drug resistance led to development of combination therapiesand use of artemisinin combination drugs for treatment of malaria. TuYouyou, a Chinese pharmaceutical chemist received the 2015 Nobel prize in Medicine for her discovery of artemisinin. However, this currently effective drug has also witnessed several cases of partial resistance in many South East Asian countries.

Chloroquine, a derivative of quinine is still considered the first line of treatment in Pv caused malaria. Another derivative primaquine is effective against latent liver stage hypnozoites. Several reports on chloroquine resistant *vivax*malaria and adverse effects of primaquine had highlighted the need for developing newer drugs against Pv caused malaria. A single dose drug tafenoquinehas been approved by the Food and Drug Administration (FDA), USA in 2018 as an effective alternative to primaquine for recurrent Pv malaria (3). Tafenoquine is the first new drug discovered against malaria in the past 60 years.

Vaccines against malaria

Apart from the search of newer drugs against malaria, attempts are being made for design and discovery of vaccines to prevent this disease. The malaria parasites cycle between two hosts: the human host where they complete their asexual cycle and the mosquito vector where sexual stages of *Plasmodium* develop. The *Plasmodium* parasites cycle through the pre-erythrocytic stages (sporozoites, merozoites), erythrocytic stages (rings, trophozoites and schizonts) and sexual stages (gametocytes, gametes, ookinete, oocyst etc.). Continuous efforts are being made to identify and test the potential of parasite proteins from different life cycle stages that are likely to act as vaccine targets. Sequencing of the *P. falciparum* genome in 2002 led to a better understanding of the critical proteins involved in parasite biology, and initiated an exponential phase in identification of new vaccine candidates. Proof of concept for malaria vaccine development came from use of irradiated *Plasmodium* sporozoites to immunize mice that provided protection from later challenges with live sporozoites. While several scientists are trying to build whole sporozoite based malaria vaccine, the idea is limited by its economy and difficulty in producing sporozoites on a large scale. Malaria vaccine development using sporozoites consists of three different approaches: genetically attenuated sporozoites, radiation attenuated sporozoites, and wild-type sporozoites in combination with chemoprophylaxis (4). Efficacy of these whole sporozoite vaccines ranges from 35-100% depending upon the prior exposure to malaria, where individuals having no prior exposure are better protected. Subunit vaccines using *Plasmodium* proteins against which clinical trials are underway include TRAP, Pfg27, Pfs25, AMA-1, MSP-3 etc. and multivalent vaccines that target many proteins in a single formulation (5). The first malaria vaccineis RTS,S which consists of *P.falciparum*circumsporozoite protein (CSP-a pre-erythrocyticsporozoite) fused with an

antigen from hepatitis B (6). It acts by eliciting an antibody response that prevents invasion of human liver cells and generates a cellular immune response to destroy infected hepatocytes. Though the efficacy of this vaccine is only approximately 50% and dose-dependent, it is likely to provide a huge benefit in malaria endemic regions. The recent advances in malaria vaccine and drug development would help in fighting this dreadful disease.

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Conflict of interest

Authors declares no conflict of interest

Compliance with Ethical Standards

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors

Author contributions

PCM: Designed the study and prepared manuscript

RH: manuscript Preparation and editing

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