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Review On Malaria Vaccines: The Panacea for Africa

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Abstract: - *Plasmodium* speciesare protozoa parasites responsible for clinical manifestations associated with malaria. The most prevalent are *P. falciparum* (Africa), *P. vivax* (Americas), *P. ovale*, *P. malariae* and *P. knowlesi*. Malaria control in Africa has been an endless battle. Global mortality for malaria in 2020 was 627,000 deaths with a significant portion of these occurrences in little children resident in Sub-Saharan Africa. Nevertheless, medical breakthroughs in vaccine technology have shown recorded success in highly endemic regions of Africa. The most promising being RTS,S- ASO1, R 21, PFSPZ with the R21 meeting the 75% efficacy threshold set by WHO and the RTS,S endorsed for widespread administration in high transmission areas. The success of these vaccines is largely due to their Pre-erthrocytic, erythrocytic and liver stage mode of action against the parasite. The circumsporozoite proteins (CSP) which are the most secreted antigens from the sporozoite stage of the *Plasmodium* parasite is the ideal biomolecule to serve as focus for heightened immune alertness in the circulatory and hepatic systems of Man. CSP in conjunction with several adjuvants and proteins serve to maintain a significant antibody titre over a period of months post vaccination hence drastically reducing the chances of malaria associated morbidities or mortality. This feat perhaps heralds a glimmer of hope on the possibilities of malaria eradication when integrated control options are employed in the fight against malaria.

Key words: *Plasmodium falciparum*, Malaria vaccines, RTS,S /ASO1, PFSPZ, R21, Africa.

I. Introduction

Malaria is established following the biological activities of invasive *Plasmodium* species in the circulatory and hepatic systems of vertebrates. Clinical manifestations associated with the disease are heightened by the aggressive efforts of the hosts' immune system to find and neutralize the parasite, usually at the peril of delicateneighboring cells.There are over 150 different species of *Plasmodium*,with *P. falciparum, P. malariae, P. vivax, and P. ovale* reported as definitive hosts in humans. The parasite is transmitted by a tiny, adaptable, and mobile vector, the female *Anopheles* sp. (CDC, 2020; Okwa *et al*., 2012; Okwa, 2016).

WHO estimated 241 million cases of malaria occurred in 2020, with 228 million (95%) reported in Africa. Mortality associated with malaria in 2019 was reported at 558,000, an increase of 12% to an estimated 627,000 people, after years of steady declines.54% of malaria mortality was registered in only 4 countries: Nigeria (31.9%), Congo D.R (13.2%), Tanzania (4.1%) and Mozambique (3.8%) (WMR, 2021).The malaria prevalence in Nigeria for 2021 was such that 60% of outpatient's visits to hospitals were due to the disease as well as 23% child mortality and 11% maternal mortality (The Guardian, 2022). By 2030, WHO set goals include the distribution of fully licensed vaccines with efficacy levels at least at 75% to reduce malaria morbidity worldwide, especially in endemic areas (MVFG, 2013).

The wide spread implementation of long lasting insecticide-treated nets, sanitary practices, as well as coatings on the inner walls of households with residual insecticides have all reduced the disease burden over time, but chemotherapy with artemisinin combination therapy (ACTs) is the most popular and perhaps effective approach for malaria control in endemic areas, as it keeps the parasite count in the blood at a relatively low level (WMR, 2021).There is no whole immunity against the parasites activity in the circulatory system and this is in part due to the complex forms of the parasite (Okwa *et al*., 2012). Hence recurrent bouts of the disease occur within a year in high transmission areas. The only viable option to *Plasmodium* control in humans is to keep the immune system primed to the presence of certain antibodies secreted by the parasite, a sort of "antibody policing". This action is what is known as vaccination.

II. Vaccination against malaria and the challenges

The most effective way to prevent a disease is by vaccination which stimulates the host protective immune response. Vaccinationis perhaps the most significant health invention in modern times. It ensures the body system encounters a foreknowing of the metabolic process required for the survival of a pathogen in the host. Hence the immune system isn't overwhelmed in the incidence of an eventual transmission. The administration of vaccines have ensured the eradication of small pox, near elimination of polio and increased the incidence of herd immunity against harmful bacteria and viruses such as anthracis, ebola, as well as a reduction in the prevalence of the SARS/COVID-19 pandemic (Curtiss, 2002; Toniasso *et al*., 2021) . Malaria vaccines have been in development

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within the last 70 years and there are over 10 vaccine prototypes in development of which RTS,S/AS01, PFSPZ and R21 are the most promising (CDC, 2021).

The challenges hampering the establishment ofan outrightvaccine for malaria are linked to the complex epidemiology of the parasite and political will. Although the life stages of the parasite, host biology, method of transmission andenvironmental preferences are all well understood, the polymorphic, highly antigenic nature, and complex biochemical processes enables it to establish impunitive measures inside the host, which eventually leads to its burgeoning with little resistance rather tolerance (Otubanjo, 2013; Nega *et al*., 2016). The parasite is able to switch off surface rich proteins on its outer coat such as *Plasmodium falciparum* rich histidine proteins (PFHRP 2 and PFHRP 3) (Rogier *et al.*, 2022; Jejaw-Zeleke *et al*., 2022). Hence it will be undetectable during immunoassays using rapid diagnostic tests primed with histidine proteins and improbable to tell *P. falciparum* species from *P. vivax*. This alteration sequence significantly increases the risks of false negative results. In addition, the World Health Organization (WHO) mandates that malaria test show a positive result before chemotherapy, an unfortunate case of misdiagnosis could lead to mortality (WHO, 2010).

III. Candidate Vaccines

RTS,S /ASO1 Vaccine

The 1987 creation of the RTS, S prototype vaccine was by the united efforts of GlaxoSmithKline (GSK) and the Walter Reed Army Institute of Research (WRAIR) (Clyde *et al.*, 1973) with improved financing from the Bill and Melinda Gates foundation and PATH Malaria initiative to accelerate research and development from 2001, leading to the establishment of the RTS,S/ASO1 which is the premier viable malaria vaccine following successful clinical and fieldtrials (Laurens, 2020; PATH, 2022). The circumsporozoite protein (CSP) antigen of *Plasmodium* sp., being the most prevalent on the outermost layer of the sporozoite stage was earmarked as the ideal protein to elicit an immunological reaction (Zavala *et al*., 1985). It was obtained by the weakening of sporozoites by radiation and the incorporation of surface antigens of hepatitis B utilized as conveyer for the CSP central repeat region (Vreden *et al.*, 1991).

RTS, S was denoted as thus, the “R” representing the medial repeat loci, a multipeptide sequence on the CSP and “T” representing the epitopes of the T-lymphocyte (Th2R and Th3R). These biomolecules are conjoined to the N-terminal loci of Hepatitis B surface antigen (HBsAg), which is a strong immunogen. The Surface portion "S" is fused with yeast cells (*Saccharomyces cerevisiae*), which serves as a platform for the attachment of both CSP and S epitopes. A unique portion of the HBsAg, "S" is repeated and spontaneously fused to the RTS component. The repetitive nature increases the likelihood of an immune response and higher antibody titre (Laurens, 2020). ASO1 is a biomolecule that is added to vaccines to act as an adjuvant by promoting stronger immunostimulatory actions through CD4 T cell Lymphocytes mediated responses after the vaccine has been administered. It is a concoction of QS-21 (tree bark extract of *Quillaja saponaria*) and 3-0-desacyl-4'-monophosphoryl lipid A (endotoxin extract of *Salmonella enterica*) (Didierlaurent *et al*., 2017). Hence the coalescence of these biomolecules is effectively at eliciting a response from the innate immune system of the host.After phase 3 RTS, S-ASO1 field trials in Burkina Faso, Kenya, Tanzania, Mozambique, Gabon, Malawi, and Ghana, where 6537 newborns within the ages range of 6 to 12 weeks and 8922 kids within the age range of 5 to 17 months were injected intravenously over a 20-month period, results showed the latter had higher antibody titres than the former and locations with titres of 121 EU/mL had a 50% reduction in malaria incidence. Overall effectiveness of the vaccine against clinical malaria was 26% in newborns and 36% in children (White *et al*., 2015). This at the time was regarded as a significant stride because the study group was historically the most endangered age grade to the malaria disease and they dwelt in the most malarious region.

Following this huge success, the European Medicines Agency approved RTS, S-ASO1 for the Immunization of children within the ages of 6 weeks to 17 months (Gosling and von Seidlein, 2016) and on October 6, 2021, WHO endorsed RTS, S/ASO1 as the first vaccine against malaria (PATH, 2022). It still remains the most widely accepted vaccine for immunization against malaria. The vaccine remains the most advanced of its class in the quest against malaria eradication.

PFSPZ vaccine

The vaccine name is eponymous for the *Plasmodium* (PF) sporozoites (SPZ) and prepared by Sanaria Incorporated, United States. It is made up of irradiated forms of the sporozoite stage. Unlike in the RTS/ASO1, there are neither repeat proteins incorporated nor adjuvants in the purified form of the vaccine. The vaccine has demonstrated significant protection against *falciparum* malaria in African adults including pregnant women after 22 trials. On the strengths of the success recorded in preliminary trials, Sanaria Inc. announced a pilot study from July 2022 for stage II trials ongoing in Bancoumana, Mali with the subjects being 6- 10 year olds and in Sumatra, Eastern Indonesia with the subjects being indigenous soldiers on a 6-9 months assignment. These tworegions are regarded as highly malaria endemic regions in Africa and Asia. The vaccination exercise in Mali is such that three-dose regimen over the course of four weeks are administered while the other study has incorporated, a second-generation PfSPZ vaccine called

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the PfSPZ-CVac (Chemoprophylaxis vaccine). The vaccine design is such that non-attenuated *Plasmodium falciparum* sporozoites are administered. This will allow for the parasites propagation for a brief period in the liver and the blood. This ensured an elevated amount of *falciparum* protein titre, invariably priming the immune system. A third generation PfSPZ vaccine (PfSPZ-LARC2) has been formulated and undergoing trials. The sporozoite stage in this case has been attenuated by the deletion of specific genes required for the parasite to switch from the docile hepatic stages to the virulent erythrocytic stages (Sanaria, 2022).

R 21 Vaccine

The newestof the thriving malaria vaccines was created by robust collaborations between scientists at the University of Oxford, Wellcome Trust , NIHR Oxford Biomedical Research Centrewith funding from the European and Developing Countries Clinical Trials Partnership (MC, 2022). It exhibited 78% efficacy in early stage trials hence could indicate a significant stride against malaria. The R21 vaccine is foremost to attain W.H.O objective of 75% potency. According toinvestigations, the vaccine is both safe and highly effective. The Oxford team created their COVID vaccine (with AstraZeneca) on the back of its studies into malaria vaccinations, and field investigations began in 2019, long before the corona virus took prominence.

The R21 immunogen shares many properties with RTS,S, as they target the blood stage sporozoites before liver schizogony is reached. They are incorporated with a rich composition of CSP, with core repetitionsof the CSP fused to the C-terminus. However, RTS,S only contains 20% fusion protein moieties and the rest 80% are HBsAg protein monomers singly incorporated, whereas R21 solely contains fusion protein moieties. This perhaps reduced CSP interactions with the virus-like particle surface in the RTS-ASO1 vaccine (Regules *et al*., 2011; Collins *et al.*, 2017). 450 children aged 5 – 17 months took part in the second phase double-blind, absolutely randomized and controlled trial held between 2019 and 2020 in Nanoro, Burkina Faso. An even distribution of all participants into three batches: batch 1 injected with 5 µg R21/25 µg MM, batch 2 injected 5 µg R21/50 µg MM, and batch 3 immunized with the rabies vaccine. An efficacy of 77% was observed in the infants who were injected 5 µg R21/50 µg MM. A year post-study investigations noted that antibodies were effectively elevated to values corresponding to initial periods of vaccinations (Datoo *et al*., 2021a; Datoo *et al*., 2021b). Hence maintaining the 75% and above efficacy rate of the WHO. A landmark triumph of its kind in the fight against malaria morbidity (OX, 2022).

IV. Conclusion

Perhaps in some years, we will be welcoming the incidence of herd immunity in some communities against malaria owing to aggressive malaria control campaigns and preventive measures. Conclusively, the best approach to keeping an intruder at bay is to fight it at the door, hence pre-erythrocytic and erythrocytic stage vaccines seem to be the right approach to a reduction in malaria transmission rates, morbidity and ultimately mortality.

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