Mini Review

First Malaria Vaccine RTS, S: A Step toward the Eradication of Malaria

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ABSTRACT

Malaria is a mosquito-borne, life-threatening illness caused by the parasite, *Plasmodium*. Around 50% of the world's population is endangered by this infectious disease. The antimalarial drug, artemisinin (ART), which is extracted from the plant *Artemisia annua*, has become a fundamental part of the treatment regime for malaria across the world. The use of ART-based combination therapies against uncomplicated malaria has been endorsed by the World Health Organization (WHO). As per the latest World Malaria Report in 2022, around 247 million malaria cases were reported in 2021 from 84 malaria-endemic nations, including the territory of French Guiana, a considerable upsurge from the 245 million reported in 2020. One of the foremost reasons for this increase was linked with disturbances to services for prevention, diagnosis, and treatment measures during the recent COVID-19 pandemic. On October 6, 2021, the WHO suggested the RTS,S vaccine as the first malaria vaccine to be used against *Plasmodium falciparum* malaria in children residing in areas with moderate to high transmission. In July 2022, the WHO granted prequalification support for this vaccine. Over one million children living in African countries, mainly in Ghana, Kenya, and Malawi, have gotten at least one dose of this groundbreaking malaria vaccine through programs coordinated by the WHO, as well as international and country-level partners. RTS,S is a significant initial step in the path to the production of other highly protective and multi-stage vaccines that may become part of malaria eradication programs in the near future. Several malariologists are working on the early clinical development or trial phases of first-generation and next-generation malaria vaccines, such as R21/Matrix-M, using mRNA technology.

Keywords: Malaria, *Plasmodium*, Artemisinin, RTS,S/AS01 vaccine

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1. Introduction

Malaria is a serious disease caused by a single-celled parasite called *Plasmodium*. There are five parasite species that are the sources of malaria in human beings, namely *Plasmodium falciparum* (*P. falciparum*), *P. ovale*, *P. malariae*, *P. vivax*, and *P. knowlesi*. Of these, *P. falciparum* and *P. vivax* pose major global public health problems. *Falciparum* malaria is the deadliest and most predominant in the African region. Each year, on April 25, the World Health Organization (WHO) celebrates 'World Malaria Day' to "underscore the collective energy and commitment of the global malaria community in uniting around the common goal of a world free of malaria". This year, the WHO announced that 'World Malaria Day 2023' will be marked under the theme "Time to deliver zero malaria: invest, innovate, implement" to raise awareness about the tools and strategies available against this disease, predominantly among unreached populations. The World Malaria Report 2022 estimated 247 million malaria cases in 2021 in 84 malaria-endemic countries, including the territory of French Guiana, 245 million cases in 2020, and 230 million cases in 2015 (1). The malaria case frequency (reported cases per 1000 people at risk) was 82 in 2000 and 57 in 2019, before increasing to 59 in 2020. There was no alteration in case incidence between 2020 and 2021. One of the foremost reasons for this increase noticed in 2020 was linked with disturbances to services for prevention, diagnosis, and treatment measures during the recent COVID-19 pandemic. In 2021, 95% of all malaria cases were from the WHO African region (estimated 234 million malaria cases). Globally, malaria deaths from 2000 to 2021, as per the World Malaria Report 2022, were 897000 in 2000, 577000 in 2015, 568000 in 2019, 625000 in 2020, and 619000 in 2021 (1). Since 2000, malaria deaths have decreased steadily from 2015 to 2019, but in 2020, the mortality rate increased before declining slightly in 2021. The percentage of malaria mortality among children below five years has shown a decrease over the past 20 years, from 87.3% in 2000 to 76.8% in 2015, but since then, the percentage has remained unchanged (1). Nine malaria-endemic nations in the WHO Southeast Asian region reported 5.4 million malaria-affected patients and 2% of the global malaria burden in 2021. In 2016, Sri Lanka was certified malaria-free, and the Timor-Leste region reported zero indigenous cases in 2021 (1). The WHO's malaria control and elimination across malaria-endemic countries is covered under various malaria programs and intervention strategies, such as prevention, diagnosis, treatment, elimination, and surveillance. Globally, between 2010 and 2020, about 3.1 billion rapid diagnostic test kits for testing malaria parasites were retailed by various manufacturers. The WHO recommended the use of artemisinin (ART)-based combination therapies (ACTs) against uncomplicated malaria, which is recognized as the best treatment for malaria. ACTs have become a fundamental part of the current accomplishments in malaria control programs, forming a rapid and reliable intervention strategy. However, few ACTs have shown reduced effectiveness in the WHO Southeast Asian region. The development of drug-resistant *falciparum* parasites against antimalarial medicines, such as ART or ACTs, will be a key challenge in the execution of global malaria eradication and elimination programs. Malaria vaccines, such as RTS,S, could be added to these programs and campaigns in the future to improve treatment efficacy and fight drug resistance against malaria.

2. Objectives

2.1 Artemisinin-Based Combination Treatments and Antimalarial Drug Resistance

P. falciparum is highly resistant to all common antimalarials, such as chloroquine, sulfadoxine-pyrimethamine, and mefloquine, in most malaria-affected areas. However, ART (Figure 1), isolated from the medicinal shrub, *Artemisia annua*, is the most effective drug of all antimalarials, with half-lives of approximately one hour (2). ACTs are regarded as the first-line antimalarial drugs for uncomplicated *falciparum* malaria in almost all countries where malaria is endemic, but the access and supply of ACTs are still inadequate in most parts of these countries where malarial parasites are prevalent. The ART derivative has a high antimalarial potency and inhibits a large percentage of the parasite's growth. ACTs consist of an ART derivative coadministered with a longer-acting combination drug to provide sustained antimalarial activity. The WHO presently recommends the following six different ACTs: artesunate-amodiaquine, artesunate-mefloquine, artesunate-pyronaridine, artesunate plus sulfadoxine-pyrimethamine, artemether-lumefantrine, and dihydroartemisinin-piperaquine. The appearance and spread of ART-resistant parasites in malaria-endemic regions have raised the risk of wiping out these crucial antimalarial drugs, threatening global malaria control and elimination programs. The first clear evidence of resistance to ART and its derivatives in *P. falciparum* parasites appeared in Western Cambodia in the early 2000s (2,3). Further reports of the independent development and potential spread of ART-resistant *P. falciparum* parasites have been reported in the Cambodia-Thailand border, the six Southeast Asian states that constitute the Greater Mekong Subregion, and Africa (4). The molecular profiling and monitoring of the *P. falciparum* Kelch 13 gene have been found to be a primary marker to trace ART resistance (5). According to the World Malaria Report 2022, recent studies have confirmed the appearance of ART partial resistance in some areas of Africa, noticeably in Eritrea, Rwanda, and Uganda (1). With the increasing number of reports on drug resistance against antimalarials (6) and the lack of effective treatment programs for these vector-borne diseases, the next-generation vaccines present one of the most effective prophylactic treatments to save millions of lives every year. Novel synthetic compounds or phytochemicals that reduce dependence on ART are urgently needed (7,8). They also open the door for new drug combination options in the future. Antiplasmodial

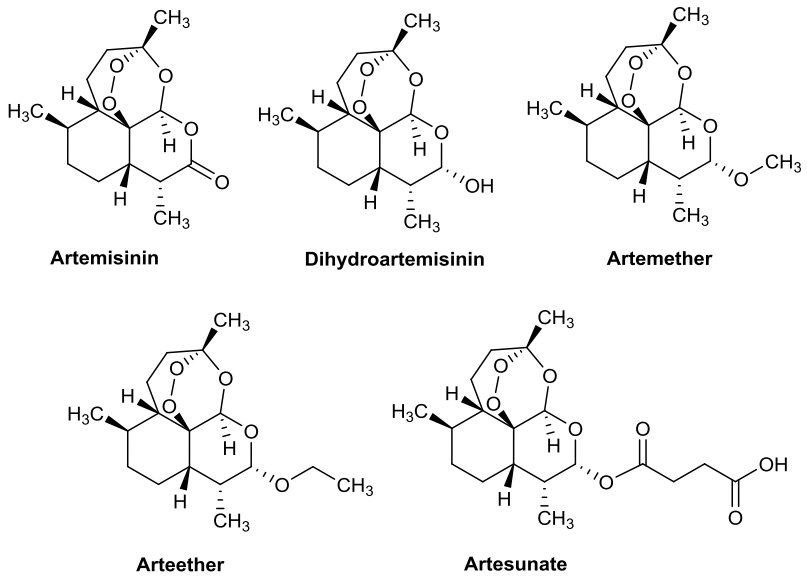

Figure 1. Artemisinin (Qinghaosu) derived from extracts of sweet wormwood (*Artemisia annua*) and various derivatives of Artemisinin.

interactions between ART and synthetic chalcone derivatives have shown promising *in vitro* results, and such combinations pave the way for the development of novel ACTs (9).

2.2 The RTS,S/AS01 Vaccine: First-Generation Malaria Vaccine

RTS,S/AS01 (RTS,S) is a first-generation malaria vaccine that targets the deadliest parasite, *P. falciparum*, which is widespread in Africa. On October 6, 2021, the WHO announced the implementation of the RTS,S malaria vaccine for use in infants and children of Sub-Saharan Africa and in other malaria-endemic regions with modest to alarming levels of *P. falciparum* infection (10). The WHO approval was based on clinical trial reports from a recent malaria vaccine pilot program in several malaria-endemic areas, including Ghana, Kenya, and Malawi. These regions have vaccinated more than 900,000 children since 2019. This vaccine is now approved for administration through routine immunization services by the regulatory authorities of three participating countries, namely Ghana, Kenya, and Malawi, with support from the WHO, as well as international and country-level partners, including the Program for Appropriate Technology in Health (PATH), GlaxoSmithKline (GSK), and UNICEF. Mosquirix™ is the trademarked name given by GSK to this vaccine. The accomplishment of this vital landmark was due to the productiveness of more than 30 years of experimentation by various research institutes, associates, and collaborators. The RTS,S vaccine candidate was first shaped in 1987 as part of a partnership between GSK and the Walter Reed Army Institute of Research (WRAIR) that got initiated in 1984 (reviewed in M.B. Laurens, 2020) (11). Malaria infection starts when a parasite-infected female *Anopheles* inoculates its sporozoites into an individual during a blood meal. Within the human body, the malarial parasites nurture and divide in the hepatic cells, where they invade hepatocytes (known as the exoerythrocytic cycle) and then in the RBCs (known as the erythrocytic cycle). During the asexual cycle, the key surface protein of *Plasmodium* sporozoites, known as the circumsporozoite protein (CSP) antigen, plays a major role in the infective phase. In the 1980s, two papers were published in the Science Journal (12,13), which identified the target epitope of the immune response as CSP, making it a rational target for a vaccine candidate against *P. falciparum*. One of the rationales for the use of CSP as a synthetic vaccine candidate is that it contains species-specific immunodominant epitopes designed by tandem repeats of amino acids (13). In 1984, the U.S. National Institutes of Health, WRAIR, and various research groups cloned and sequenced the DNA segment of *P. falciparum* CSP (12). In 2001, the RTS,S vaccine candidate moved to phase trials through a public-private partnership between GSK and PATH's Malaria Vaccine Initiative with funding from the Bill and Melinda Gates Foundation. The foremost objective of this collaboration was to prepare a malaria vaccine (RTS,S) to protect infants and young children living in Sub-Saharan Africa. The RTS,S antigen was synthesized by GSK Biologicals. The letters in the RTS,S vaccine represent its structure; 'R' represents the central repeat region of *P. falciparum* CSP, 'T' represents the T-lymphocyte epitopes of the CSP separated by immunodominant CD4+ and CD8+ epitopes (Th2R and Th3R), and the 'S' stands for the N-terminal of Hepatitis B surface antigen (HBsAg). The CSP is a

polypeptide chain consistent in structure with a highly conserved tandem repeat tetrapeptide 'NANP' amino acid sequence. They are fused into one fusion protein ('RTS') and translated into yeast cells with free HBsAg. The second 'S' portion is a free 'S' protein spontaneously assembled into the RTS component, and thus it was called 'RTS,S'. It also contains a newer vaccine adjuvant scheme, AS01, which includes liposomes, such as MPL and QS-21, to stimulate and boost the RTS,S immunogenicity in trial volunteers. This vaccine candidate was usually referred to as 'RTS,S/AS01'. Multiple adjuvants were checked with RTS,S, such as AS01, AS02, AS03 oil-in-water emulsion, and AS04, during the clinical trials. The Phase 3 trial results of the RTS,S/AS01 vaccine's efficacy, immunogenicity, and safety were published in the Lancet Journal in April 2015 (14). The RTS,S/AS01 candidate showed modest results but still provided substantial public health benefits, especially in areas with high malaria cases, when supplemented with other effective control procedures (14). For clinical studies, around 8,922 children (5 to 17 months of age) and 6,537 young infants (6 to 12 weeks of age) were registered at 11 test units in seven countries of the Sub-Saharan African region (ClinicalTrials.gov, number NCT00866619). RTS,S/AS01 is administered as a lyophilized suspension via intramuscular injection. Four vaccine prescriptions are now specified for kids, with the initial shot to be given to infants at five months of age. The first three shots are directed once a month, and the tertiary dose should be completed before the age of nine months. The last quarter of the dose should be given at the age of 15 to 18 months. The efficacy results of Phase 3 testing exhibited that among young infants and children who received four doses of RTS,S/AS01, vaccine effectiveness against clinical malaria was 25% and 36%, respectively. Furthermore, the candidate vaccine efficacy of both the three- and four-dose schedules against clinical malaria and severe malaria was lower in young infants than in children (Table 1). The trials suggested higher vaccine-induced immunogenicity in children than in infants. (11, 14).

3. Results and Discussion

3.1 Future Perspectives: Opportunities and Challenges

Over the last two decades, noteworthy improvement has been achieved toward malaria abolition. Since 2015, nine countries have been granted the WHO's accreditation of malaria elimination certification (as malaria-free for at least three consecutive years), namely Maldives (2015), Sri Lanka (2016), Kyrgyzstan (2016), Paraguay (2018), Uzbekistan (2018), Argentina (2019), Algeria (2019), El Salvador (2021), and China (2021). Various malaria vaccine development tactics have been in progress since the 1960s. Several vaccine candidates are under development and are majorly designed to block three life cycle stages in humans, that is pre-erythrocytic, erythrocytic, and transmission phases. Nevertheless, several projects are in early clinical development or trial phases to develop first-generation and next-generation malaria vaccines, such as R21/Matrix-M, using mRNA technology (15).

3.2 Conclusion

The genome of the malarial parasite, *Plasmodium*, is very complicated and complex, and only a limited number of parasite proteins have been shortlisted for vaccine-making programs (16). Due to these factors, despite several bacterial and viral vaccines, vaccine development has been scientifically challenging. However, within the last decade, substantial progress occurred with the WHO recommendation for the deployment of RTS,S malaria vaccine (Mosquirix^{TM}), which is the first and, to date, the only vaccine to be approved and rolled out to combat malaria in regions reporting moderate-to-severe transmission rates. Other vaccines with similar or higher efficacy and better safety profiles that could complement this first-generation vaccine will play an important role in the years to come. Further understanding of new vaccine targets will also help our chances and insights to develop highly effective malaria vaccines in the future. Therefore, there is an urgent need for scientific innovations that translate new vector control approaches, diagnostics, medicines, and vaccines into the times ahead to defeat malaria.

Table 1: Phase 3 efficacy results (with 95% confidence intervals) of the RTS,S/AS01 malaria vaccine dose against clinical/severe malaria in both age groups (Table adapted from M.B. Laurens, 2020 (11)).

Vaccine Efficacy	Young Infants (age 6-12 weeks)	Children (age 5-17 months)
Three-dose regimen against clinical malaria	18.3% (11.7 to 24.4)	28.3% (23.3 to 32.9)
Four-dose regimen against clinical malaria	25.9% (19.9 to 31.5)	36.3% (31.8 to 40.5)
Three-dose regimen against severe malaria	10.3% (-17.9 to 31.8)	1.1% (-23.0 to 20.5)
Four-dose regimen against severe malaria	17.3% (-9.4 to 37.5)	32.2% (13.7 to 46.9)

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Authors' Contribution
AB developed the original idea and analyzed the data. AB and NB contributed to writing and preparing the manuscript. All authors read and approved the final manuscript.

Ethics
Not applicable.

Conflict of Interest
The authors declare no conflicts of interest.

Data Availability
The data that support the findings of this study are available on request from the corresponding author.

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