



Update on Malariology and Malaria Vaccines

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Abstract

For centuries, malaria one of mankind's oldest known diseases, has plagued civilizations, shaping the course of history with its devastating toll. From Sir Ronald Ross's groundbreaking discovery of the mosquito-borne transmission in 1897 to the long and arduous journey of vaccine development, the battle against this parasitic menace has been relentless. The long-awaited breakthrough came with the introduction of RTS,S/AS01 (Mosquirix) and R21/Matrix-M, marking a historic milestone in the global efforts to curb malaria's burden.

Keywords: Malaria; Vaccines; Plagued Civilizations; Mosquirix; Mosquito-Borne Transmission

Abbreviations

WHO: World Health Organization; RBCs: Red Blood Cells; RDTs: Rapid Diagnostic Tests; HRP-2: Histidine-Rich Protein 2; pLDH: Lactate Dehydrogenase; DDT: Dichlorodiphenyltrichloroethane; ACTs: Artemisinin-Based Combination Therapies; GMMs: Genetically Modified Mosquitoes; SDGs: Sustainable Development Goals; CSP: Circumsporozoite Protein; VLPs: Virus-Like Particles; SAGE: Strategic Advisory Group of Experts on Immunization; MPAG: Malaria Policy Advisory Group; TRAP: Thrombospondin-Related Anonymous Protein; LARC: Late Liver-Stage Replication-Competent; CHMI: Controlled Human Malaria Infection.

Introduction

For centuries, malaria one of mankind's oldest known diseases, has plagued civilizations, shaping the course of history with its devastating toll. From Sir Ronald Ross's groundbreaking discovery of the mosquito-borne

transmission in 1897 to the long and arduous journey of vaccine development, the battle against this parasitic menace has been relentless. The long-awaited breakthrough came with the introduction of RTS,S/AS01 (Mosquirix) and R21/Matrix-M, marking a historic milestone in the global efforts to curb malaria's burden [1].

In 2023, an estimated 263 million malaria cases were reported worldwide, with an incidence rate of 60.4 cases per 1,000 individuals at risk. This marked an increase of 11 million cases compared to 2022, where the incidence was 58.6 per 1,000. The WHO African Region remained the most affected, accounting for approximately 94% of global malaria cases. The WHO Eastern Mediterranean Region also saw a significant rise in cases, with a 57% increase since 2021, reaching 17.9 cases per 1,000 at-risk individuals in 2023. Among the countries with the highest malaria burden, Nigeria accounted for 26% of cases, followed by the Democratic Republic of Congo (13%), Uganda (5%), Ethiopia (4%), and Mozambique (4%). Malaria-related deaths were estimated at 597,000 in 2023, with a global mortality rate



of 13.7 per 100,000 population. The WHO African Region bore the greatest impact, contributing to 95% of all malaria-related deaths worldwide. Despite these challenges, progress was also made in malaria elimination [2,3].

The WHO Global Technical Strategy aims to reduce the global malaria burden as well as mortality by at least 90% and eliminate indigenous malaria cases by 2030. The World Health Organization grants malaria elimination certification to countries that successfully maintain zero indigenous malaria cases for three consecutive years. World Health Organization (WHO) has certified 45 countries as malaria-free. This milestone was achieved following Georgia's certification in Jan 2025 [4].

However, not all countries are progressing as expected toward this goal of significantly lowering malaria incidence and mortality rates. Several nations face persistent challenges stemming from socio-economic disparities, ecological conditions, and weaknesses in health systems, all of which hinder their efforts to achieve malaria elimination [5].

India has made significant advancements in malaria control through targeted interventions, including indoor residual spraying, widespread deployment of long-lasting insecticidal nets, and prompt diagnosis followed by comprehensive treatment. However, the pursuit of a highly effective vaccine remains indispensable in the nation's overarching mission to eradicate malaria [6].

Malaria Pathogenesis and Immune Response

Malaria is caused by protozoan parasites of the genus *Plasmodium* and transmitted to humans through the bites of infected female Anopheles mosquitoes. The primary *Plasmodium* species responsible for human malaria include *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*. India's malaria transmission is predominantly attributed to six primary vector species: *Anopheles culicifacies*, *Anopheles fluviatilis*, *Anopheles minimus*, *Anopheles stephensi*, *Anopheles baimaii*, and *Anopheles sundaicus*. Among these, *Anopheles culicifacies* and *Anopheles stephensi* are notably significant. *Anopheles culicifacies* is responsible for approximately 65–75% of malaria cases in India, particularly in rural regions. Conversely, *Anopheles stephensi* serves as the primary vector in urban areas, effectively transmitting malaria even at low population densities [7].

The transmission cycle begins when an infected Anopheles mosquito injects sporozoites into the human bloodstream during a blood meal. These sporozoites travel to the liver, invade hepatocytes, and undergo asexual replication over several days. Upon rupture, hepatocytes release merozoites into the bloodstream, initiating the erythrocytic

stage, where the parasites invade red blood cells (RBCs), mature, multiply, and cause cell rupture. This cycle leads to clinical manifestations such as fever, chills and anemia. *P. falciparum* is particularly known for causing severe disease due to its ability to adhere to vascular endothelium, resulting in microvascular obstruction and organ dysfunction. Some merozoites differentiate into gametocytes, the sexual form of the parasite, which are ingested by another Anopheles mosquito during a blood meal. Inside the mosquito, gametocytes undergo sexual reproduction, forming sporozoites that migrate to the mosquito's salivary glands, ready for transmission to a new host [8].

In the human host, the *Plasmodium* parasite undergoes a complex life cycle, but only a specific stage namely asexual erythrocytic stages is responsible for clinical manifestations. However, a significant proportion of malaria-infected individuals globally exhibit minimal or no symptoms. The clinical presentation of malaria results from a complex interplay between the parasite's intrinsic biological programming and the host's pathophysiological responses. Several factors introduce variability to this host-parasite interaction including genetic diversity of key parasite proteins, co-infections, co-morbidities, delays in treatment, human genetic polymorphisms, and environmental determinants [9].

Malaria Management and Control

Malaria diagnosis necessitates prompt and precise identification of *Plasmodium* parasites in individuals exhibiting symptoms such as fever, chills, and headaches. The gold standard for diagnosis is microscopic examination of Giemsa-stained thick and thin blood smears, allowing for detection and species identification of the parasite. Rapid diagnostic tests (RDTs), which primarily detect two antigens: histidine-rich protein 2 (HRP-2), specific to *Plasmodium falciparum*, and lactate dehydrogenase (pLDH), present in all *Plasmodium* species, including *P. vivax*, offer a valuable alternative, especially in those settings which are lacking microscopy expertise; however, they may not quantify parasitemia or detect certain species [10].

Malaria control relies on two primary strategies-preventing infection by reducing mosquito bites and using antimalarial drugs to avert disease progression. Protective measures like mosquito nets serve as a barrier against infected vectors. In addition to this, malaria control strategies also include elimination of potential breeding sites along with space spraying and indoor residual spraying with insecticides such as dichlorodiphenyltrichloroethane (DDT), malathion, pyrethroids, permethrin, and deltamethrin etc. [11].

The evolution of malaria treatment has been driven by the continuous adaptation of *Plasmodium* parasites and the emergence of drug resistance, necessitating a dynamic approach to disease management. The WHO-led Global Malaria Eradication Program, launched in 1955, aimed to eliminate malaria through the mass deployment of chloroquine for chemoprophylaxis and treatment, coupled with extensive DDT spraying for vector control. These efforts yielded significant success, particularly in India and Sri Lanka, where malaria-related mortality saw a marked decline. However, by the early 1970s, the widespread emergence of chloroquine-resistant *Plasmodium falciparum* and DDT-resistant Anopheles mosquitoes rendered the program unsustainable, leading to its discontinuation in 1972 [12].

Following this setback, the search for alternative therapeutic agents gained momentum. The late 20th century saw the introduction of additional antimalarial drugs such as mefloquine and halofantrine, along with plant-derived compounds like artemisinin. However, the relentless adaptability of *Plasmodium* soon led to resistance against these drugs as well, necessitating the implementation of combination therapies. In response, WHO introduced Artemisinin-based Combination Therapies (ACTs) as the standard for treating *P. falciparum* infections, pairing artemisinin with agents like lumefantrine, mefloquine, amodiaquine, sulfadoxine-pyrimethamine, piperazine, or chlorproguanil-dapsone [13].

Current treatment protocols are tailored based on the infecting *Plasmodium* species, clinical severity, and patient demographics. For uncomplicated malaria, *P. vivax* and *P. ovale* infections are typically managed with chloroquine to clear blood-stage parasites, followed by primaquine to eliminate latent hypnozoites in the liver, preventing relapses. In regions where *P. falciparum* has developed resistance to chloroquine, ACTs are recommended to enhance efficacy and curb resistance evolution [14].

Severe malaria, characterized by complications such as cerebral involvement and organ dysfunction, requires immediate hospitalization. Intravenous artesunate is the preferred treatment, administered alongside intensive supportive care, including continuous monitoring of respiratory function, neurological status, glucose levels, and urine output. In cases of high parasitemia, exchange transfusion may be considered to rapidly lower the parasite burden.

The efficacy of malaria control strategies hinges on strict adherence to these guidelines, regular surveillance, and the continuous refinement of treatment protocols based on emerging evidence. The persistent evolution of *Plasmodium*

underscores the necessity for an adaptive, evidence-driven approach to malaria management, ensuring that therapeutic interventions remain effective against this ever-resilient pathogen. As one of humanity's most persistent and deadly foes, malaria continues to be a major public health concern in numerous countries. This growing threat underscores the need for additional strategies to combat its spread. The development of an effective malaria vaccine which has long been a formidable challenge for medical science, is poised to enhance public health outcomes and reinforce global malaria eradication strategies [15].

Vaccine Development

The journey of modern malaria vaccine development commenced in the early 1960s with experimental studies conducted on primates, rodents, and humans to evaluate the efficacy of irradiated sporozoites. A significant breakthrough emerged in the 1967 when Victor and Ruth Nussenzweig documented high protective efficacy in individuals exposed to repeated bites from irradiated, infected mosquitoes. This approach was further refined in 2002 when complete protection was achieved using gamma-irradiated sporozoites. The circumsporozoite protein, a key antigen, was identified in the 1980s, raising hopes for a blood-stage vaccine, but early trials showed poor efficacy. In 1988, the peptide-based SPf66 vaccine from Colombia showed promise in initial trials but failed in large-scale studies in Africa and Asia. Despite these challenges, early research laid the foundation for future malaria vaccine development [16].

Types of Malaria Vaccines

- Pre-Erythrocytic-Stage Vaccines**
 These vaccines work by targeting the sporozoite stage, and therefore preventing liver infection and subsequent blood-stage progression. Whole-parasite vaccines like Sanaria's PfSPZ Vaccine have achieved up to 79% efficacy in adults who have not been exposed to malaria but showed reduced effectiveness in infants due to weaker immune responses. Chemoprophylaxis with sporozoites (PfSPZ-CVac) has demonstrated high protection in controlled settings but lacks efficacy in high-transmission areas. Genetically attenuated sporozoite vaccines, such as PfGAP3KO, arrest parasite development in the liver, inducing stronger immunity. Late liver-stage replication-competent (LARC) GAPs are emerging as next-generation candidates. Innovations in sporozoite production, including in vitro methods, aim to streamline vaccine manufacturing for large-scale deployment [17].
- Advanced Pre-Erythrocytic-Stage Malaria Vaccines: Non-CSP Subunit Vaccines:** Thrombospondin-related anonymous protein (TRAP)-based vaccines utilize viral

vectors, such as ChAd63 and MVA, to deliver ME-TRAP, which contains CD8+ T-cell epitopes from *P. falciparum*. These vaccines aim to elicit potent cellular immunity against infected hepatocytes. While a Phase IIb trial in Kenya reported 67% efficacy, results in Senegal and Burkina Faso were inconclusive, necessitating further optimization [18].

CSP-Based Vaccines: Circumsporozoite protein (CSP)-based vaccines, the most extensively studied, include RTS,S and R21. These vaccines target sporozoites and liver-stage parasites, inducing antibody-mediated protection [19].

RTS,S Vaccine (Mosquirix): Developed by GlaxoSmithKline (GSK) in collaboration with PATH Malaria vaccine using a hepatitis B surface antigen (HBsAg) platform, RTS,S includes conserved CSP NANP repeats and T-cell epitopes. In CHMI trials, adjuvants played a crucial role in efficacy, with RTS,S/AS02 providing superior protection compared to AS04 and AS03. Phase III trials in African children showed efficacy against clinical malaria ranging from 28–55%, though protection waned over time. A booster dose modestly improved long-term efficacy, and immune responses correlated with CSP-specific antibody titers. The WHO recommended RTS,S for routine use in malaria-endemic regions, marking the first malaria vaccine deployment [20]. To enhance efficacy, fractional-dose regimens demonstrated improved immunogenicity, while prime-boost strategies integrating viral vectors yielded mixed results. A promising approach combined RTS,S with seasonal malaria chemoprevention, significantly reducing malaria incidence and mortality [21].

- **R21 (Matrix-M) Vaccine:**

A next-generation CSP-based vaccine, developed by Serum Institute of India along with University of Oxford, R21 incorporates a higher CSP density on virus-like particles (VLPs) than RTS,S. When formulated with Matrix-M adjuvant, R21 demonstrated 77% efficacy against clinical malaria in Burkinabe infants, with a booster dose sustaining 80% efficacy over two years. R21 has met the WHO target of >75% efficacy [22].

The approval of the Matrix-M (MM)-adjuvanted R21 vaccine by three nations, followed by its formal endorsement by the World Health Organization upon the counsel of two authoritative bodies—the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Group (MPAG) for pediatric malaria prophylaxis in 2023, marks a seminal advancement in global malaria eradication efforts. These developments highlight progress in malaria vaccine research, yet further refinement is needed to enhance durability, optimize immune responses, and improve protection across different transmission intensities [23].

- **Erythrocytic (Asexual Blood-Stage) Vaccines:**

These vaccines aim to reduce parasite burden and prevent clinical malaria by inducing antibodies that block merozoite

invasion, inhibit pRBC adhesion, and enhance phagocytosis [24].

Whole-Parasite Blood-Stage Vaccines: Few candidates have progressed beyond preclinical studies. Chemically or genetically attenuated whole-parasite *P. falciparum* vaccines have shown promising immune responses in malaria-naïve adults but require further refinement to minimize risks like alloimmunization [25].

Sub-Unit Blood-Stage Vaccines: Sub-unit vaccine candidates have shown limited success in CHMI and field trials. Some, such as MSP1 and AMA-1-based vaccines, demonstrated allele-specific efficacy but failed in broader trials. Multivalent vaccines targeting multiple antigens (e.g., GMZ, FMP2.1/AS01) have shown modest efficacy. Future strategies include identifying conserved antigens, multi-protein formulations, and enhanced adjuvants to improve immunogenicity [26].

Placental Malaria Vaccines: Pregnant women in endemic areas are highly susceptible to malaria, leading to adverse maternal and fetal outcomes. Placental malaria vaccines target VAR2CSA, the parasite antigen responsible for pRBC sequestration in the placenta. PRIMVAC and PAMVAC, recombinant sub-unit vaccines, have shown immunogenicity in Phase I trials, but further improvements are needed to enhance antibody function against diverse parasite strains [27].

Transmission-Blocking Vaccines: These vaccines aim to prevent parasite transmission by inducing antibodies against sexual-stage parasites in mosquitoes. Despite challenges in antigen production and short-lived immune responses, candidates like Pfs230 and Pfs25 have demonstrated partial transmission-blocking activity in clinical trials, particularly when conjugated to immunogenic carriers [28].

Clinical Evaluation of Malaria Vaccines

Malaria vaccine efficacy is assessed through Controlled Human Malaria Infection (CHMI) studies and field trials. CHMI studies, conducted after Phase I trials, expose vaccinated individuals to malaria parasites via mosquito bites or direct injection of sporozoites or parasitized red blood cells (pRBCs). These studies measure infection progression using microscopy or qPCR. While traditionally performed on malaria-naïve adults, recent CHMI trials include malaria-exposed individuals to evaluate vaccine effectiveness in endemic regions [29].

Field trials assess vaccine protection in naturally exposed populations, measuring endpoints such as time to first infection, incidence of clinical disease, or severe malaria cases. Preceding drug treatment ensures accurate efficacy evaluation by eliminating prior infections. Recent CHMI findings suggest that persistent asymptomatic *P. falciparum* infections may suppress immune responses, potentially underestimating vaccine efficacy in untreated individuals [30].

Comparative Performance of Malaria Vaccines Across Transmission Settings

- Low Transmission Settings:** Low malaria transmission refers to areas with sporadic or unstable transmission and minimal population immunity, typically defined by an annual parasite incidence of less than 10 cases per 1,000 population per year and often approaching elimination [31]. In low-transmission or near-elimination settings, the primary goal is interrupting transmission rather than reducing individual disease burden. Pre-erythrocytic vaccines such as RTS,S/AS01 and R21/Matrix-M may show relatively higher proportional efficacy, but the absolute number of cases averted is small, limiting their cost-effectiveness for mass use. Whole-sporozoite vaccines (PfSPZ) and transmission-blocking vaccines are more epidemiologically relevant here, as even modest reductions in transmission can significantly influence elimination efforts [32].
- Moderate Transmission Settings:** Moderate transmission settings are characterized by stable but not intense transmission with partial population immunity, where malaria contributes substantially to morbidity, usually corresponding to an annual parasite incidence between 10 and 250 cases per 1,000 population per year [31]. These areas represent the optimal context for malaria vaccine deployment. RTS,S and R21 demonstrate higher and more sustained effectiveness, with meaningful reductions in clinical malaria and severe disease. Waning immunity is slower than in high-transmission settings, and booster doses are operationally feasible. Consequently, the World Health Organization prioritizes vaccine use in moderate-transmission settings, where both individual protection and population impact are maximized [33].
- High Transmission Settings:** High transmission settings denote areas with intense, perennial or near-perennial transmission, early acquisition of partial immunity, and a heavy burden of disease, particularly among young children, commonly defined by an annual parasite incidence greater than 250 cases per 1,000 population per year or high entomological inoculation rates, as per the World Health Organization Global Malaria Programme [31]. In these settings, repeated exposure and high parasite challenge reduce relative vaccine efficacy of RTS,S and R21. However, because baseline incidence is very high, the absolute number of cases, severe episodes, and deaths averted remains substantial. Vaccine-induced immunity wanes more rapidly, necessitating boosters and integration with vector control and chemoprevention. Whole-sporozoite and transmission-blocking vaccines are currently

impractical as standalone tools in these settings but may contribute as part of combination strategies [34].

Malaria Vaccine Challenges

The development of a malaria vaccine has been a six-decade-long challenge, inspired by the success of vaccines against diseases like polio and measles. However, *Plasmodium* parasites exhibit complex biology and immune evasion mechanisms, making vaccine development particularly difficult. Their genome, with over 5,400 coding genes, undergoes frequent antigenic variations, preventing long-term immunity [35].

Unlike viruses that elicit strong immune responses, malaria infection leads only to partial resistance. The RTS,S vaccine marks a significant breakthrough but has limitations, as *P. vivax* and *P. ovale* can remain dormant in the liver, and antigenic mimicry in blood cells further complicates immune response. The lack of suitable animal models has slowed preclinical testing, as *Plasmodium* species that infect humans do not naturally infect most small animals. Other challenges include antigen variability, immune evasion through invasion pathway switching, and a short window for antibody action before RBC invasion. Financial constraints have also hindered progress, as malaria primarily affects low-income countries, making vaccine development less lucrative for pharmaceutical companies. Strict regulatory requirements further increase costs, limiting private sector investment. However, public-private partnerships and initiatives like the Malaria Vaccine Initiative, supported by the Bill & Melinda Gates Foundation, have played a vital role in advancing malaria vaccine research [36].

Emerging Strategies

Advancements in malaria prophylaxis are embracing mRNA-based vaccines, synergistic immunization strategies, and the application of genetic engineering alongside monoclonal antibodies. mRNA vaccines, exemplified by BioNTech's BNT165b1, have entered Phase I clinical evaluation, targeting the circumsporozoite protein (CSP) of *Plasmodium falciparum*, with aspirations for rapid adaptability to antigenic variations. Concurrently, combinatorial vaccine regimens, such as the R21/Matrix-M formulation, have demonstrated enhanced efficacy. Genetic engineering endeavors have yielded attenuated parasites, exemplified by Sanaria's PfSPZ-LARC2, designed to arrest late liver-stage development, thereby enhancing safety and immunogenicity. Moreover, monoclonal antibodies like MAM-01 are under investigation for their potential to confer immediate and durable immunity, particularly in regions with seasonal malaria transmission [37-39].

Conclusion

The incorporation of malaria immunization into existing prophylactic measures demands careful coordination to enhance overall effectiveness. Strengthening and integrating conventional strategies such as insecticide-treated bed nets and antimalarial drugs with vaccines like RTS,S and R21 has the potential to significantly reduce malaria-related morbidity and mortality. However, the economic viability and logistical practicality of integrating these vaccines into public health programs remain contentious, particularly in resource-limited settings where infrastructural and financial constraints pose significant challenges.

To overcome these barriers, increased global financial commitments are crucial to facilitate widespread vaccine accessibility and equitable distribution. Recent analyses indicate that rapid and extensive vaccine rollout could prevent nearly 300,000 pediatric deaths, highlighting the urgent need for immediate and substantial investment in malaria immunization programs [40,41].

Leveraging private sector expertise, innovation, and capital can prove instrumental in malaria control [42]. The use of genetically modified mosquitoes (GMMs) with gene drive technology presents a promising avenue for reducing malaria transmission, but it requires thorough ecological risk assessments and ethical considerations [43]. Aligning malaria control with Sustainable Development Goals (SDGs), particularly SDG 3.3, necessitates a multisectoral approach involving agriculture, education, and tourism to mitigate malaria's impact on public health and economic stability [44].

In urban settings, high population density, poor sanitation, and insecticide resistance exacerbate malaria transmission, reducing the efficacy of vector control measures. Integrating vaccination with urban malaria control requires addressing these challenges through targeted immunization strategies, improved surveillance, and intersectoral coordination to enhance vaccine uptake and sustainability in densely populated areas [45].

Malaria vaccination represents a significant breakthrough in disease control, offering moderate yet valuable protection. Strengthening immune response, extending efficacy duration, and optimizing distribution strategies remain critical challenges. Future advancements should explore mRNA-based platforms, multi-target vaccines, and monoclonal antibody therapies to enhance effectiveness. Global commitment to sustained funding, policy innovation, and fair access is essential for meaningful progress in malaria-endemic regions.

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