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Narrative Review of Malaria Vaccine Development Efforts

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ABSTRACT

Malaria remains a major global public health challenge, with an estimated 247 million cases and 619,000 deaths in 2021, predominantly affecting children in sub-Saharan Africa. Efforts to develop an effective malaria vaccine have spanned over a century, with significant progress achieved in the last two decades. Vaccines such as RTS, S/AS01 (Mosquirix®), PfSPZ Vaccine, and R21/Matrix-M target different stages of the Plasmodium life cycle, including pre-erythrocytic, erythrocytic, and transmission stages. Despite advances, achieving high and durable efficacy has been hampered by the complex parasite life cycle, antigenic variation, and immunological challenges. Clinical trials have demonstrated modest protective efficacy, with generally favorable safety profiles. Ongoing research emphasizes novel vaccine platforms, combination vaccines, adjuvant optimization, and strategies to enhance immune responses across multiple parasite stages. Public-private partnerships, ethical oversight, community engagement, and robust regulatory frameworks remain critical to ensuring equitable access and successful implementation. Continued innovation in vaccine design and delivery is essential to reduce malaria morbidity and mortality and to advance global malaria eradication efforts.

Keywords: Malaria vaccine**,** RTS, S/AS01**,** Pre-erythrocytic stage**,** PfSPZ Vaccine**,** and Transmission-blocking vaccines.

INTRODUCTION

Malaria vaccines have been studied for more than a century. They are considered a pivotal intervention for malaria control and eradication. Mosquirix®, a pre-erythrocytic vaccine based on the circumsporozoite protein (CSP) of Plasmodium falciparum, became the first malaria vaccine to be recommended by the World Health Organization (WHO) in October 2021. The next generation of vaccines, PfSPZ Vaccine and R21, also comprises pre-erythrocytic vaccines based on radiation-attenuated sporozoites and the circumsporozoite protein, respectively. RTS, S, PfSPZ Vaccine, R21, PRIMVAC, and PAMVAC are vaccines that target the pre-erythrocytic and placental stages of the parasite. Other approaches, such as gametocyte antigen vaccines and erythrocytic vaccines that target sexual and asexual parasites, as well as transmission-blocking vaccines, are also under development. To date, a highly efficient vaccine has not been developed, primarily due to the complex life cycle of the parasite, the diverse immunological challenges at various developmental stages, and the complex regulatory approval processes. The burden of malaria remains unacceptably high, with an estimated 247 million cases worldwide in 2021 and 619,000 fatalities. The incidence of malaria has also increased, jumping from 59 cases per 1000 at-risk individuals in 2019 to 59.4 cases per 1000 in 2020. Children account for the largest proportion of new cases and fatalities, with 70% of fatalities attributable to children aged less than five years. The current epidemic of COVID-19 has contributed to increasing the prevalence of malaria due to pressure on health and social systems.

Background on Malaria

Malaria remains a leading global cause of morbidity and mortality, with an estimated annual burden of approximately 247 million cases and 619,000 deaths. Despite low curative cost, ranging from less than 1 US dollar to approximately 5 US dollars per course, several factors limit potential disease control effectiveness. No highly effective vaccines are available, and increasing drug and insecticide resistance emphasize the urgent need for effective vaccines [1, 7]. Malaria is caused by Plasmodium parasites transmitted through the bite of a female Anopheles mosquito. Parasites that enter the bloodstream migrate to the liver, where they infect hepatocytes, mature to merozoites, and are released back into the bloodstream to invade red blood cells, a stage that replicates

exponentially. Gametocytes taken up during a blood meal continue the parasite life cycle through sexual reproduction in the mosquito midgut [8, 9].

Historical Context of Vaccine Development

Attempts to develop an efficacious malaria vaccine began early in the twentieth century [1, 5]. The development of an efficacious vaccine has proved challenging, largely due to the complex parasite life cycle, which is divided between the mosquito and the vertebrate host. An effective vaccine should target several phases of the parasite either simultaneously or via a multi-component formulation [1, 3]. At the beginning of the twentieth century, malaria therapy was commonly used for the treatment of neurosyphilis; patients were deliberately infected with the blood stage of malaria with the hope that the febrile episodes of the disease would kill the Treponema pallidum. This mode of treatment was extremely effective until the discovery of penicillin. Although the development of an efficacious vaccine began early, no such vaccine exists at present [2, 4]. The USA-based Walter Reed Army Institute of Research (WRAIR) has conducted extensive research over two decades, producing the advanced SPf66 vaccine. Subsequent studies have also validated many potential malaria vaccines.

Current Malaria Vaccines

Development of an effective malaria vaccine has been a longstanding priority in global health efforts. Vaccines targeting different stages of the malarial parasite's life cycle are needed [6]. Infected Anopheles mosquitoes transmit sporozoites through a blood meal into the host, where they quickly migrate to the liver and begin the pre-erythrocytic stage of development inside hepatocytes for roughly 7 days (liver-stage). Maturation culminates in a massive replicative burst and release of merozoites into the bloodstream, which initiates the erythrocytic stage of infection (blood-stage) [7]. A small fraction of blood-stage parasites commit to becoming gametocytes, the sexual stage forms responsible for disease transmission [1, 2]. The mosquito picks up these distinct stages during another blood meal, and gametocytes quickly mature into gametes and fertilize inside the mosquito midgut. These sexual cycle stages are the targets of transmission-blocking vaccines (TBVs). Panamanian military scientists were the first to conduct clinical trials of a malaria vaccine based on irradiated sporozoites. They published their results in 1967, although these initial efforts were largely unrecognized at the time. Vaccine development today largely focuses on the circumsporozoite protein (CSP), which abundantly covers the surface of sporozoites and forms polysporozoite invasion tubules (POSIT). PfCSP, a major target of sporozoite-neutralizing antibodies, was a key screening tool that defined the degree of attenuation and migration to the liver. [5, 7]

RTS, S/AS01 Vaccine

Four licensed Plasmodium falciparum vaccines target the pre-erythrocytic stage: RTS, S/AS01 (Mosquirix), Sanaria's PFSPZ vaccine, and two vaccines recently approved in China [1]. These are complemented by transmission-blocking vaccines (TBVs) and erythrocytic vaccines currently in clinical trials [4]. Of approved products, RTS, S/AS01 (Mosquirix, GSK) is the most widely distributed and the first to receive a positive opinion from the European Medicines Agency (EMA). Declared a major advance, the vaccine has been administered in 12 countries within pilot programmes and introduced broadly in sub-Saharan Africa and other regions under WHO leadership [2]. Ongoing phase 3 clinical trials aim to complete the assessment of long-term safety and efficacy, with programme expansion planned for the near future [3].

PfSPZ Vaccine

PfSPZ vaccine is a candidate vaccine composed of aseptic, purified, radiation-attenuated, cryopreserved Plasmodium falciparum sporozoites. Sanaria Inc. developed and holds the license for this vaccine. When administered intravenously, the PfSPZ vaccine targets the Plasmodium parasite's liver phase, operating by inducing an immune response against the sporozoites before they can establish infection in the liver. Immunization with this vaccine generates serum immunoglobulin G (IgG) antibodies and T cell responses, which together contribute to preventing the development of liver-stage parasites [11]. Placing the PfSPZ vaccine in the historical context of malaria vaccine development reveals its innovative approach. Early work by Jon Salk demonstrated that radiation-attenuated pathogen vaccines could confer protection, providing a conceptual foundation for the PfSPZ vaccine strategy. In 2013, the vaccine's safety profile and mechanism of action received designation from the European Medicines Agency (EMA) [12]. A randomized, placebo-controlled, double-blind clinical trial conducted by NIAID, published in the New England Journal of Medicine, reported that a 3-dose regimen of cryopreserved, radiation-attenuated, nonreplicating PfSPZ was well tolerated and safe in malaria-experienced adults in Mali. However, the vaccine demonstrated only modest protective efficacy against naturally transmitted Plasmodium falciparum infection [13].

Other Candidate Vaccines

The PfSPZ vaccine (Sanaria) uses weakened sporozoites of P. falciparum, the target being the first stage in the parasite life cycle that infects the liver. The vaccine, which completed Phase I trials, showed a promising 100% efficacy in preventing infections and was considered safe. However, despite several promising PfSPZ vaccine

candidates still in clinical trials, to date, none has been approved for clinical use [7]. Another vaccine candidate, R21, is based on the Hepatitis B surface antigen fused with CSP. In May 2023, it was approved for use in children in Burkina Faso following a Phase IIb trial conducted in the country between May 2021 and March 2022. R21 targets the pre-erythrocytic phase. Other candidate vaccines under development, in early phases, include attenuated whole sporozoite vaccines, vectored vaccines targeting blood-stage antigens, and transmission-blocking vaccines that prevent parasite development in mosquitoes or the progression to sexual forms [8].

Mechanisms of Action

Between its mosquito vector and human host, the malaria parasite oscillates through biological phases that are targeted by all existing vaccine candidates. In-depth knowledge of these phases sheds light on the modes of action of vaccines approved or in late-stage clinical testing [4]. The first detectable parasite structures in infected humans are the sporozoites injected into the skin alongside mosquito saliva. After burrowing into blood vessels, sporozoites rapidly reach and enter hepatocytes. During the subsequent intrahepatic developmental stage of 5 to 7 days, each parasite replicates into thousands of daughter merozoites [4]. The liver-borne merozoites are undetectable in circulation due to their prompt invasion of red blood cells, where the blood-stage cycle begins. Lasting approximately 48 hours, the cycle culminates in the lysis of infected erythrocytes and the release of hundreds of daughter parasites that re-initiate a count of the medium as a drug target [4].

Pre-erythrocytic Stage Vaccines

Many vaccine candidates under development target the liver stage, out of which an asymptomatic infection develops in humans. Sporozoite or hepatocyte stage targets may not directly influence the development of the symptomatic stage of the Plasmodium infection, but they may induce sterile immunity. Pre-erythrocytic (PE) vaccines target the sporozoite and liver stages of the parasite [1, 2]. The goal of these vaccines is to prevent the development of clinical parasites in the blood by inhibiting the progression of hepatocyte stages to the blood. PE vaccines work by preventing the initial infection of red blood cells by malaria parasites. Pre-erythrocytic vaccines prevent the sporozoite from gaining entry into the liver, thus preventing mobile sporozoites from infecting the individuals who are vaccinated [3]. These vaccines prevent the sporozoite stage of the parasite from reaching the liver. Once an individual is vaccinated with a pre-erythrocytic vaccine, the vaccine produces antibodies that target the sporozoites, thus preventing them from entering the cells that infect the liver [9]. The pre-erythrocytic stage-blocking vaccines prevent the hepatic stage development into blood-stage parasites. The merozoites that develop inside the hepatic cells enter the bloodstream and invade the erythrocytes to develop into tissue-cyst-like asexual blood stages [8]. The occurrence of TECs inside the erythrocytes inflicts the intracellular merozoites with a "dream stage" to combat the unsupportive immunity of the host cells. The maturation of TECs is associated with the synthesis of less immunogenic surface proteins or altered versions of the merozoite surface proteins on the outer surface of the TECs as well as merozoites [7]. This altered microenvironment aids the escape of TECs from host immune attacks. Research is ongoing to identify new vaccine candidates and improve the protective efficacy of the partially effective candidates. The mechanized protective immunity of PE malaria vaccines is mainly through antibody-mediated WM immunity; thus, the sporozoite-expressing antigen becomes the prime candidate for developing subunit PE vaccines. Examples of PE vaccines under development include RTS, S, a subunit vaccine that targets the circumsporozoite protein; attenuated sporozoite vaccines such as PfSPZ (radiation-attenuated sporozoites), PfSPZ-CVac (sporozoite chemoprophylaxis vaccine concept), and genetically attenuated parasites; and viral-vectored vaccines encoding liver-stage antigens such as ChAd-63 ME-TRAP (chimpanzee adenovirus encoding ME-length tachyzoite surface protein) [5].

Erythrocytic Stage Vaccines

Current efforts to develop vaccines that interrupt blood-stage infection have thus far failed to identify a candidate that affords a useful degree of protection [4]. Merozoite invasion of human erythrocytes is mediated by coordinated multi-step protein–protein interactions between ligand(s) carried on the merozoite surface or apical secretory organelles and the host erythrocyte surface [5]. Multiple merozoite surface and apical organelle proteins mediate distinct events during this invasion process. Parasite proteins perform essential functions during this lifecycle stage, guaranteeing their expression in natural infection, whereas many circulating antigens involved in pre-erythrocytic infection appear redundant and/or downregulated during in vivo infection. However, an important gap in the erythrocytic stage vaccine development effort remains the absence of clearly validated vaccine candidates. Conventional blood-stage antigen vaccine candidates have produced highly variable results, ranging from improved infection to partial efficacy or complete lack of protective efficacy [2]. Encouragingly and unusually for parasite antigens, one member of the P. falciparum RH5–CyRPA–Ripr complex, PfRH5, has been shown to induce in vitro strain-transcendent neutralization, to be well conserved and essential for blood-stage growth, and vaccine-induced anti-PfRH5 antibodies can reduce parasite growth in both Aotus monkeys and humanized mice. Two complementary blood-stage antigens contained within the same ternary RH5–CyRPA–Ripr complex, CyRPA and Ripr, can induce similarly neutralizing antibodies in vitro, showing that a combination

blood-stage vaccine targeting multiple invasion ligands, and thereby multiple functionally active pathways of invasion, is feasible. Combining an RH5–complex blood-stage vaccine candidate with the leading pre-erythrocytic candidates is likely to be necessary in order to achieve the high levels of efficacy required for licensure [2, 4, 5].

Transmission-Blocking Vaccines

Transmission-blocking vaccines aim to interrupt the life cycle of Plasmodium parasites, and this type of vaccine is also an important component of malaria vaccine development efforts [6]. The sexual stage of Plasmodium falciparum and P. vivax in the human circulation is essential for the propagation of malaria parasites in the mosquito. A special type of vaccine development, labeled "transmission-blocking vaccine," targets the sexual reproductive stages of Plasmodium falciparum and P. vivax and, more importantly, the subsequent development of infectious sporozoites in the mosquito [7]. Transmission-blocking vaccines target asexual parasite proteins, such as the Pfs and Pvs 230–25 complexes, which appear to be the most promising transmission-blocking antigens to date [8].

Challenges in Vaccine Development

Certain features unique to malaria impose challenges to vaccine development [9]. The parasite is genetically and pathophysiologically complex, with a genome far larger and more complicated in form and function than in most bacteria or viruses [3]. Moreover, malaria journeys through a complicated life cycle in humans, advancing through multiple anatomically distinct stages that require dramatically different immune responses for control. Because different stages predominantly express distinct subsets of genes, protective antibodies generated against one developmental form often exhibit little or no reactivity to other stages of the parasite life cycle. Antigenic variation of circulating strains of P. falciparum further complicates this challenge [9]. Consequently, it has proven difficult to identify antigens capable of eliciting broadly neutralizing immunity. Because few other infectious diseases share these features, developed licensure criteria concerning disease likelihood, time to resolution, and rate of evolution, as well as immune correlates and surrogate markers generally lack relevance to malaria, adding a further obstacle to the development of new vaccines [4].

Antigenic Variation

Immunity against Plasmodium falciparum requires multiple exposures [10]. Limited exposure produces strain-specific immune responses directed towards polymorphic antigens or unexposed subdominant epitopes, while widespread exposure yields broader immunity against non-polymorphic epitopes shared by multiple strains [10]. The foremost challenge in malaria vaccine development is antigenic variation, which complicates the selection of representative parasite lines. Consequently, most currently developed vaccines employ highly conserved organisms, well-characterized laboratory strains, single variants designed for a monovalent immune response, or complex mixtures of many different parasite strains [10]. These solutions are not perfect, but whole-organism vaccines offer greater redundancy, which may effectively circumvent the problem of antigenic variation.

Immunological Challenges

The complex and multifaceted immunology of malaria is a key consideration for vaccine development, as both the parasite and disease have features that impair the development of a fully protective anti-malaria immune response[2]. Parasites pass through three immunologically distinct phases: pre-erythrocytic, blood-stage, and sexual-stage, which complicates immune activation [4]. Malaria confers only partial and short-lived immunity, even in individuals repeatedly exposed to the disease; this immunity is not sterile, and the disease still develops in previously infected patients. Additional challenges are posed by key antigens, for example, the var-family of proteins involved in cytoadherence and modulation of the immune response and the protective immune processes needed in humans, which are still not fully understood [11]. Successful blood-stage malaria vaccines require the induction of potent and heterogeneous immune effectors to fully neutralise the parasite and the associated immunosuppression [12].

Regulatory Hurdles

Adhering to regulatory standards is a crucial component of malaria vaccine development [13]. Organizations such as the US Food and Drug Administration and the European Medicines Agency oversee clinical trials to ensure safety and efficacy while restricting unproven products [1, 3]. Following approval, intensified post-marketing surveillance activities monitor any emerging adverse effects, maintain quality control of production processes, and assess overall vaccine effectiveness [2].

Clinical Trials Overview

Malaria vaccines, presently in varying stages of clinical development, strive to elicit immune responses against the Plasmodium parasite lifecycle, thereby aiming to eliminate infections, halt transmission, or alleviate associated disease [1, 5]. Malaria vaccines have been systematically tested in clinical trials since the late 1960s. However, the translation of many candidates into effective human vaccines remains challenging due to parasite biology and technical difficulties with existing platforms [1, 3]. The only vaccine licensed for public use is RTS, S/AS01,

under brand names Mosquirix and Mosquirix-RTS, S. This protein-based vaccine targets the circumsporozoite protein of P. falciparum sporozoites and provides partial protection to children living in endemic regions. Despite its limited overall efficacy, its rollout in endemic countries represents a historic milestone in malaria control [1, 7]. Sanaria's PfSPZ Vaccine, which comprises live, attenuated, aseptic, purified, cryopreserved sporozoites, has demonstrated over 90% protection in malaria-naive adults. However, the rigorous front-loading dosing regimen presently differs substantially from routine infant immunization schedules. Additionally, the vaccine is delivered by direct venous inoculation, necessitating specific personnel training and assistance during administration. Novel virus-vectored prime-reboost vaccine candidates are also in development, with design improvements intended to enhance immunogenicity, efficacy, tolerability, and delivery. A pipeline of vaccines at different stages of clinical development also targets other stages of the parasite lifecycle[2, 3]. Candidate vaccines with a transmission-blocking property rely on antibodies that briefly circulate within the human bloodstream and inhibit the parasite from further developing within the mosquito. Non-RTS, S life-cycle-stage vaccines against malaria are summarized, and the targets and mechanisms of action for malaria vaccines are detailed [1].

Phases of Clinical Trials

Clinical trials employing malaria vaccines have been carried out in the endemic zones of America, Europe, and Africa [3]. The safety and immunogenicity of all vaccine candidates have been demonstrated in controlled human malaria infection (CHMI) studies involving small numbers of participants. Progression of more promising candidates (PfSPZ and RTS, S/AS01) into field efficacy trials has been characterized by the extensive financial support of organizations such as the Bill and Melinda Gates Foundation (BMGF) and Walter Reed Army Institute of Research (WRAIR). Small-scale trials (phase I and IIa) were followed by large field trials (phase IIb and III) and ongoing pilot implementation projects [5]. Clinical phases in malaria vaccine development, the first publications that describe a particular trial phase are cited. Phase IV post-marketing surveillance studies have not yet been described. Not listed vaccines are in earlier stages of development. ADR, adverse drug reaction; mm, millimeter; MSP-3, merozoite surface protein 3; RBM, receptor-binding motif; ULV, ultralong-acting injectable; VAC053 is a ClinicalTrials.gov identifier [4]. Licensed vaccines RTSS/AS01 and PfSPZ compared with R21/Matrix-M and other vaccine categories presently under development for malaria disease control [7]. The percent of vaccine efficacy (%VE) afforded by RTS, S/AS01, and PfSPZ malaria vaccines is presented, in addition to key information on R21/Matrix-M, a subunit vaccine with very recent promise, as well as virally vectored vaccines, genetically attenuated parasite (GAP), chemically prophylactic immunization (CPS) vaccines, and vaccines derived from sporozoites. NAI, naturally acquired immunity [8].

Key Findings from Trials

The malaria vaccine known as RTS, S/AS01, developed by GlaxoSmithKline, is the only product to have completed Phase IV clinical trials and is prequalified by the World Health Organization [14]. The vaccine has demonstrated an efficacy range of 39% to 50% against clinical malaria following a booster dose, underscoring the progress achieved in vaccine development [14].

Safety and Efficacy Outcomes

Malaria vaccines have shown a generally favorable safety profile, with most candidates exhibiting mild, transient adverse effects [9]. Typical symptoms include headache, myalgia, fever, rash, injection-site pain, erythema, swelling, and induration, which are generally well tolerated. Long-term monitoring has revealed no specific side effects attributable to vaccination, with the exception of a limited number of focus-related indirect deaths after RTS, S/AS01 immunization. Special consideration is warranted for the risk of hypo responsiveness in the context of vaccination schedules involving multiple doses of tetanus-containing vaccines. Ultimately, malaria vaccines do not present a toxicity profile distinct from other vaccination regimens [15]. The heterogeneity of candidate malaria vaccines makes the comparison of efficiency results complicated. In general, they are evaluated in terms of efficacy against infection, morbidity, or mortality either by assessment of protection under controlled human malaria infection (CHMI) or by evaluation of clinical protection in malaria-endemic areas [16]. The ultimate goal of vaccination against malaria is the prevention of clinical malaria, preferably uncomplicated disease, severe disease, and mortality in this order. Besides direct efficacy against infection and disease, the presence of an indirect effect that would augment protective efficacy or the durability of protection is a clinical research priority and of policy relevance [13]. Efficacy against infection is considered by some to be a surrogate for clinical protection. Clinical efficacy is determined by protection against naturally transmitted infection in endemic areas, in which the outcome of infection morbidity is influenced by background immunity, acquired through repeated exposure to the parasite. Repeated exposure to the parasite is considered to induce an immune response that modifies the susceptibility to a new infection [17].

Global Health Impact

Malaria, a life-threatening parasitic disease, is transmitted by infected female Anopheles mosquitoes. Globally, it affected approximately 247 million people and caused around 619,000 deaths in 2021, predominantly in the African region [15]. The RTS, S/AS01 vaccine, a pre-erythrocytic vaccine, was approved by regulatory agencies in 2015 and has significantly influenced malaria vaccination efforts[15]. The piloting of the vaccine has been underway since 2019 with promising outcomes, and widespread use is anticipated within the next decade. An effective malaria vaccine capable of targeting multiple Plasmodium stages is urgently needed to assist in the eradication of malaria infection from endemic regions and susceptible populations [15].

Burden of Malaria

Malaria exacted an estimated 247 million cases worldwide in 2021 despite unprecedented control efforts during the twenty-first century [13]. Due to increased levels of resistance to insecticides and antimalarial drugs, the WHO recommends a multipronged approach to malaria reduction that includes vector control, diagnosis, treatment, and vaccination [13]. Malaria vaccination is especially promising for vulnerable populations, such as children in sub-Saharan Africa (SSA), where 95% of malaria fatalities occur. Moreover, the emergence of COVID-19, a pandemic diarrhoeal illness, has contributed to a resurgence of malaria cases in 2020–2021 [16]. The complex life cycle of Plasmodium parasites, combined with their ability to evade damage, remains the primary impediment to the development of highly effective vaccines against human malaria [16].

Impact of Vaccines on Malaria Incidence

Malaria remains a global health priority, with over 219 million cases and 435,000 deaths estimated in 2017. Vaccination plays an integral role in control efforts, which also include antimicrobial therapy and vector control. The deployment of the RTS, S/AS01 vaccine is expected to hasten progress in reducing cases in sub-Saharan Africa [17]. The mechanism of action of the PfSPZ vaccine holds promise for protection against both Plasmodium falciparum and Plasmodium vivax. Other vaccine candidates currently in clinical development hold promise for complementing or surpassing the efficacy achieved to date [17]. The wide implementation of an effective malaria vaccine represents the best chance to eliminate the global burden of disease and save lives [17].

Future Directions in Vaccine Research

Continued malaria vaccine research encompasses multiple platforms and formulations designed to enhance safety, immunogenicity, and production cost [2]. The RTS, S/AS01 platform lends itself to fine-tuning of adjuvants and incorporation of additional antigens, with combinations such as RTS, S/AS01 or R21/Matrix-M paired with the pre-erythrocytic viral-vectored candidate ME-TRAP entering early clinical trials. Combining vaccines that target various stages of the parasite's life cycle is an alternative approach that may also improve efficacy. Additional whole sporozoite vaccines are in development, including genetically attenuated parasites and purified, metabolically active sporozoites, each with potential advantages over the PfSPZ vaccine currently in clinical testing [4]. Novel antigens formulated with strong adjuvants or delivered by next-generation viral vectors also continue to generate interest. The magnitude and functional profile of the protective T cell response are key considerations. Malaria vaccine strategies are summarized by their stage-specific mechanisms of action. Pre-erythrocytic vaccines aim to prevent infection by inducing immune responses against sporozoites and liver stages, thereby avoiding the symptomatic blood stage [5]. Erythrocytic (blood)-stage vaccines reduce parasitemia and case severity without preventing infection or transmission, thus exerting limited impact on overall incidence. Transmission-blocking vaccines interrupt the parasite's passage from human to mosquito by targeting antigens such as Pfs25 and Pfs230, functioning through complement-dependent mechanisms but not directly protecting the vaccinated individual. Corresponding vaccine candidates include RTS,S/AS01, PfSPZ, PfSPZ-CVac, R21/Matrix-M, ChAd63-MVA ME-TRAP (pre-erythrocytic); Rh5/AS01, ChAd63-MVA RH5, MVA RH5 (blood); and Pfs25-EPA, Pfs230D1-EPA (transmission-blocking) [2]. The development of vaccines that protect populations directly and disrupt transmission remains a major objective of ongoing efforts [2].

Novel Vaccine Platforms

Malaria is a mosquito-borne parasitic disease profoundly affecting human health and society. Vaccination is an effective strategy for infectious disease control, including malaria. Malaria vaccines fall into different classes depending on the parasite life cycle stages targeted: pre-erythrocytic, erythrocytic (blood-stage), transmission-blocking, or multi-stage [8]. The only vaccine with regulatory approval, RTS, S/AS01, limits clinical episodes but does not protect against infection or interrupt transmission. Another blood-stage vaccine, PfRH5-based, provided clinical proof-of-concept for survival and growth inhibition [7]. Single-dose administration of radiation-attenuated Pf sporozoites safely induces sterilizing immunity, with stronger evidence regarding protection from infection. New vaccines with enhanced efficacy or conferring protection to special populations are needed. Most next-generation candidates comprise combinations of viral vectored or recombinant protein immunogens formulated with potent adjuvants and are delivered using multi-dose schedules [2]. Novel platforms such as

mRNA-based vaccines are revolutionizing the development of new vaccine candidates for malaria and other infectious diseases [2].

Combination Vaccines

Combination vaccines constitute a promising approach to malaria immunisation capable of reducing parasite transmission more effectively than single-component vaccines. To date, several antigens have been formulated for combination vaccines [2, 9]. These are defined as three or more components, either antigens or varying biological forms of a single antigen that collectively surpass the protective efficacy of individual elements [2]. Primarily designed to elicit anti-sporozoite and anti-blood-stage immunity, combination vaccines may also reduce the emergence of resistant parasite strains because the parasite would need to simultaneously develop mechanisms to evade all targeted components [9]. Furthermore, they can include antigens that confer transmission-blocking activity, thereby curtailing spread within the human population.

Advancements in Adjuvants

Historically, adjuvants aimed to prolong antigen release and stimulate a robust and long-lasting immune response. The wealth of information accumulated during recent decades in both immunology and vaccinology improved the understanding of how effective immune responses originate and persist, which in turn dictated the production of new adjuvants [4]. The adjuvant development to enhance the immunogenicity of malaria vaccines and vaccines against many other human diseases (e.g., cancer and autoimmunity) did not go unnoticed, since two licensed malaria vaccine candidates (RTS, S/AS01B and R21/Matrix-M) were developed with the aid of potent adjuvants [4]. Various approaches to enhance innate signaling include pattern recognition receptor (PRP) ligands and Toll-like receptor (TLR) ligands [e.g., monophosphoryl lipid A (MPLA, TLR4), polyinosinic-polycytidylic acid (poly I: C, TLR3), and CpG oligodeoxynucleotide (CpG, TLR9)] [18]. With the elimination of several molecules as promising adjuvants, only a few candidates (including flagellin, delta inulin, matrix-M, and AFCo1) have progressed to clinical trials. Among adjuvants still in the pipeline, the investigation of the AFCo1 adjuvant, a cochleate-based microparticle derived from meningococcal B, was recognized as the only adjuvant able to enhance both the antibody and T-cell immune responses against merozoite surface proteins 4 and 5 (MSP4 and MSP5) of Plasmodium falciparum [4]. Continuous assessment of adjuvant effects has remained a major focus of investigational efforts to enhance specific immune response quality and durability [4].

Funding and Collaboration

Significant financial and moral support for malaria vaccine development originates from groups such as the WHO Malaria Vaccine Advisory Committee, the Malaria Vaccine Model, and the Medicines for Malaria Venture [19]. Public–private partnerships play a vital role in vaccine development, especially through support of large clinical vaccine trials [19].

Role of Global Health Organizations

The World Health Organization (WHO), GAVI, the Vaccine Alliance, and other global health organizations have made it a teaching priority to advocate for malaria vaccination among high-risk groups, such as young children and pregnant women, to complement existing preventive measures and reduce the burden of disease [13]. The Global Fund, a financial organization dedicated to fighting HIV, tuberculosis, and malaria, supports the purchase of malaria vaccines by eligible countries and coordinates with GAVI on procurement, transportation, and delivery [13]. Formed in 2000, Unitaid invests in various projects that improve infectious disease treatment, including initiatives that develop supply chain infrastructure capable of handling the difficult logistical demands of the malaria vaccine [13]. Created by the Quebec government in 2006 and adopted by a consortium of UN organizations, the International Finance Facility for Immunization (IFFIm) uses vaccine bonds that leverage donor commitments to generate immediate cash for the purchase of vaccines on the ground.

Public-Private Partnerships

Global health organizations have played a vital role in the development of malaria vaccines through the provision of considerable financial and logistical support [20]. In particular, the Malaria Vaccine Initiative (MVI) has encouraged an eclectic range of novel approaches and served as the most dominant source of encouragement, motivation, early funding, support, and advocacy [20]. Often, collaborations emerge between private companies and universities to facilitate knowledge sharing. However, strict regulations are now being implemented to protect new, potentially valuable vaccine projects [21]. Governments have also encouraged and, on occasion, mandated reciprocal agreements that steer a portion of the proceeds derived from licences towards the funding of vaccine development programmes. Further encouragement is provided by the Gates Foundation, the Wellcome Trust, and Medicines for Malaria Venture (MMV), which is earning industry trust through patient funding mechanisms [20, 21].

Ethical Considerations

Malaria vaccine research presents a number of ethical considerations and dilemmas [22]. To begin with, informed consent represents a significant concern, as many vaccine studies involve adult participants in endemic rural regions, where cultural and educational differences may impede comprehension of study objectives and procedures. Furthermore, some investigators report strong agreement in principle with the philosophy of free and equitable distribution, but also reservations about the feasibility and practicality of such an approach in the prevailing financial and logistical context [22]. Such reservation is exacerbated by the recognition that free public-sector universal access cannot guarantee wide uptake of the vaccine, especially in weak health systems and where given to children born at home [22]. An informed appreciation of these considerations remains essential to ensure that malaria vaccine development, ultimately, continues to be undertaken in an ethical manner [22].

Informed Consent in Trials

Informed consent constitutes a fundamental ethical imperative for clinical research involving human participants. Nevertheless, empirical investigations repeatedly document substantial impediments concerning its achievement in diverse study settings, particularly within low-income, multicultural countries [23]. Notwithstanding legal and regulatory recognition, difficulties persist in communicating study information clearly, ensuring participant comprehension, and securing voluntary agreement [24]. Participants often retain incomplete knowledge about research goals, study procedures, and risks and benefits, with misunderstandings further arising from therapeutic misconception and trust in biomedical authorities [23]. Moreover, adequate documentation of consent remains challenging among illiterate individuals, underscoring the need for culturally appropriate approaches that combine oral, written, and community-based methods [24]. Proposed improvements comprise simplified language, visual aids, interactive techniques, enhanced fieldworker training, and continuous monitoring of consent practices. Consequently, aggressive efforts to enhance comprehension and promote voluntariness constitute ethical necessities across a broad spectrum of research typologies in malaria-endemic regions [23, 24].

Equity in Vaccine Distribution

Malaria is the leading cause of morbidity and mortality in children in sub-Saharan Africa (SSA). In October 2021, the World Health Organization (WHO) recommended the widespread delivery of the malaria vaccine RTS, S/AS01 among children at risk in SSA [10]. The vaccine was highly effective in early trials, at one point reducing the burden of severe malaria by 30%, but lower overall efficacies were observed during Phase 3 trials: 36.3% against clinical malaria in children aged 5 to 17 months, and 25.9% in infants aged 6 to 12 weeks; importantly, efficacy was sustained over a 7-year follow-up period. Combining RTS, S/AS01 vaccination with chemoprevention resulted in fewer malaria cases than either intervention alone in young children in areas with a very high Plasmodium falciparum prevalence [13]. Vaccine improvement is therefore still needed to meet the 75% efficacy goal set for 2030 by the Malaria Vaccine Technology Roadmap. To ensure the equitable delivery of a highly effective malaria vaccine, key stakeholders must address potential hurdles to delivery and uptake, increase funding, engage with local communities, and actively involve healthcare providers [13].

Community Engagement and Education

Effective malaria vaccine implementation, as demonstrated by the RTS, S/AS01 programme, necessitates strong community engagement and awareness to ensure successful uptake [14]. Unsuccessful trials provide valuable insights, highlighting the critical role of community participation and education campaigns to raise public awareness and dispel concerns prior to vaccine introduction [25].

Importance of Community Involvement

Community involvement ensures malaria elimination programs are effective and sustainable, as studies consistently show that those in endemic areas underestimate their personal risk [12]. Community participation in malaria initiatives enhances proactive transmission-reducing behaviors, increases vaccination acceptability, and encourages the treatment of infected individuals. Insights from African meningitis vaccination campaigns underline that engaging communities through advocacy, social mobilization, and communication about vaccine safety and efficacy fosters acceptance and uptake of new vaccines. Successful immunization efforts rely on community awareness regarding vaccination locations and the broader benefits of vaccination for community health [14]. A high level of community understanding is essential to realizing the full potential of a malaria vaccine. Community participation is particularly critical given historical misperceptions about malaria vaccines and awareness that active malaria transmission can occur without overt symptoms. Informed consent in sero-epidemiological studies further ensures participants' understanding of the study's objectives, potential risks and benefits, and mechanisms to maintain the malaria burden within the community [16]. Participation in controlled human malaria infection (CHMI) models extends these ethical considerations. Although currently no serological test for malaria infection is licensed for clinical use, serology plays an important role in clinical trials of malaria vaccines and other control interventions [17]. Because the osmotic fragility test is reliable but labor-intensive and

lacks quality control procedures, the monkey model, with blood stages collected under controlled conditions, is preferred. Sufficient community understanding thus becomes pivotal for voluntary consent and compliance in vaccine-related trials [10].

Educational Initiatives

Community engagement and education are fundamental components for the success of malaria vaccines [9]. Malaria vaccination is an efficacious method that can dramatically reduce transmission both in the community and downstream and indirectly protect individuals [8]. To achieve this result, it is essential to implement adequate community participation and raise appropriate awareness. This would improve vaccine acceptability when vaccines become available [9].

Regulatory Approval Processes

Licensing has been granted for three malaria vaccines. RTS, S/AS01 (Mosquirix®), which targets the P. falciparum pre-erythrocytic phase, received a favourable opinion from the European Medicines Agency (EMA) in 2015. PfSPZ Vaccine (Sanaria®), a whole sporozoite formulation, received a Breakthrough Therapy designation from the United States Food and Drug Administration (FDA) in 2016 [18]. R21/Matrix-M™ is an RTS, S-like vaccine currently undergoing pivotal Phase 3 trials. Consequently, the RTS, S/AS01 vaccine has become the first human antimalarial parasitic vaccine to pass regulatory scrutiny [2]. Following the 2015 EMA favourable opinion, the World Health Organization (WHO) in 2017 recommended pilot implementation programs in Malawi, Ghana, and Kenya to evaluate safety and impact on mortality in routine use [20]. These programs commenced in 2019, and subsequent positive safety and mortality impact analyses triggered the WHO to formulate guidance on RTS, S/AS01 adoption. Globally, the complexity of regulatory approval processes is compounded by the absence of clearly delineated WHO international standards and guidelines specific to malaria vaccine evaluation and licensure [23].

FDA and EMA Guidelines

Licensure of vaccines in the United States usually involves four phases of investigational studies, culminating in large-scale randomized clinical trials designed to evaluate efficacy [26]. In 2012, the European Medicines Agency (EMA) recommended that the Malaria Programme on RTS, S/AS01 vaccine receive a positive scientific opinion, indicating the potential for marketing authorization, which has since been granted [2]. Two leading malaria vaccines, RTS, S (Mosquirix™) and PfSPZ (Sanaria®), have been evaluated in humans, yet regulatory approval remains outstanding. Regulatory guidance addresses the continuity of marketing-authorized vaccines for travelers (Supplementary WHO Material). Post-marketing, vaccine manufacturers must submit periodic safety update reports with cumulative analyses of adverse events, including serious and unexpected ones [25]. The EMA's emerging Pharmacovigilance Risk Assessment Committee activities include scientific advice on vaccine safety surveillance and encourage timely and accurate investigation of unexpected or serious adverse events [3].

Post-Marketing Surveillance

The approval of RTS, S/AS01 by the FDA and EMA requires that its safety be continuously monitored through post-marketing surveillance [14]. This process usually begins once a vaccine is distributed to the public. Known as pharmacovigilance, adverse events related to the vaccine are systematically reviewed to form recommendations for corrective actions [14]. Continuous monitoring collects information on additional rare adverse events and provides persistent protection over extended periods. Additionally, it identifies optimal supportive interventions and clarifies the vaccine's impact on parasite transmission and evolution alongside other measures [2].

Case Studies

Evaluating malaria vaccine efforts benefits from studying implementation successes and failed trials that offer instructive insights [15]. For instance, an attenuated blood-stage malaria vaccine progressed through an initial human trial with twelve healthy volunteers. Although the small cohort prevents efficacy demonstration, the study confirmed the trial approach's viability and safety; coupled with a rationale for further optimization and cellular correlates, these findings underscore the need for expanded investigations [17]. Such results expand understanding of protective blood-stage immunity and contribute to broader vaccine-development strategies [12]. Conversely, the RTS, S/AS01 vaccine advanced to phase 3 testing, and the WHO pilot introduction illustrates difficulties in translating efficacy to routine rollout. Achieving 45% protection in African children during the first twenty months of the pivotal trial, the program promptly restarted vaccination campaigns in Ghana, Kenya, and Malawi to assess impact on illness incidence and sustain mass immunization. Real-world effectiveness may nevertheless fall short of trial results: factors such as receptivity, infrastructure, and cold-chain requirements reduce benefits. Addressing implementation challenges will be decisive for vaccine programs to reach full potential [14].

Successful Vaccine Implementations

Successful vaccine implementations provide real-world insights to guide ongoing and future malaria vaccine development efforts [19]. The RTS, S/AS01 vaccine (RTS, S) represents the most advanced malaria vaccine candidate, having been recommended by the WHO for widespread use. Malaria immunization offers protection against Plasmodium falciparum infection by eliciting antibodies to circumsporozoite protein (CSP) and inducing T-cell immune responses directed against liver-stage parasites. RTS, S targets pre-erythrocytic parasites in the liver to avert the initiation of blood-stage infection [2]. Phase 3 trials of RTS, S revealed a modest efficacy of approximately 40% over four years in reducing clinical malaria episodes among African children who received three priming doses followed by a booster 17. Accordingly, the WHO's Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) have advised pilot implementation of RTS, S in three sub-Saharan African countries. Four thousand volunteers from each country have been enrolled in the pilot program to assess safety, feasibility, and efficacy, with vaccine deployment approved in 2019 [25]. Whole-organism vaccines have demonstrated promise in controlled human malaria infections (CHMI). Sanaria's PfSPZ vaccine, containing radiation-attenuated P. falciparum sporozoites, achieved sterilizing protection in malaria-naïve individuals after five doses. Sanaria's PfSPZ-CVac, which utilizes three doses of infectious sporozoites administered alongside chloroquine chemoprophylaxis, induced sterilizing immunity in experimentally infected individuals following three doses within 56 days in non-endemic adults [24].

Lessons from Failed Trials

The publication of several malaria vaccine efficacy trials that were stopped prematurely due to futility or a high incidence of adverse effects was a salutary reminder of the difficulties faced in developing an effective malaria vaccine [1]. In addition, a few failures of malaria vaccine candidates against severe P. falciparum or P. vivax malaria that may relate to inadequate protection or the role of other antigens or epitope variants in mediating severe disease were noted. Such failures highlight the difficulties in bringing malaria vaccines to licensure, with the declaration of a first vaccine being only the initial step on the path to malaria control [4]. The experience gained with candidate malaria vaccines that did not reach licensure nevertheless provides valuable insights that will help refine future malaria vaccine developments. In particular, four important lessons can be drawn from these early failures. Active areas of vaccine research have subsequently addressed these, and improved knowledge allows the design of more effective vaccines. Informed analysis of the reasons for the trial failures will improve the likelihood that newer malaria vaccine candidates can succeed [26-29].

CONCLUSION

Malaria vaccine development has made substantial strides, exemplified by the licensure and pilot implementation of RTS, S/AS01, and the promising efficacy of PfSPZ and R21 vaccines. While current vaccines provide partial protection, significant challenges persist due to the parasite's complex life cycle, antigenic diversity, and immunological evasion mechanisms. Multi-stage and combination vaccine strategies, improved adjuvants, and novel delivery platforms offer promising avenues to enhance efficacy. Successful malaria control will require integrating vaccines with vector control, chemoprevention, and strong community engagement. Ethical considerations, informed consent, and equitable distribution must guide vaccine implementation, particularly in endemic regions. Continued investment, collaboration, and innovation are essential to achieve long-term reductions in malaria transmission, morbidity, and mortality, bringing global malaria eradication closer to reality.

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