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REVIEW

Current Developments in Malaria Vaccination: A Concise Review on Implementation, Challenges, and Future Directions

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Introduction: Malaria remains a persistent challenge in global health, disproportionately affecting populations in endemic regions (eg, sub-Saharan Africa). Despite decades of international collaborative efforts, malaria continues to claim hundreds of thousands of lives each year, with young children and pregnant women enduring the heaviest burden. This concise review aimed to provide an up-to-date assessment of malaria vaccines progress, challenges, and future directions.

Methods: A PubMed/MEDLINE search (2015–2024) was conducted to identify studies on malaria vaccine development, implementation barriers, efficacy, and vaccination hesitancy. Clinical trials, reviews, and global health reports were included based on relevance to the review aims. No strict inclusion criteria were applied, and selection was guided by key review themes and policy relevance.

Results: The introduction of pre-erythrocytic malaria vaccines (RTS,S/AS01 and R21/Matrix-M), represents an important milestone in malaria control efforts with promising results from the erythrocytic vaccine RH5.1/Matrix-M in recent clinical trials. However, the approval of these vaccines is accompanied by significant challenges such as the limited efficacy, the complexity of multi-dose regimens, and numerous barriers to widespread implementation in resource-limited settings. The review identified the complex challenges to broad malaria vaccination coverage, including logistical barriers, healthcare infrastructure effect, financial limitations, malaria vaccine hesitancy, among other obstacles in malaria-endemic regions. Promising developments in malaria vaccination, such as next-generation candidates (eg, mRNA-based vaccines), hold the potential to offer improved efficacy, longer-lasting protection, and greater scalability. There is a critical need to integrate malaria vaccination efforts with established malaria control interventions (eg, insecticide-treated bed nets, vector control strategies, and anti-malarial drugs).

Conclusion: Achieving sustained control of malaria morbidity and mortality will require strong global collaboration, sufficient funding, and continuous efforts to address inequities in access and delivery of malaria control measures including the malaria vaccines.

Keywords: malaria control, malaria vaccine, *Plasmodium falciparum*, vaccine efficacy, immunization programs, public health

Introduction

Malaria is one of the big three infectious diseases along with human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS) and tuberculosis.[1,2] This life-threatening infectious disease is caused by *Plasmodium* parasites, primarily transmitted to humans through the bites of infected *Anopheles* mosquitoes.[3] Of the five *Plasmodium* species capable of infecting humans (*P. falciparum, P. malariae, P. ovale, P. vivax, and P. knowlesi*), *P. falciparum* is responsible for the majority of severe malaria cases and fatalities.[4]

Despite the ancient origins of malaria, it remains a significant global health threat.[5] Advances in understanding the life cycle of *Plasmodium* in the 19th and early 20th centuries laid the foundations for vector control strategies, the

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development of anti-malarial drugs, and the availability of malaria rapid diagnostic tests (RDTs).[6–8] However, the *Plasmodium* ability to develop and select resistance to treatment and the mosquito's adaptation to control measures have made malaria eradication a challenging task.[9,10]

Malaria control and prevention remain important priorities, as this tropical infectious disease continues to exert a substantial burden on global health, particularly across the tropical and sub-tropical regions.[11,12] The World Health Organization (WHO) World Malaria Report 2023 indicated that in 2022 there were an estimated 249 million malaria cases in 85 endemic countries, marking an increase of 5 million cases from 2021.[13] Children under five years of age remain the most vulnerable group to malaria burden, accounting for the majority of malaria-related deaths, especially in sub-Saharan Africa (SSA).[14] Pregnant women and immunocompromised patients are also considered as other malaria at-risk groups.[15–18]

In Africa, malaria control efforts face notable challenges.[19–21] These challenges include climate change which shifts transmission dynamics,[22,23] poverty which weakens healthcare infrastructure,[24] and substandard services in healthcare hindering effective control measures.[19] The growing resistance to anti-malarial drugs and insecticides, coupled with the emergence of new vector species and increased outdoor transmission are additional challenges.[25–29] Beyond Africa, malaria persists as a serious public health threat. In South America, the Amazon basin remains a focal point, where *P. vivax* predominates and complicates treatment due to its relapse-prone biology.[30–32] Meanwhile, in Southeast Asia's near-elimination settings, progress is impeded by several challenges.[33,34] These include asymptomatic infections, cross-border malaria transmission, resistance to anti-malarial drugs, and the difficulty of pinpointing infection hotspots in remote regions.[34–36] These regional complexities highlight the need for innovative surveillance systems, adaptive intervention strategies, and global cooperation to achieve sustained malaria control.

While malaria incidence has declined over the last few decades, progress in malaria prevention and control is still needed.[37–39] Challenges in sustaining effective malaria control measures have been exacerbated by the emergence of *Plasmodium* resistance to various anti-malarial drugs.[40–43] Beyond the issue of drug resistance, sustaining malaria control requires community engagement, enhanced resistance surveillance, anti-malarial quality monitoring, and building capacity to track mosquito behavior changes as illustrated recently by Guyant et al.[44]

It is also important to point out that the socio-economic toll of malaria remains profound.[45,46] This malaria toll perpetuates poverty by disrupting education, workforce productivity, and economic stability, especially in regions with fragile healthcare systems.[47–49] Further complicating these challenges that face malaria control is the rising insecticide resistance among the mosquito vector.[50,51] Taken together, the negative impacts of malaria and the challenges faced in its control highlight the continuous need for sustainable, innovative control measures such as the implementation of vaccination.[12,52,53]

The quest for an effective malaria vaccine has spanned more than seven decades.[54,55] These efforts were primarily driven by the need for a long-term cost-effective measure to complement other malaria control measures such as insecticide-treated bed nets and anti-malarial drugs.[56,57] For example, an early study by Sauboin et al estimated that malaria vaccination at 6, 10, and 14 weeks could prevent over 5 million clinical cases and 31,000 deaths in 42 countries over 10 years, while vaccination at 6, 7.5, and 9 months could avert 12.5 million cases and 65,400 deaths.[58] In both scenarios, coverage was assumed to reach 75% of the diphtheria-tetanus-pertussis (DTP3) vaccination coverage, accounting for the greater difficulty in reaching children at older ages compared to the standard DTP schedule.[58] However, the complex life cycle of *Plasmodium*, involving both human and mosquito hosts, has posed unique challenges for malaria vaccine development.[59–61]

Early malaria vaccine strategies targeted various stages of the *Plasmodium* life cycle, including the pre-erythrocytic, blood-stage, and transmission phases.[62–67] The first-generation malaria vaccine, RTS,S/AS01 (Mosquirix), targets the pre-erythrocytic stage of *Plasmodium* by generating an immune response against the *P. falciparum* immunodominant circumsporozoite protein (CSP).[68,69] Following decades of research and extensive clinical trials, the WHO recommended RTS,S/AS01 in 2021 for children in areas of moderate to high transmission.[70–72] Data showed over 47% RTS,S/AS01 vaccine efficacy against clinical malaria and hospitalizations within 12 months post-third dose, though efficacy declines to 34% at 30 months without a booster dose.[73] Another promising development was the approval of the Oxford R21/Matrix M vaccine, which also targets the pre-erythrocytic stage and builds upon the RTS,S/AS01 by incorporating a higher antigen-to-adjuvant ratio to potentially enhance immune response.[74–77] Additional malaria vaccines, including those based on next-generation technologies like mRNA, are currently in development, offering hope for more efficacious malaria control measures in the near future.[78–81] An important issue that should be considered in malaria vaccination with the efficacies reported for the approved vaccines is the

rapid waning of protection despite high initial efficacy. This limitation, likely due to insufficient immunological memory in individuals with prior malaria exposure, could be addressed through annual mass vaccination campaigns timed before seasonal transmission peaks (seasonal vaccination).[82–85]

Viral-vector malaria vaccines have shown potential in targeting both pre-erythrocytic and sexual stages of *P. falciparum*.[78] The ChAd63-MVA prime-boost regimen encoding multiple epitope–thrombospondin-related adhesion protein (ME-TRAP) induced strong CD8+ T-cell responses and reduced infection risk in endemic settings.[86,87] Transmission-blocking vaccines (TBVs) using Pfs25-IMX313 demonstrated safety and immunogenicity but had limited transmission-reducing activity, emphasizing the need for further optimization.[87,88]

A deeper understanding of vaccine implementation challenges, particularly in resource-limited settings, is critical. Lessons from the rollout of COVID-19 vaccines underscore the importance of robust global partnerships, equitable access strategies, and community engagement to overcome logistical and sociopolitical barriers. Malaria vaccine initiatives must build on these insights to tackle similar obstacles, including vaccine hesitancy, funding gaps, and infrastructural limitations.

The current review aimed to concisely address the following objectives. First, the review aimed to describe the latest estimates on the global burden of malaria, highlighting its persistent impact on health and socioeconomic development, particularly in endemic regions. Second, the review aimed to outline the critical historical milestones and challenges in malaria vaccine development. Third, the review aimed to evaluate the barriers to malaria vaccination implementation, with a focus on the issue of vaccine hesitancy. Finally, the review explored future directions, including the potential of next-generation vaccine candidates, the integration of vaccination with other malaria control measures, and the importance of global collaboration and sustained funding. The ultimate aim of the current review was to offer insights that can help to strengthen global malaria control efforts.

Methods

An ad hoc literature search was conducted in PubMed/Medline to identify recent and relevant studies on malaria vaccination, guided by the key objectives of this review. These objectives included description of the global burden of malaria and the key milestones in malaria vaccine development; evaluation of the malaria vaccine implementation barriers, including vaccine hesitancy; and investigation of the future directions in vaccine candidates, integration with other control measures, and the role of global collaboration.

The exact search strategy was: ((“malaria”[Title/Abstract] AND “vaccine”[Title/Abstract]) AND ((“RTS,S”[Title/Abstract] OR “R21/Matrix-M”[Title/Abstract]) OR (“efficacy”[Title/Abstract] OR “safety”[Title/Abstract] OR “vaccine hesitancy”[Title/Abstract] OR “implementation”[Title/Abstract] OR “challenges”[Title/Abstract] OR “next-generation vaccines”[Title/Abstract]))) OR (“Malaria Vaccines”[MeSH Terms] AND “Vaccination”[MeSH Terms]) AND (2015:2024[Date - Publication]) AND (“English”[Language]) AND (“Africa”[MeSH Terms] OR “Asia, Southeastern”[MeSH Terms]) AND (clinical trial[Publication Type] OR review[Publication Type]) which yielded 96 records. Articles published between 1 January 2015, and 1 December 2024, were included.

Given the narrative nature of this review, rather than being a systematic review, no strict inclusion or exclusion criteria were applied for study selection. Instead, two independent authors (the first and senior authors) conducted the literature review for the retrieved records guided by the study objectives. Articles were considered for inclusion based on their relevance to key review themes, including the global burden of malaria, milestones in vaccine development (notably RTS,S/AS01 and R21/Matrix-M), real-world implementation data, vaccine efficacy, challenges in vaccination coverage, and the socio-political factors influencing vaccine uptake. Special emphasis was placed on published studies that addressed barriers to malaria vaccine implementation, such as malaria vaccine hesitancy/resistance. Reports and policy documents from global health organizations, particularly the WHO, were also included to ensure the inclusion of the most current and policy-relevant evidence on malaria vaccination.

Overview of Malaria Burden Worldwide

Malaria remains a formidable global health challenge.[19,89,90] This challenge is particularly pronounced in the tropical and subtropical regions, where it disproportionately affects vulnerable populations and perpetuates cycles of poverty.[11,19,91] As stated in the introductory section of this review, and according to the WHO World Malaria Report 2023, there were an estimated 249 million malaria cases worldwide in 2022, with an increasing trend of 5 million cases compared to 2021 across 85 endemic countries.[13]

Malaria endemicity classification helps determine transmission intensity, though no single measure is entirely satisfactory.[92–94] Traditionally, parasite rate or spleen rate in children aged 2–9 years have been used to define levels of endemicity as follows: hypo-endemic (0–10%), meso-endemic (10–50%), hyper-endemic (>50%), and holo-endemic (≥75% consistently, with low adult spleen rates).[95] This system reflects that parasite density decreases significantly between ages 2 and 5, impacting endemicity assessments.[95] Despite its limitations, this classification remains a useful framework for prioritizing interventions in are areas with high burden of malaria.[92,95,96]

The heaviest burden of malaria is observed in SSA, accounting for approximately 95% of malaria cases and deaths globally.[19] In 2022, the WHO African region reported an estimated 233 million cases and 580,000 deaths due to malaria.[97] Children under five years of age are particularly vulnerable, representing about 80% of all malaria deaths in the African region.[98] For example, Nigeria alone accounted for 27% of global malaria deaths, followed by the Democratic Republic of the Congo (DRC), Tanzania, and Niger.[12] The global distribution of malaria incidence in 2022 and mortality rates in 2021 based on the WHO data are shown in (Figure 1).

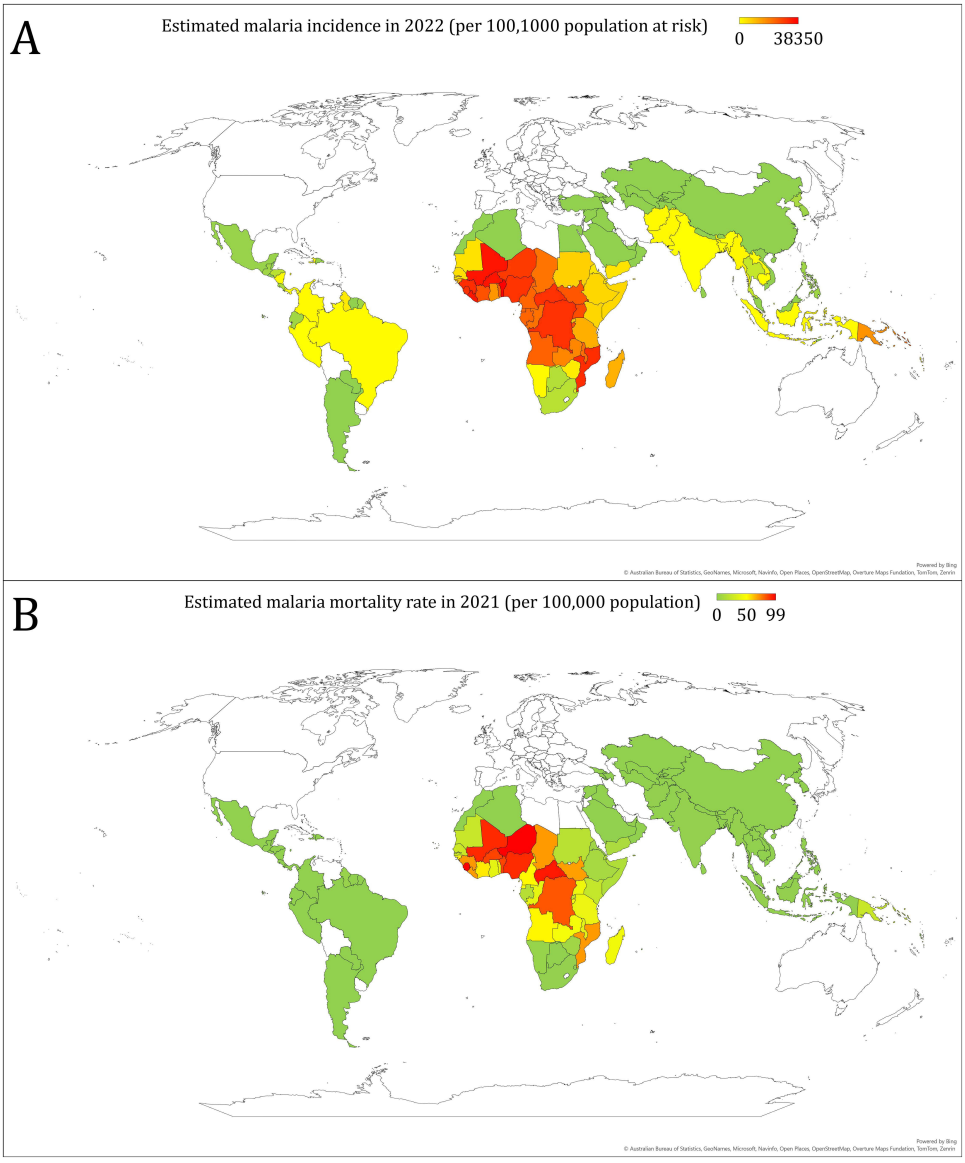

Figure 1 Global distribution of malaria incidence and mortality rates. (**A**) Estimated malaria incidence per 100,000 population at risk in 2022. (**B**) Estimated malaria mortality rate per 100,000 population in 2021. Data source: World Health Organization Global Health Observatory, 2022.[99] The maps were generated in Microsoft Excel, powered by Bing, using geospatial data from the Australian Bureau of Statistics, GeoNames, Microsoft, Navinfo, TomTom, and Wikipedia. We remain neutral regarding jurisdictional claims depicted in the maps.

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Historical Development of Malaria Vaccines

The quest for a malaria vaccine has been one of the most complex and enduring challenges in tropical medicine.[100,101] Unlike many other infectious diseases, malaria is caused by a eukaryotic parasite with a highly complex life cycle involving mosquito and human hosts.[102] This life complexity, besides the ability of *Plasmodium* to evade the human immune system through antigenic variation, has historically made the development of an effective vaccine particularly challenging.[54,59,103] A timeline of the major milestones in malaria vaccine development is illustrated in (Figure 2).

Initial attempts to develop a malaria vaccine in the mid-20th century primarily focused on the erythrocytic stage where *Plasmodium* infects erythrocytes.[115] However, these early malaria vaccines faced significant limitations, as they failed to generate strong or lasting immune responses.[78,116] It was not until the identification of key antigens involved in the sporozoite stage—specifically the CSP of *P. falciparum*—that a major breakthrough occurred.[104,117] The CSP, expressed on the surface of the sporozoite stage of *Plasmodium*, became the target for a pre-erythrocytic vaccines designed to prevent the parasite from reaching the liver, where it matures and multiplies.[118–120]

The development and approval of RTS,S/AS01 (Mosquirix) by the WHO in 2021 was a landmark achievement.[68,105] RTS,S is a recombinant protein vaccine based on the CSP of *P. falciparum*, fused with the hepatitis B surface antigen (HBsAg), and formulated with the AS01 adjuvant to enhance the immune response.[121] The name RTS,S/AS01 reflects the vaccine composition: RTS,S includes repeated T-cell epitopes from *P. falciparum* CSP and HBsAg to enhance immune response.[72] AS01 is a liposome-based adjuvant with 3-O-desacyl-4′-monophosphoryl lipid A (MPL) and QS-21 saponin, which together boost innate and adaptive immunity, significantly increasing the vaccine efficacy against *P. falciparum*.[122]

Based on data from the RTS,S/AS01 Malaria Vaccine Implementation Programme report, the RTS,S/AS01 vaccine, evaluated in Phase 3 trials in SSA, showed an efficacy of around 36% in reducing clinical malaria cases in young children over four years, with a favorable safety profile.[123] After these promising results, the WHO recommended large-scale pilot programs in 2015, which were launched in Ghana, Kenya, and Malawi.[124] In 2021, following positive pilot

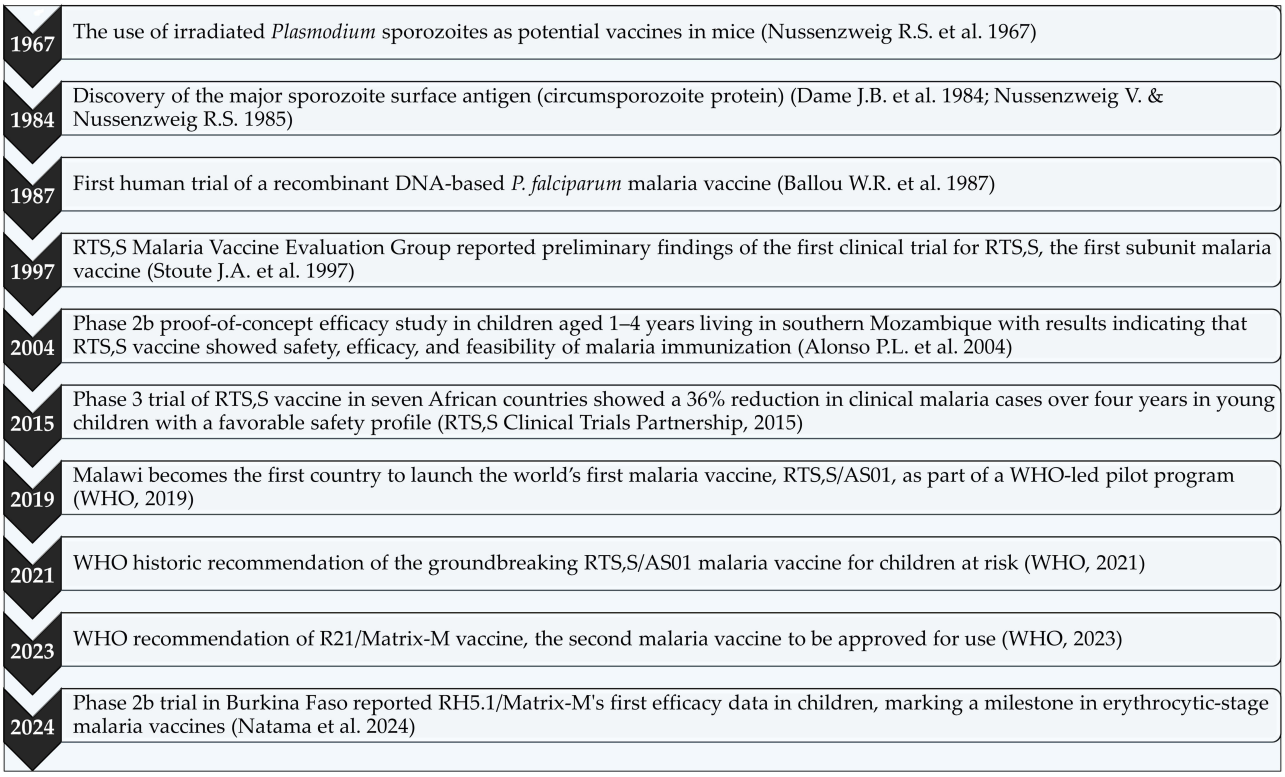

Figure 2 Timeline of major milestones in malaria vaccine development. Sources of data are in.[76,104–114]

outcomes, WHO recommended RTS,S for broader use in children in high-transmission regions, despite challenges like modest efficacy, a four-dose schedule, and waning immunity.[125,126]

The Oxford R21/Matrix-M malaria vaccine, a promising malaria vaccine, demonstrated high efficacy rates in early-stage trials.[75] The efficacy of R21/Matrix-M was reported at up to 80% in African children over a one-year period, particularly in those receiving the higher adjuvant dose.[127–129] This led to its approval by the WHO in 2023 the second malaria vaccine for malaria prevention in children after reviewing its safety and efficacy.[76,130] The smaller dosage and improved immunogenicity profile of R21/Matrix-M, alongside the use of a potent adjuvant (Matrix-M), offer enhanced protection,[131] although its potential to outperform RTS,S/AS01 has not been tested yet.[75,76]

A significant breakthrough in malaria vaccine research is the reticulocyte-binding protein homolog 5 (RH5) RH5.1/Matrix-M vaccine, a blood-stage *P. falciparum* vaccine candidate.[106,132,133] The RH5.1/Matrix-M vaccine is specifically designed to target the parasite during its erythrocytic phase, after exiting the hepatocytes while entering the bloodstream.[134,135] This different vaccination approach addresses a critical gap left by pre-erythrocytic vaccines such as RTS,S/AS01 and R21/Matrix-M, which are unable to protect against blood-stage parasites.[136]

In a recent phase 2b trial conducted in Burkina Faso, RH5.1/Matrix-M showed promising results in children aged 5–17 months.[106] The vaccine was well-tolerated with a favorable safety profile and demonstrated robust immunogenicity.[106] The encouraging results suggest that RH5.1/Matrix-M vaccine could serve as a valuable addition to the malaria vaccine arsenal, complementing the existing approved vaccines by offering protection against the erythrocytic stage of *P. falciparum*.[137]

Since the start of the new millennium, malaria vaccine research has diversified beyond pre-erythrocytic targets.[138–140] Blood-stage vaccines, including candidates such as merozoite surface protein (MSP) and glutamate rich protein (GLURP), have been evaluated for their potential to inhibit erythrocyte invasion and reduce parasitemia.[141,142] Among blood-stage vaccine candidates, GMZ2 which comprised conserved domains of GLURP and MSP3, showed modest but statistically significant efficacy in preventing naturally acquired *P. falciparum* infection in clinical trials.[143,144] However, its limited protective effect led to a shift toward identifying novel blood-stage vaccine targets or enhancing efficacy.[138]

Vaccines composed of attenuated *P. falciparum* sporozoites (PfSPZ) have also been undergoing clinical trials to test for protection against malaria as reviewed by Richie et al.[145] The first-generation PfSPZ vaccine employs gamma irradiation to achieve attenuation, rendering sporozoites non-replicative while preserving immunogenicity.[146] Second-generation chemo-attenuated PfSPZ vaccines showed improved efficacy against heterologous strains but require co-administered drugs, presenting safety concerns due to the risk of parasitemia recrudescence.[145,147] Ongoing clinical trials continue to evaluate sporozoite immunization across diverse populations, aiming to optimize immunogenicity, dosing regimens, and cross-strain protection.[148–150]

New malaria vaccine candidates, including viral vector and mRNA-based vaccines, aim to provide stronger, longer-lasting immunity compared to current options like RTS,S.[54,78,151] Viral vector vaccines use modified viruses to deliver malaria antigens, enhancing cellular immunity with fewer doses.[152–154]

Building on coronavirus disease 2019 (COVID-19) vaccine success, mRNA vaccines offer rapid production and adaptability, enabling tailored responses across different *Plasmodium* stages.[155–157] By eliciting robust humoral and cellular immunity, these next-generation malaria vaccines could have the potential to improve individual protection and reduce transmission, supporting malaria elimination goals in high-burden areas.[137,158]

Malaria Immune Response and Vaccine Mechanisms

The immune response to *Plasmodium* infection is complex, with the involvement of both innate and acquired immunity.[159–163] Early on during malaria infection, innate immune mechanisms are activated with the action of dendritic cells (DCs) among other innate cells to recognize parasite-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs).[160,164,165] The major PAMPs identified in *P. falciparum* include glycosylphosphatidylinositol anchors, hemozoin, and immunostimulatory nucleic acid motifs, which trigger DC maturation and initiate downstream immune signaling.[166,167]

The acquired immune response follows, with activation of T and B lymphocytes and antibody production.[168,169] During the pre-erythrocytic stage, when sporozoites are inoculated into the skin by an infected mosquito, the CSP is a primary target of the host immune response.[170,171] Sporozoites spend hours in the dermis, which provides an

opportunity for antigen presentation and priming of the immune cells.[172,173] Neutralizing antibodies targeting CSP can prevent hepatocyte invasion, while CD4+ T cell responses contribute to protective immunity.[161,174,175]

The currently approved malaria vaccines, including RTS,S/AS01 and R21/Matrix-M, utilize recombinant CSP antigens to elicit robust anti-sporozoite antibody responses.[176,177] However, the RTS,S/AS01 vaccine's limited efficacy is partly attributed to its narrow immunological focus with minimal induction of CD8+ T cell responses, which are critical for eliminating infected hepatocytes.[178] The absence of substantial CD8+ T-cell-mediated immunity, a key component in rodent models of malaria protection, represents a notable limitation of current vaccines.[168,179] Overcoming this issue requires novel vaccines capable of eliciting both humoral and cytotoxic responses, including the identification of broadly conserved CD8+ T cell epitopes presented by MHC class I molecules across diverse human populations.[180,181] Additionally, genetic variability in CSP among *P. falciparum* strains may reduce vaccine efficacy against heterologous parasites, highlighting the need for broader antigenic coverage in future vaccine designs.[182–184]

Vaccine Efficacy and Safety of RTS,S/AS01 and R21/Matrix-M Malaria Vaccines

The RTS,S/AS01 and R21/Matrix-M vaccines offer protective immunity against *P. falciparum*.[185] These vaccines provide a remarkable milestone in the ability to control malaria; however, it is important to delineate their efficacy, safety, and cost in relation to successful implementation in endemic regions.

The RTS,S/AS01 vaccine demonstrated a modest efficacy of approximately 33–36% in reducing clinical malaria cases over four years, with waning protection observed without booster doses.[186–189] Notably, no significant efficacy against severe malaria was observed in younger infants even with a booster dose.[190] Immunogenicity data reveal that the RTS,S/AS01 booster dose increases total IgG levels against vaccine antigens, with notable differences observed in IgG subclasses.[191] Additionally, variable efficacy of RTS,S/AS01 has been shown to depend on the genetics of the local *P. falciparum* population.[192]

Post-approval safety evaluations confirmed a favorable safety profile for RTS,S/AS01, with mild injection site reactions and transient fever as the most common adverse events.[186,193,194] Rare febrile seizures were observed within seven days post-vaccination but resolved without long-term complications.[186] Importantly, no fatal adverse events were causally linked to the vaccine.[195] A phase 3b clinical trial conducted in Ghana further confirmed the RTS,S/AS01 vaccine safety profile, whether administered alone or co-administered with other vaccines such as yellow fever and measles-rubella.[196]

The Oxford R21/Matrix-M vaccine, approved in 2023, demonstrated promising efficacy, achieving up to 75% protection in children aged 5–17 months, particularly when a booster dose is administered one year after the initial three-dose regimen.[131,197] Its safety profile is favorable, with no significant adverse effects reported during clinical trials.[75] Mild reactions, such as localized pain and fever, were the most commonly observed side effects.[75,128]

Comparatively, the RTS,S/AS01 and R21/Matrix-M vaccines demonstrated similar efficacy and safety profiles in preventing malaria, particularly in children.[198] While evidence directly comparing their efficacy is lacking, early analyses suggest that both vaccines would provide a cost-effective approach for malaria prevention.[199,200] Despite their potential, the modest efficacy of RTS,S/AS01 and R21/Matrix-M highlights the need for continued efforts needed to achieve more durable, high-impact malaria vaccines essential for eradication efforts.[201]

Challenges in Malaria Vaccine Implementation

There is no doubt that the introduction and approval of the RTS,S/AS01 and R21/Matrix-M malaria vaccines offered a new hope in the fight against malaria.[202] Nevertheless, achieving a malaria vaccine that provides high efficacy and long-lasting immunity remains challenging.[203] Additionally, achieving the full potential of malaria vaccines requires addressing complex logistical, operational, and social challenges, particularly in malaria-endemic regions with limited resources.[52,204] Specifically, the challenges of implementing malaria vaccination range from infrastructure limitations to community perceptions as highlighted in (Figure 3).

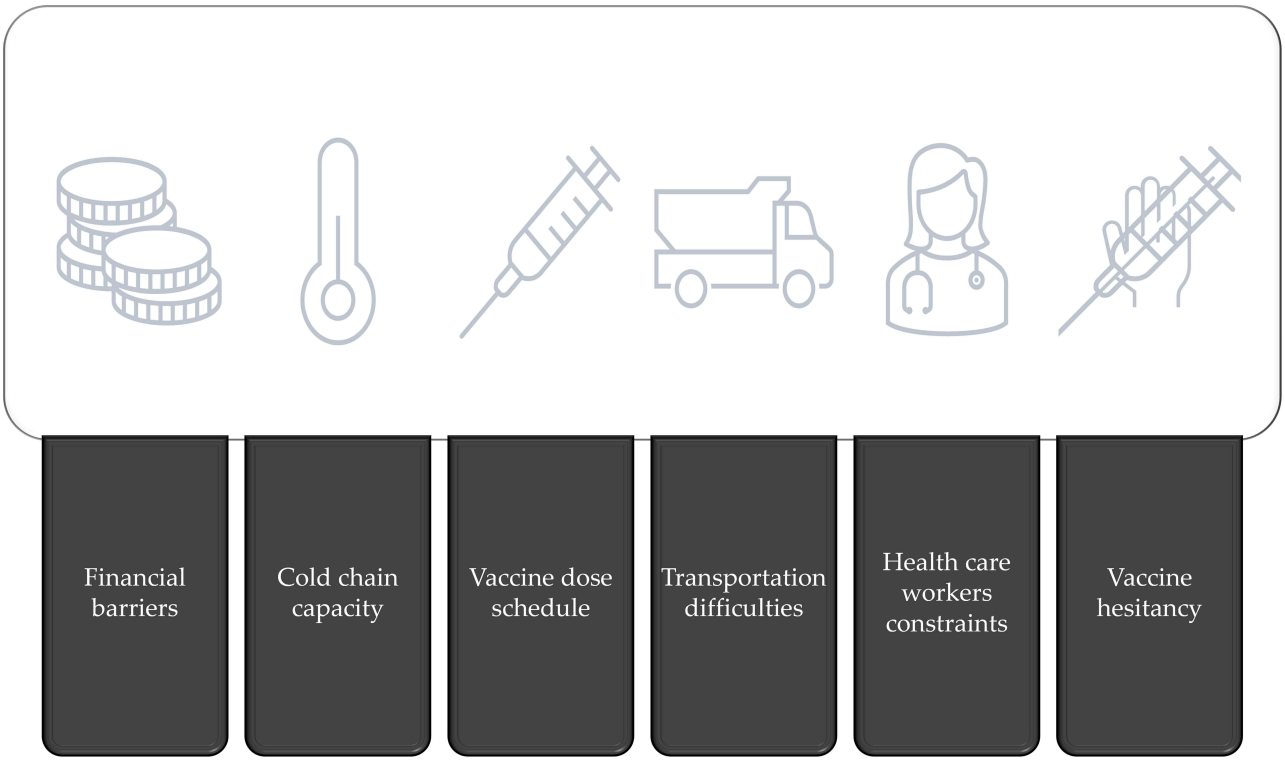

Figure 3 Key challenges in implementing malaria vaccination in resource-limited settings.

Logistical and Infrastructure Barriers

A major logistical challenge is the RTS,S/AS01 vaccine four-dose schedule: the first three doses are given at months 0, 1, and 2, with a crucial booster at 18 months.[205] In rural areas in SSA where travel to healthcare centers can be difficult, completing this schedule poses a significant challenge.[206] Missed doses, common in settings where healthcare access is inconsistent, can compromise the malaria vaccine efficacy.[207]

Moreover, the malaria vaccine requires a cold chain capacity, which can be problematic in regions with limited electricity and high temperatures.[204,208] Transportation difficulties and inconsistent cold storage infrastructure can also disrupt vaccine delivery in remote areas, risking loss of efficacy if the malaria vaccine temperature range is not maintained.[209]

Healthcare Workforce Constraints

Healthcare workers constraints can complicate logistical barriers to the successful implementation of malaria vaccination.[210] Many malaria-endemic countries, such as those in SSA, already struggle with a shortage of healthcare providers trained to administer and monitor vaccination programs, particularly in under-resourced areas.[21,211]

Success in implementing RTS,S/AS01 and R21/Matrix-M vaccines can be enhanced by integrating it effectively into routine immunization schedules without overburdening health systems that are already strained by the demands of child immunizations and maternal care.[212] A study by Hill et al in Kenya highlighted that integrating RTS,S/AS01 malaria vaccine into the Essential Programme on Immunisation could streamline its delivery and strengthen uptake.[205] Despite initial challenges with the four-dose schedule and resource limitations, this approach can enhance the vaccine impact without overburdening healthcare systems.[205]

Financial Barriers

Financial issues can also be a critical barrier in implementing malaria vaccination with the procurement, storage, and delivery of RTS,S/AS01 requiring substantial investment, a challenge for many low-income countries where malaria is

endemic.[213] While organizations such as Gavi, the Vaccine Alliance, have committed support for this goal, securing sustainable funding remains essential.[214] In SSA, where healthcare budgets are constrained, the cost of maintaining large-scale malaria vaccine campaigns, along with ongoing malaria control efforts, requires long-term commitments from global health stakeholders.[24]

Vaccine Hesitancy as a Barrier to Successful Malaria Vaccine Implementation

Public acceptance of malaria vaccines is equally important for malaria vaccination program success with evidence pointing to high acceptance in Africa.[215–217] Vaccine hesitancy, often rooted in distrust of health care systems or cultural beliefs, can limit malaria vaccine uptake.[218] In a study by Bam et al, caregivers in Ghana showed generally positive perceptions of the RTS,S/AS01 malaria vaccine for children, citing benefits like reduced hospital visits and cost savings, although concerns about potential side effects highlighted the need for targeted health education to address vaccine hesitancy and promote broader malaria vaccine uptake.[219]

In an early study by Ojakaa et al, 88% of caregivers in Kenya expressed willingness to accept a malaria vaccine for children, with acceptance highest in malaria-endemic areas.[220] More recently, in a study by Nyalundja et al, only 7.26% of adults in eastern DRC were aware of the malaria vaccine, though 52.6% were willing to vaccinate their under-five children, with higher acceptance associated with factors such as middle-income and semi-rural residence.[221]

In another study by Mtenga et al, 84.2% of Tanzanian mothers expressed strong acceptance of a malaria vaccine for their children, with additional support from community stakeholders who saw the vaccine as a valuable complement to existing prevention strategies, though they raised questions about efficacy, side effects, and eligibility.[222] Outside Africa, in a study by Amin et al, 70% of parents in malaria-endemic areas of Bangladesh indicated willingness to vaccinate their under-five children against malaria, with higher acceptance associated with residence, education, income, and family size.[223]

In the context of these challenges, an important study by Grant et al, highlighted key implementation challenges of malaria vaccination in Ghana, including issues with the dosing schedule, eligibility criteria, and logistical support, such as cold-chain and transport limitations.[206] This qualitative study revealed that community rumors leading to vaccine refusals emphasized the need for robust, culturally tailored vaccine promotion efforts.[206] These findings by Grant et al offered critical insights for scaling RTS,S/AS01E in Ghana and future malaria vaccine rollouts across Africa.[206]

A recent systematic review by Ansar et al analyzed 18 studies involving 18,561 participants, revealing an overall RTS,S/AS01 malaria vaccine acceptance rate of 87.5%, with rates ranging from 32.3% to 99.3%.[224] Countries like Ghana and Nigeria showed particularly high vaccine acceptance, driven by factors such as prior vaccination experiences, knowledge about malaria, and community engagement in prevention behaviors.[224]

Future Directions

As malaria continues to claim hundreds of thousands of lives annually, particularly in SSA, the development of more effective malaria vaccines remains an urgent global health priority.[52,225–227] While RTS,S/AS01 and R21/Matrix-M vaccines approval marked historic achievements and can be viewed as important benchmarks to compare with other novel vaccines, their modest efficacy highlights the need for next-generation malaria vaccines with improved efficacy profiles, easier administration, and long-lasting protection.[186,228] The future of malaria vaccine development relies on innovative scientific approaches, enhanced global collaboration, and integration of vaccination with other malaria control strategies.[229]

In addition, other *Plasmodium* species, such as *P. vivax*, which can cause severe malaria, have historically received less focus compared to *P. falciparum*.[230] The importance of focus on *P. vivax* is highlighted by being a predominant *Plasmodium* species in most non-African endemic countries.[230] The view that *P. vivax* might not be a priority for prevention compared to *P. falciparum* can be challenged as follows. Dormant *P. vivax* hypnozoites, capable of reactivating months after initial infection, high transmission potential, coupled with asymptomatic carriers and outdoor-biting mosquito vectors, the ability of *P. vivax* to cause severe disease justify the quest for effective vaccines targeting this species.[231,232] Vaccines targeting *P. vivax* are essential to prevent relapses, reduce disease burden, and disrupt transmission, addressing critical gaps in the global effort to eliminate malaria.[233,234]

Next-Generation Vaccine Candidates

The limitations of RTS,S/AS01 and R21/Matrix-M vaccines, particularly its modest efficacy, emphasize the need for vaccines that provide more robust and longer-lasting immunity.[125] Therefore, new vaccine types are being explored in the context of malaria prevention, including mRNA-based vaccines and vaccines targeting different stages of the *Plasmodium* life cycle.[80,235]

The success of mRNA vaccines in the COVID-19 pandemic raised the interest in applying this novel vaccine type to malaria prevention.[235] mRNA vaccines have the advantage of rapid scalability, adaptability to new antigens, and the ability to elicit strong immune responses.[236] Efforts to develop mRNA vaccines targeting *P. falciparum* are already underway, with preclinical studies showing promising results.[137] Similarly, mRNA-based transmission-blocking vaccines are under development, aiming to interrupt the mosquito-to-human transmission cycle by targeting the sexual stages of the parasite within the mosquito.[237–239] These approaches could complement existing malaria vaccines and offer new and enhanced opportunities for malaria prevention.

Integration with Other Malaria Control Measures

Malaria vaccines must be viewed as part of a comprehensive approach to malaria control rather than as a stand-alone solution.[240,241] Future malaria control strategies require the incorporation of malaria vaccination with established effective measures such as insecticide-treated bed nets, indoor residual spraying, RDTs, and effective anti-malarial drugs.[242,243]

Combination strategies, such as using malaria vaccines alongside seasonal malaria chemoprevention (SMC), have already shown potential for synergistic effects, particularly in high-transmission areas as shown in a recent study by Dicko et al.[84] Operational research can also be critical to understand the best approach for malaria vaccines' deployment within specific epidemiological contexts, to ensure they complement existing interventions and maximize the public health impact of malaria vaccination.[244]

Global Collaboration and Funding

To address malaria challenges, it is essential to stress that collaborative concerted global efforts are needed to ensure that malaria vaccines are successfully developed, manufactured, and distributed.[245,246] International partnerships between governments, research institutions, pharmaceutical companies, and global health organizations (eg, the WHO, Gavi, and the Bill & Melinda Gates Foundation), are examples of the helpful efforts needed to drive progress in malaria prevention through vaccination.[247,248]

Future collaboration would be critical to secure the necessary funding for ongoing research, in order to ensure equitable access to malaria vaccines and to maintain the momentum toward malaria elimination.[249,250] These efforts are recommended to help establish cold chain infrastructure, ensure equitable vaccine delivery, and support community engagement to build public trust in malaria vaccination in the endemic regions.[21,24,204,212,251] Additionally, integrating malaria vaccines into national immunization programs with coordinated international support can be viewed as an important step toward reducing the malaria burden and its eventual elimination.[252–254]

Conclusions

Malaria vaccination has moved from aspiration to reality with the introduction and approval of RTS,S/AS01 and R21/Matrix-M vaccines which are considered two milestones in the protection of young children in high-endemic regions from severe malaria. In addition, the recent phase 2b efficacy data for the RH5.1/Matrix-M vaccine represents another critical development, targeting the erythrocytic stage of *P. falciparum* and filling gaps left by pre-erythrocytic vaccines. While the approved malaria vaccines have limitations in efficacy and require a multi-dose schedule, the approval of these vaccines highlights both the promise and the challenges of malaria vaccination. Next-generation malaria vaccine candidates, including the emerging mRNA-based vaccines, bring renewed hope to the area of malaria control and prevention with the potential for higher efficacy and long-lasting immunity. However, real progress will depend on combining vaccination efforts with proven effective interventions to reduce malaria burden such as vector control and anti-malarial drugs. These measures should be sustained by global collaboration and dedicated funding. So far, the

progress that has been made in malaria vaccination efforts offers valuable insights into the ultimate goal of malaria elimination; however, significant challenges remain and need to be addressed by global collaborative efforts.

Data Sharing Statement

Data supporting this review are available in the reference section. In addition, the analyzed data that were used during the current systematic review are available from the corresponding author on a reasonable request.

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This paper has been uploaded to Preprints.org as a preprint which can be accessed through the following link: https://www.preprints.org/manuscript/202412.1635/v1.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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