



# RTS,S/AS01 vs R21/Matrix-M Malaria Vaccines and Implementation Perspectives in Developing Countries: A Narrative Review

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**Abstract.** Malaria remains a significant public health challenge in Indonesia, particularly in regions like Papua and Nusa Tenggara Timur (NTT). Despite various control efforts, the country continues to struggle with high malaria incidence, highlighting the need for new interventions. The recent WHO approval of malaria vaccines RTS,S/AS01 and R21/Matrix-M offers a potential game-changer in the fight against malaria. This review aims to assess the prospects and challenges of integrating these vaccines into Indonesia's national malaria control strategy, including an in-depth comparison of the two WHO-approved vaccines. A comprehensive search of scientific databases and grey literature was conducted, focusing on studies published between 2015 and 2024. The review included articles, government reports, and WHO documents, analyzing data on vaccine efficacy, safety, and implementation challenges specific to Indonesia's unique epidemiological landscape. The findings indicate that while the high efficacy of these vaccines against *Plasmodium falciparum* (*P. falciparum*) presents a promising opportunity, the presence of other *Plasmodium* species, particularly *P. vivax*, in Indonesia requires further research. Additionally, significant logistical challenges, such as cold chain management and healthcare infrastructure limitations, pose obstacles to widespread vaccine implementation. The conclusion, while the integration of malaria vaccines could significantly advance Indonesia's goal of malaria elimination by 2030, successful implementation will require tailored strategies addressing the country's specific challenges. Future research and pilot studies in Indonesia are essential to evaluate vaccine efficacy in the local context and to develop effective deployment strategies.

**Keywords:** Malaria Vaccines, Indonesia, RTS,S/AS01, R21/Matrix-M, Vaccine Implementation Challenges

## 1. Introduction

Malaria remains a significant public health concern in Indonesia, particularly in certain regions. As of 2022, the country reported around 800,000 malaria cases, making it the second highest in Southeast Asia after India [1]. The Indonesian government aims for malaria elimination by 2030, yet the number of cases has remained relatively stable over recent years. Approximately 130 million Indonesians reside in high-risk areas, although 68.3% of districts were certified free of malaria as of 2022 [2].

Despite successful elimination in many districts, Eastern Indonesia, particularly Papua, West Papua, and NTT, still face high malaria prevalence, emphasizing the need to understand local perceptions and behaviors for effective prevention and treatment [3]. Additionally, studies on malaria treatment-seeking behavior in Indonesia highlight a range of approaches, including self-treatment and traditional medicine, influenced by factors like education level and socioeconomic status [4]. Considering these challenges, the introduction of malaria vaccines in Indonesia holds significant promise. The potency of these vaccines could potentially bolster the country's efforts towards malaria elimination by providing an additional tool to complement existing control measures. Understanding local epidemiological factors and healthcare-seeking behaviors will be crucial for the successful implementation of vaccination programs across diverse regions, including those in Eastern Indonesia where malaria remains a persistent public health concern.

The integration of the WHO-approved malaria vaccine, including RTS,S/AS01 and R21, into Indonesia's national malaria control program holds significant promise. The vaccine has been endorsed by the World Health Organization (WHO) as safe and suitable for incorporation into routine immunization programs and existing malaria control measures [5]. This approval signifies a crucial step in combating malaria, especially in regions like Indonesia with multidrug-resistant malaria and reduced capacities for integrated malaria control management programs [6]. The use of the vaccine as part of a comprehensive malaria control strategy aligns with the WHO's recommendation for utilizing multiple interventions concurrently to achieve the highest impact in malaria control [7].

Given Indonesia's multifaceted challenges in combating malaria, the WHO-approved malaria vaccine offers a crucial opportunity to enhance the national malaria control strategy. The RTS,S/AS01 and R21/Matrix-M™ vaccines have already been implemented in several African countries, demonstrating notable effectiveness and efficacy in reducing malaria incidence and mortality. The RTS,S/AS01 and R21/Matrix-M™ malaria vaccines have shown promising results in reducing disease burden and potentially contributing to herd immunity against malaria. The RTS,S/AS01E vaccine has demonstrated moderate protection against symptomatic disease, with significant vaccine efficacy (VE) against new infections and a reduction in the total number of new infections [8]. On the other hand, the R21/Matrix-M™ vaccine has shown an efficacy of 75% in protecting young children against clinical malaria, leading to WHO's recommendation for its deployment alongside other effective interventions [9].

These results highlight the promising implications of these vaccines for Indonesia. However, these vaccines have not yet been applied in Indonesia, making it essential to explore their prospects and the unique challenges associated with their implementation. This study aims to provide a comprehensive understanding of how these WHO-approved malaria vaccines can be integrated into Indonesia's national malaria control program towards malaria elimination.

## 2. Method

This review utilized a comprehensive literature review methodology to analyze the potential integration of WHO-approved malaria vaccines, RTS,S/AS01 and R21, into Indonesia's national malaria control strategy. The literature search was conducted across multiple scientific databases, including PubMed, Google Scholar, and Scopus, covering publications from 2015 to 2024. Keywords used in the search included "RTS,S malaria vaccine," "R21 malaria vaccine," "Indonesia malaria epidemiology," "Plasmodium," "malaria vaccine implementation," and "vaccine challenges in Indonesia." The review also considered grey literature, including reports from the World Health Organization (WHO), the Indonesian Ministry of Health, and other relevant public health organizations. Data were synthesized to identify key themes and insights related to the effectiveness of the RTS,S/AS01 and R21/Matrix-M vaccines, the specific malaria burden in Indonesia, and the logistical and cultural challenges of implementing a vaccination program in the country. The findings from the literature were critically analyzed to provide recommendations for future research and policy development.

## 3. Malaria in Indonesia

Indonesia is one of the nine malaria-endemic countries in Southeast Asia, accounting for 15.6% of reported cases and 22% of malaria deaths in the region [10]. The highest incidence of malaria is found in eastern Indonesia, particularly in Papua Province, where 86% of all malaria cases in Indonesia occur. Other high-endemic areas include NTT and Papua Barat [11].

Indonesia is home to all five species of human malaria parasites: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi*. *P. falciparum* and *P. vivax* are the most common species causing malaria infections [12]. The national Annual Parasite Incidence (API) value in 2018 was 0.84 per 1000 people, with significant variations across provinces. Papua Province has the highest API value at 52.99 per 1000 people, while NTT Province has an API of 3.42 per 1000 people [13].

The Indonesian government and WHO have implemented various strategies, including early diagnosis and treatment, long-lasting insecticidal nets, indoor residual spraying, and intensive mass drug administration in high-endemic areas [10]. These efforts have led to a significant decrease in malaria cases, with the number of cases decreasing from 1.1 million in 2015 to 659,000 in 2019 [10]. Despite progress, challenges remain, particularly in eastern Indonesia, where high-endemic areas continue to pose significant obstacles to elimination [13].

Despite significant progress in reducing malaria cases, Indonesia faces ongoing challenges in its fight against the disease. The rugged and isolated terrain of eastern Indonesia, particularly in Papua and West Papua Provinces, poses logistical difficulties in delivering healthcare services, including malaria prevention and treatment [14]. The region's diverse and transient population, including migrant workers and indigenous communities, further complicates efforts to achieve universal coverage with interventions like insecticide-treated nets (ITNs) and indoor residual spraying (IRS). Additionally, the emergence of drug-resistant strains of *P. falciparum* and *P. vivax* adds to the complexity of malaria control in these high-endemic areas [6]. Climate change and environmental factors, such as deforestation and changes in land use, have also altered mosquito breeding patterns, potentially increasing the risk of malaria transmission in previously low-endemic regions [15].

Moreover, the COVID-19 pandemic has disrupted malaria control efforts by diverting resources and attention away from ongoing public health campaigns. This disruption has led to delays in the distribution of bed nets, reductions in community-based malaria programs, and challenges in maintaining routine surveillance and case management activities [13]. As Indonesia works toward its goal of malaria elimination by 2030, it must address these multifaceted challenges through a coordinated and sustained approach that includes strengthened surveillance, targeted interventions in high-risk areas, and greater investment in healthcare infrastructure and personnel training (World Health Organization, 2021a). The collaboration between government agencies, international partners, and local communities will be crucial in overcoming these barriers and achieving long-term malaria control and elimination in Indonesia.

#### **4. Method to Prevent and Control Malaria Infections and Their Limitations**

Preventing and controlling malarial infections involves several strategies, each with its own limitations. Firstly, the use of insecticide-treated bed nets (ITNs) is one of the most effective methods, significantly reducing the incidence of malaria by protecting individuals from mosquito bites during sleep [16]. However, the limitation lies in the proper use and maintenance of the nets, as well as the development of insecticide resistance among mosquito populations [17]. Indoor residual spraying (IRS) with in-

secticides is another method that targets mosquitoes resting on walls, but its effectiveness diminishes over time due to the need for repeated applications and the same resistance issues [18]. Environmental management, including eliminating stagnant water where mosquitoes breed, can reduce mosquito populations but is often difficult to sustain over large areas and requires community cooperation [19].

Antimalarial medications, such as chemoprophylaxis, are crucial for travelers and high-risk populations. While anti-malaria drugs have successfully eliminated malarial infections, the emergence of drug resistance poses a challenge, leading to a resurgence of malaria caused by both drug resistance and new malarial species [20]. Quinine, derived from the cinchona tree, was the first antimalarial drug used in the 17th century. Chloroquine, introduced in 1945, became the most widely used synthetic antimalarial drug until the 1960s, when resistance began to emerge. The first case of chloroquine-resistant *P. falciparum* malaria was reported in Thailand in 1957, and this resistance spread rapidly [21]. Alternative drugs such as sulfadoxine-pyrimethamine and mefloquine were introduced, but they too developed resistance. Artemisinin, rediscovered in the 1970s, became widely available in the 1990s and was initially effective but has since shown signs of partial resistance. Contributing to resistance include mass drug administration, lack of regulation, and social and economic conditions [22]. Factors. Current efforts include the use of combination therapies, such as artemisinin-based combination therapies (ACTs), however it growing resistance primarily due to mutations in the *P. falciparum* kelch13 gene, leading to delayed parasite clearance. Initially identified in Southeast Asia, this resistance complicates treatment as it also affects partner drugs used in ACTs. The resistance results in longer symptomatic periods and higher transmission rates [23].

Lastly, the development of malaria vaccines offers hope for long-term control. The most effective way of stopping the transmission of malarial infection is a vaccine that works with optimal efficiency and efficacy, working in a way that starts by inhibiting the initial phase of pathogen growth followed by the prevention of the subsequent stages [24].

## 5. WHO-Approved Malaria Vaccine

### A. *RTS,S/AS01*

The first malaria vaccine approved by the World Health Organization (WHO) is RTS,S/AS01, also known as Mosquirix. It was developed by GlaxoSmithKline, a British pharmaceutical company, and approved in October 2021 [25]. The vaccine targets the *P. falciparum* parasite, which is the most prevalent malaria pathogen [26].

#### 1. *Structure of RTS,S/AS01*

The vaccine's active ingredient, RTS,S, comprises the RTS and S antigens. The RTS antigen includes the central repeat region and T-cell epitopes of the circumsporozoite protein (CSP), a critical surface protein involved in the malaria parasite's ability to infect liver cells, which are fused with the hepatitis B surface antigen (HBsAg) [27]. The S antigen consists of HBsAg alone, produced in yeast cells, forming virus-like particles that enhance the immune response. The RTS,S antigen features recombinant CSP regions (NANP repeat regions and T-cell epitope domain) linked to HBsAg, with

the T-cell epitope domain subdivided into specific epitopes: TH2R, Region II, TH3R, and CS-T3 as seen in Figure 1 [28].

## 2. Mechanism of Action of RTS,S/AS01

RTS,S/AS01 is a monovalent pre-erythrocytic recombinant protein vaccine composed of segments of the *P. falciparum* CSP that are known to elicit both humoral (R region) and cellular (T region) immune responses [32]. These CSP regions are covalently linked to the hepatitis B virus surface antigen (HBsAg). The RTS component, co-expressed with free HBsAg in yeast cells, forms virus-like particles (VLPs), which are used in the vaccine. RTS,S/AS01 is formulated with GlaxoSmithKline's proprietary AS01 adjuvant system, which enhances the immune response by stimulating both humoral and cellular immunity against CSP expressed on the surface of sporozoites - the infectious stage of *P.* transmitted by mosquitoes [33] as seen in Figure 2. In unvaccinated individuals, sporozoites migrate to the liver, where they invade hepatocytes and develop into hepatic merozoites. CSP is expressed during the early liver stages but is not present in liver-stage merozoites. Antibodies against CSP, produced following RTS,S vaccination, immobilize the sporozoites, preventing them from infecting hepatocytes [34]. However, the protective effect of RTS,S against infection and severe disease diminishes over time and is linked to the level of anti-CSP antibodies. The immune response triggered by RTS,S does not affect the ability of plasmodium gametocytes to infect mosquitoes. Therefore, even after vaccination, many children will still carry parasites capable of infecting mosquitoes, meaning that transmission within the population remains unchanged [34].

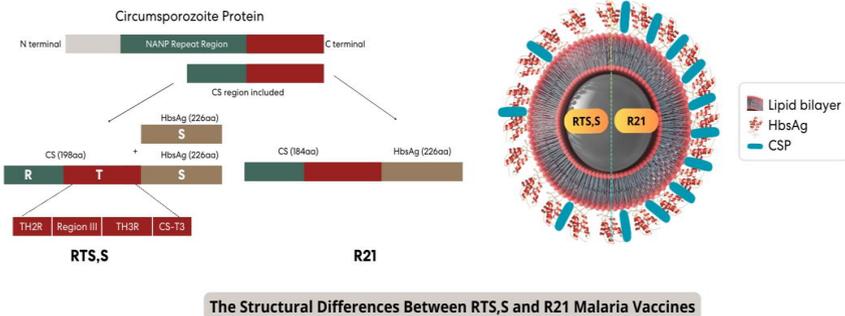


Fig. 1. Illustration of RTS,S and R21 Malaria Vaccine Constructs Based on CSP. The RTS,S antigen features recombinant CSP regions (NANP repeat regions and T-cell epitope domain) linked to HBsAg, with the T-cell epitope domain subdivided into specific epitopes: TH2R, Region II, TH3R, and CS-T3.

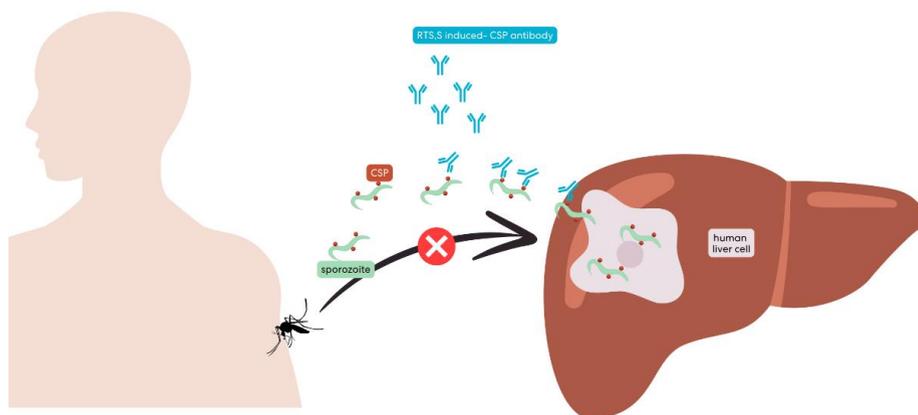


Fig. 2. Mechanism of Action of RTS,S Vaccine in Preventing Malaria Infection. This illustration shows how the RTS,S vaccine induces the production of antibodies against the CSP on the surface of *P. falciparum* sporozoites. These antibodies immobilize the sporozoites, preventing them from infecting liver cells and thereby reducing the risk of malaria infection.

The adjuvant system, AS01, is designed to enhance the body's immune reaction to the RTS,S antigen [29]. AS01 contains Monophosphoryl Lipid A (MPL), a detoxified derivative of lipopolysaccharide (LPS) from *Salmonella minnesota*, and QS-21, a saponin derived from the bark of the *Quillaja saponaria* tree [30]. These components are formulated in liposomes, which are small vesicles made of lipid bilayers. MPL acts as a Toll-like receptor 4 (TLR4) agonist, stimulating innate immune responses, while QS-21 enhances antigen-specific immune responses by boosting antibody production and activating T cells [31].

### 3. Indication and Contraindication of RTS,S/AS01

RTS,S/AS01 received a positive opinion from the European Medicines Agency (EMA) for the active immunization of children aged 6 weeks to 17 months against *P. falciparum* malaria and hepatitis B [35]. However, the use of the vaccine should align with official recommendations that consider the epidemiology of *P. falciparum* malaria in different geographical areas. WHO specifically recommends RTS,S/AS01 for children from 5 months of age living in regions with moderate to high malaria transmission [36].

RTS,S/AS01 is contraindicated in individuals who have hypersensitivity to the active substance or any of the excipients of the vaccine, or who have had a previous allergic reaction to any dose of RTS,S/AS01 or to hepatitis B vaccines. The vaccine should not be administered to those who exhibit such hypersensitivities as it may lead to severe allergic reactions [26].

### 4. Dosage, Preparation, and Storage of RTS,S/AS01

The vaccination schedule consists of four doses: three primary doses administered with a minimum interval of four weeks, followed by a booster dose 12–18 months after the third dose. In areas with high seasonal or perennial malaria transmission with seasonal peaks, an optional five-dose strategy may be considered, including two annual booster doses administered before the peak malaria transmission season [26].

RTS,S/AS01 is supplied as a two-component vaccine consisting of a lyophilized powder (containing the RTS,S antigen) and a liquid suspension (the AS01 adjuvant). These components must be reconstituted before administration. Each vial, after reconstitution, yields two 0.5 mL vaccine doses, with each dose containing 25 µg of the RTS,S antigen, adjuvanted with 25 µg of 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and 25 µg of Quillaja saponaria Molina fraction 21 (QS-21) [37].

The vaccine must be stored in its original packaging to protect it from light, at temperatures between 2°C and 8°C (36°F and 46°F), and should not be frozen. The shelf life of RTS,S/AS01 is three years. After reconstitution, the vaccine should ideally be used immediately, although it has been shown to remain chemically and physically stable for up to 6 hours at 25°C. If not used immediately, the reconstituted vaccine should be stored in a refrigerator (2°–8°C) for no longer than 6 hours [26].

### **5. Efficacy of RTS,S/AS01 Against Malaria**

RTS,S/AS01 demonstrated vaccine efficacy in several phase 2 and 3 clinical trials. A pivotal phase 3 trial (NCT00866619) conducted in more than 15,000 infants and children across 11 centers in seven sub-Saharan African countries revealed that RTS,S/AS01 provided 31.1% efficacy in infants (6–12 weeks) and 55.8% efficacy in children (5–17 months) against the first and only episode of clinical malaria over 12 months after the third dose [38]. However, vaccine efficacy was lower in infants compared to older children, leading to WHO's recommendation to use the vaccine starting at 5 months of age [39]. The vaccine efficacy in children remained positive over time, though it declined without a booster dose. A booster dose at 20 months provided additional protection, with vaccine efficacy partially retained up to 46 months after the third dose. In areas with high malaria incidence, the RTS,S/AS01 vaccine was able to prevent thousands of clinical malaria cases per 1000 children over the study period [40].

Another trial focused on seasonal malaria vaccination in the Sahel regions of Africa demonstrated that RTS,S/AS01, when combined with seasonal malaria chemoprevention (SMC), provided superior protection compared to either intervention alone. The combined approach showed over 59% efficacy in preventing uncomplicated clinical malaria over three years [41].

### **6. Safety and Tolerability Profile of RTS,S/AS01**

RTS,S/AS01 has been shown to have an acceptable safety and tolerability profile in clinical trials [42]. Common adverse events (AEs) occurring within 7 days post-vaccination include fever (27%), irritability (14%), and injection site reactions such as pain (16%) and swelling (7%) [26]. Serious adverse events, such as febrile convulsions and meningitis, were reported, but these events were rare, and a causal relationship with the vaccine has not been established [43]. The safety profile of RTS,S/AS01 was generally consistent across different subgroups, including HIV-infected children and malnourished children. The vaccine was also safe when co-administered with other routine childhood vaccines [44].

Notably, the incidence of febrile convulsions was slightly higher following the booster dose, and meningitis cases were reported more frequently in the RTS,S/AS01 group than in the control group. However, these findings were not observed in other trials or large-scale pilot implementations, suggesting that they may have been chance occurrences rather than direct vaccine effects [5].

### 7. Immunogenicity of RTS,S/AS01

RTS,S/AS01 is highly immunogenic, inducing strong anti-CSP antibody responses and CSP-specific CD4+ T-cell responses [45]. These immune responses are believed to be critical in preventing malaria by neutralizing sporozoites and limiting liver infection [46]. Although a definitive threshold for protective antibody levels has not been established, a model suggests that an anti-CSP antibody titre level of 121 EU/mL could prevent 50% of malaria infections [47]. The vaccine elicits stronger immune responses in older children compared to infants, and these responses tend to wane over time, though they are significantly boosted by additional doses [26]. In preterm and malnourished infants, as well as HIV-infected children, RTS,S/AS01 remains immunogenic, although the magnitude of the response may vary slightly compared to healthy, full-term infants. Regular booster doses, particularly before malaria transmission seasons, help maintain high levels of protective immunity [43].

### 8. Public Health and Cost Implications of RTS,S/AS01

The introduction of RTS,S/AS01 is expected to have significant public health benefits, particularly in high-transmission areas in Africa [48]. Modeling studies predict that widespread use of RTS,S/AS01 could avert millions of cases of clinical malaria and thousands of malaria-related deaths over a 15-year period [49]. The vaccine is considered cost-effective, especially when administered to children aged 5–17 months. At an estimated cost of \$5 per dose, the vaccine's incremental cost-effectiveness ratio per disability-adjusted life year (DALY) averted is approximately \$200, making it a financially viable option for malaria control in resource-limited settings [50].

### 9. Current Clinical Position of RTS,S/AS01

RTS,S/AS01 is currently the only malaria vaccine approved by WHO and is being deployed in several African countries as part of a large-scale pilot implementation program [8]. The vaccine is recommended by WHO for use in children aged 5–17 months living in regions with moderate to high malaria transmission [37]. It should be integrated into existing malaria control strategies, which include the use of insecticide-treated bed nets and antimalarial treatments. Final results from the ongoing pilot studies are eagerly awaited, and additional research will continue to assess the vaccine's long-term efficacy, safety, and impact in real-world settings. Table 1 summarizing the timeline of the development path for RTS,S/AS01. This table outlines the major milestones in the development and implementation of the RTS,S/AS01 vaccine, from its inception to its current status in clinical use.

Table I. Timeline of RTS,S/AS01 Malaria Vaccine Development

Year	Event
1987	<b>Initiation of RTS,S Development:</b> The development of the RTS,S vaccine began as a collaboration between GlaxoSmithKline (GSK) and the Walter Reed Army Institute of Research (WRAIR).
1992	<b>Preclinical Studies:</b> Early preclinical studies in animal models showed promise, leading to further development and testing.
1997	<b>Phase 1 Clinical Trials:</b> The first human trials (Phase 1) were conducted to assess the safety, immunogenicity, and dosage of RTS,S in a small group of volunteers.
2001	<b>Phase 2 Clinical Trials:</b> Phase 2 trials were expanded to include more participants, primarily in malaria-endemic regions, to evaluate safety and preliminary efficacy.

Year	Event
2004	<b>RTS,S/AS01 Developed:</b> The AS01 adjuvant system was incorporated into the RTS,S vaccine to enhance its efficacy, leading to the formulation of RTS,S/AS01.
2009-2014	<b>Phase 3 Clinical Trials:</b> Large-scale Phase 3 trials were conducted across several African countries, involving over 15,000 children, to assess the vaccine's efficacy and safety in preventing malaria.
2015	<b>Positive EMA Opinion:</b> The European Medicines Agency (EMA) issued a positive scientific opinion on RTS,S/AS01, endorsing its use in children in malaria-endemic regions.
2016	<b>WHO Recommendation for Pilot Implementation:</b> WHO recommended large-scale pilot implementations of RTS,S/AS01 in selected African countries to further evaluate its impact and feasibility.
2019	<b>Pilot Implementation Launch:</b> The Malaria Vaccine Implementation Programme (MVIP) was launched in Ghana, Kenya, and Malawi, with the aim of vaccinating over 800,000 children.
2021	<b>WHO Approval:</b> RTS,S/AS01 received WHO approval, becoming the first malaria vaccine recommended for broad use among children in regions with moderate to high malaria transmission.
2022-2024	<b>Ongoing Pilot Studies and Rollout:</b> Continued monitoring and analysis of the RTS,S/AS01 rollout in African countries to assess long-term efficacy, safety, and impact on malaria transmission.

## B. R21/Matrix-M

In response to the need for a more effective vaccine, the WHO recently approved a second vaccine, R21/Matrix-M [9]. The R21 malaria vaccine, developed by the University of Oxford in collaboration with the Serum Institute of India [51].

### 1. Structure of R21/Matrix-M

The R21 vaccine features a high-dose formulation of CSP, which is produced in yeast cells and forms virus-like particles [52]. These particles are combined with the Matrix-M adjuvant as seen in Figure 1, a saponin-based substance that boosts the immune system's response to the vaccine [51]. The CSP used in R21 includes the central repeat region (NANP repeats) and several T-cell epitopes crucial for inducing a robust immune response against the malaria parasite. The vaccine's formulation aims to generate a stronger and more sustained immune response compared to previous vaccines, potentially providing higher efficacy and longer-lasting protection against malaria [46].

The Matrix-M adjuvant is a saponin-based adjuvant derived from the *Quillaja saponaria* tree [53]. It is formulated into nanoparticles that enhance antigen presentation, leading to stronger and more durable immune responses [54]. Matrix-M contains 50 µg of the saponin-based adjuvant per dose, which is divided into two fractions: 25 µg of Matrix A and 25 µg of Matrix C [53].

### 2. Mechanism of Action of R21/Matrix-M

The mechanism of action for R21/Matrix-M is similar to that of RTS,S, as both vaccines primarily target the CSP of *P. falciparum* [55]. Upon administration, R21/Matrix-M triggers the immune system to produce antibodies specifically targeting CSP. These antibodies play a critical role in preventing the malaria parasite from invading liver cells [56]. The Matrix-M adjuvant further enhances this immune response by promoting the activation of T-cells and increasing cytokine production, which are vital for coordinating the body's defense mechanisms against the parasite [53].

The CSP-specific antibodies generated by the vaccine bind to sporozoites circulating in the bloodstream, effectively neutralizing them and preventing them from

reaching the liver, where they would normally initiate infection [57]. By blocking sporozoites from entering hepatocytes, R21/Matrix-M interrupts the malaria parasite's lifecycle at an early stage, stopping it before it can mature into the merozoite stage, which is responsible for causing the symptoms of malaria [58].

### **3. *Indication and Contraindication of R21/Matrix-M***

The R21/Matrix-M malaria vaccine has shown high efficacy in protecting young children against clinical malaria in various epidemiological settings. Clinical indications for administering this vaccine include providing a four-dose regimen to children aged above 5 months, with a booster dose given 12 months after the third dose [59].

Based on the latest WHO documentation regarding the R21/Matrix-M malaria vaccine, the contraindications for this vaccine are similar to those for other vaccines. The vaccine should not be administered to individuals with known hypersensitivity to any of its components. This includes the CSP antigen, the Matrix-M adjuvant, or any other excipients used in the vaccine formulation. Additionally, individuals who have experienced a severe allergic reaction (e.g., anaphylaxis) after a previous dose of R21/Matrix-M or any vaccine containing similar components, such as the hepatitis B surface antigen, should avoid this vaccine [60].

### **4. *Dosage, Preparation, and Storage of R21/Matrix-M***

Three doses, each of 5 mcg R21 and 50 mcg Matrix-M1 should be given at monthly intervals. A fourth dose is recommended 12 months after the third dose. Administration of the vaccine is by intramuscular injection. The anterolateral thigh is the preferred site for injection in children below 24 months age, while deltoid muscle is the preferred site for injection in children above 24 months of age. However, vaccine can be administered in anterolateral thigh intramuscularly in children above 24 months of age, if there is no sufficient bulk of muscle at deltoid site [44], [59].

The vaccine is provided as a lyophilized powder that must be reconstituted with the accompanying adjuvant suspension before use. After reconstitution, each vial delivers two 0.5 mL doses [59]. The vaccine should be stored at 2°C to 8°C (36°F to 46°F) and protected from light. It should not be frozen. The reconstituted vaccine should be used within 6 hours if kept at 2°–8°C, and any unused portions should be discarded after this time [61].

### **5. *Efficacy of R21/Matrix-M Against Malaria***

R21/Matrix-M has shown promising efficacy in clinical trials. In a study involving 450 children aged 5 to 17 months in Burkina Faso, R21/Matrix-M demonstrated an efficacy of 77% against clinical malaria over 12 months when administered with a high-dose Matrix-M adjuvant. This trial was conducted during a period of high malaria transmission and showed that the vaccine's efficacy remained above the WHO-specified target of 75% for a malaria vaccine. The trial also reported that the efficacy was sustained at 71% with a booster dose at 12 months [62]. Ongoing Phase 3 trials are being conducted across several African countries, involving over 4,800 children. Preliminary data suggests that the vaccine maintains an efficacy of over 70% in preventing clinical malaria, with significant reductions in both symptomatic and severe malaria cases [59].

### **6. *Safety and Tolerability Profile of R21/Matrix-M***

R21/Matrix-M has demonstrated an acceptable safety profile. The most frequently reported adverse events include local reactions at the injection site (pain, redness, and

swelling), systemic reactions like fever, fatigue, and headaches. These symptoms are typically mild to moderate and resolve within a few days [63].

The ongoing Phase 3 trial of the R21/Matrix-M vaccine has not identified any major safety concerns that would delay its recommendation for public health use. The most notable adverse event of special interest was febrile convulsions occurring within three days post-vaccination, with five cases reported in the R21/Matrix-M group and one in the control group, equating to an attributable risk of approximately 1 per 2,800 doses. All affected children recovered without any long-term effects. Although there was an observed imbalance in the number of deaths between the vaccine and control groups, the numbers were small and not statistically significant, with no pattern linking the deaths to the timing of vaccination. Additionally, meningitis and cerebral malaria, which were also monitored as adverse events of special interest, were uncommon and showed no imbalance between the vaccine and control groups. It's important to note that febrile convulsions are a known risk with other childhood vaccines, including RTS,S/AS01 and the measles vaccine, with similar attributable risks [60].

#### **7. Immunogenicity of R21/Matrix-M**

This vaccine induces high levels of anti-CSP antibodies, with geometric mean titers (GMTs) significantly higher than those seen with RTS,S. In Phase 2 trials, anti-CSP antibody titers remained elevated even 12 months after the primary vaccination series, particularly with the high-dose Matrix-M formulation. Matrix-M has been shown to enhance the activation of both CD4+ and CD8+ T-cells. This cellular response is crucial for long-term immunity and provides an additional layer of protection by helping to clear any parasites that evade initial antibody neutralization. The booster dose administered 12 months after the primary series has been shown to sustain high levels of antibodies, suggesting that R21/Matrix-M may offer more durable protection compared to earlier malaria vaccines [64].

#### **8. Public Health and Cost Implication of R21/Matrix-M**

The introduction of the R21/Matrix-M malaria vaccine into public health systems will require significant resources for both vaccine procurement and the integration of this new vaccine into existing health services. Fortunately, the infrastructure used for current childhood vaccinations can be leveraged, potentially reducing additional costs and complexity. Support from immunization and malaria funding agencies may be available to assist certain countries in implementing the vaccine [65].

Cost-effectiveness modeling for the R21/Matrix-M vaccine has assumed a price of approximately \$3 per dose, with a range between \$2 and \$4. The costs associated with delivering the R21/Matrix-M vaccine are expected to be comparable to those of the RTS,S/AS01 vaccine, given the similarity in their delivery strategies. Previous studies have shown that the non-vaccine financial cost per dose of RTS,S/AS01 in pilot countries ranges from \$1.04 to \$2.46, depending on the country and delivery strategy. The economic costs, which include all associated expenses, range from \$1.52 to \$4.62 per dose [60].

#### **9. Current Clinical Position of R21/Matrix-M**

R21/Matrix-M is positioned as a critical tool in the global fight against malaria. It is seen as a next-generation vaccine that could surpass RTS,S/AS01 in both efficacy and durability of protection. With WHO approval and ongoing large-scale trials,

R21/Matrix-M is expected to become a cornerstone of malaria prevention strategies in endemic regions.

To better understand the key differences and similarities between the two WHO-approved malaria vaccines, RTS,S/AS01 (Mosquirix) and R21/Matrix-M, it's helpful to compare them across several critical aspects such as structure, mechanism of action, efficacy, safety, and public health implications. The following table provides a detailed comparison based on the latest available information and research findings:

Table II. Timeline R21/Matrix Malaria Vaccine Development

Year	Event
2014	<b>Initiation of R21 Development:</b> Development of the R21 antigen begins, utilizing advances from RTS,S research.
2017	<b>Preclinical Studies:</b> Early preclinical studies in animal models show high levels of protection, prompting further development.
2019	<b>Phase 1 Clinical Trials:</b> Initial human trials are conducted to assess the safety and immunogenicity of R21/Matrix-M in a small cohort of volunteers.
2020	<b>Phase 2b Trials:</b> A Phase 2b trial in Burkina Faso demonstrates up to 77% efficacy in children, significantly higher than the RTS,S vaccine.
2021	<b>Positive Results and WHO Consideration:</b> Positive trial results lead to increased interest and consideration by WHO for approval.
2021-2024	<b>Phase 3 Clinical Trials:</b> Large-scale Phase 3 trials are conducted in several African countries involving over 4,800 children to confirm efficacy, safety, and tolerability.
2023	<b>WHO Approval:</b> R21/Matrix-M receives WHO approval, becoming the second malaria vaccine endorsed for use in endemic regions, with plans for broader implementation.
2024 and Beyond	<b>Expanded Rollout and Surveillance:</b> Ongoing monitoring and expanded use of R21/Matrix-M in malaria-endemic countries, with further studies planned to confirm long-term efficacy and safety.

Table III. Comparison of WHO-Approved Malaria Vaccines: RTS,S/AS01 vs. R21/Matrix-M

Feature	RTS,S/AS01	R21/Matrix-M
<b>Developer</b>	GlaxoSmithKline (GSK)	University of Oxford and Serum Institute of India
<b>WHO Approval Date</b>	October 2021 [25]	December 2023 [9]
<b>Target Pathogen</b>	<i>P. falciparum</i>	<i>P. falciparum</i>
<b>Antigen Structure</b>	Combines CSP with HBsAg to form RTS,S antigen; adjuvanted with AS01 [29]	Higher proportion of CSP; formulated with Matrix-M adjuvant [53]
<b>Adjuvant</b>	AS01, containing Monophosphoryl Lipid A (MPL) and QS-21 [26]	Matrix-M, a saponin-based adjuvant [53]
<b>Mechanism of Action</b>	Induces antibodies against CSP, preventing liver infection and neutralizing sporozoites [32]	Similar to RTS,S, targeting CSP and enhancing T-cell response [55]
<b>Indication</b>	For children aged 6 weeks to 17 months, particularly in regions with high malaria transmission [36]	For children aged 5 months and older, with a four-dose regimen [59]
<b>Contraindications</b>	Hypersensitivity to any component, including HBsAg [26]	Hypersensitivity to any component, including CSP or Matrix-M [60]
<b>Dosage</b>	Four doses, with a possible fifth in areas with high transmission [26]	Four doses, with a booster after 12 months [59]
<b>Storage</b>	2°C to 8°C; should not be frozen [37]	2°C to 8°C; should not be frozen [61]

Feature	RTS,S/AS01	R21/Matrix-M
<b>Efficacy</b>	31.1% in infants (6-12 weeks); 55.8% in children (5-17 months) [38]	77% efficacy in children (5-17 months) over 12 months [62]
<b>Safety and Tolerability</b>	Common AEs include fever, irritability, pain at injection site [26]	Similar safety profile; febrile convulsions were most notable AESI [60]
<b>Immunogenicity</b>	High anti-CSP antibodies; response boosts with additional doses [45]	Higher antibody titers compared to RTS,S; strong T-cell activation [64]
<b>Public Health and Cost Implications</b>	Cost-effective at \$5 per dose; significant impact in high-transmission areas [50]	Estimated \$3 per dose; similar delivery costs to RTS,S [65]

## 6. Challenges in Implementing the Malaria Vaccine

Implementing a malaria vaccination program in Indonesia presents a range of significant challenges due to the country's diverse geography, healthcare infrastructure, and cultural landscape. Indonesia's vast archipelago, which consists of over 17,000 islands, poses substantial logistical difficulties for vaccine distribution, especially in remote regions such as Papua, West Papua, and the Maluku Islands [66]. These areas are not only geographically isolated but also lack the infrastructure necessary to maintain the cold chain required for vaccine efficacy. This geographical diversity results in uneven vaccination coverage across the country, particularly in regions that are hard to reach [67].

A study conducted by Ristanasari and Adisasmito (2023) in Lampung, Indonesia, focused on the challenges of cold chain management in Indonesia during the distribution of COVID-19 vaccine. The study identified significant obstacles in cold chain management, including a lack of adequate infrastructure and human resources, as well as logistical challenges related to transportation and storage in remote areas. These challenges led to difficulties in maintaining the required temperature for the COVID-19 vaccine, potentially compromising its efficacy. Additionally, the study highlighted that low coverage of the third dose of the vaccine was partly due to these logistical and infrastructural barriers, which are similar to those expected in the distribution of other vaccines, including potential malaria vaccines, in Indonesia's diverse geographical landscape [68].

Another study conducted in Jember, Indonesia evaluated the effectiveness of the immunization program and identified challenges in cold chain management for vaccines. Based on the result that cold chain management evaluation, the knowledge officer on cold chain management is still lacking good. In the some primary health care, it is known that the equipment constraints are unavailable. While in the conformity of temperature only one primary health care is not recommended. And storage activities are mostly in accordance with regulation [69].

The challenges of cold chain management and vaccine distribution observed in Jember and Lampung, both located relatively close to Indonesia's capital, Jakarta (approximately 850 kilometers from Jakarta to Jember and about 300 kilometers from Jakarta to Lampung), highlight significant concerns for implementing a malaria vaccination program in more remote, malaria-endemic regions of Indonesia. If areas like Jember and Lampung, which are relatively accessible, face substantial difficulties in maintaining the cold chain and ensuring vaccine efficacy, these issues are likely to be even

more pronounced in far-flung, geographically isolated regions such as Papua, West Papua, and the Maluku Islands, which are thousands of kilometers away from the capital (Papua and West Papua are approximately 3,500 to 4,000 kilometers away from Jakarta). The logistical complexities, combined with inadequate infrastructure and human resource shortages, could severely hamper the successful implementation of a malaria vaccination program in these high-risk, remote regions, emphasizing the need for targeted interventions to address these barriers before such a program can be effectively rolled out across Indonesia.

Healthcare infrastructure in Indonesia, especially in rural and remote areas, is often under-resourced and understaffed [70]. Effective implementation of malaria vaccines also requires robust monitoring and surveillance systems to track vaccine coverage, assess its effectiveness, and detect any vaccine-resistant strains of *P.* However, Indonesia's current surveillance infrastructure and healthcare worker is unevenly distributed, with significant gaps in data collection, particularly in remote areas. Improving this is essential to ensuring the long-term success of the malaria vaccination program. Moreover, monitoring adverse events following immunization, such as febrile convulsions, is critical, especially in areas with limited healthcare facilities where prompt response may be challenging [71]. For instance, the ratio of healthcare workers to the population in Papua is significantly lower than the national average as seen in Table 4, which limits the ability to carry out widespread vaccination campaigns and to provide adequate post-vaccination care. Human resources for health in Indonesia have also grown in the last two decades, with increases in health worker to population ratios. However, the ratio of physician to population is still lower than the WHO-recommended figure, and ongoing geographical disparities exist [72].

The Table 4 illustrates significant disparities in the distribution of healthcare resources across Indonesia, particularly highlighting the challenges faced by the Maluku-NTT-Papua region. Java-Bali, which accounts for 36.7% of the population, benefits from 57.4% of the country's total doctors, resulting in a relatively favorable doctor-to-population ratio of 0.39 doctors per 1,000 people. In contrast, the Maluku-NTT-Papua region, which covers 41.4% of Indonesia's land mass and has 4.6% of the population, only has 4.6% of the total doctors. This region has the lowest doctor-to-population ratio, with just 0.03 doctors per 1,000 people, far below the national average of 0.25. The disparity is even more stark when considering specialized doctors, where the Maluku-NTT-Papua region has only 0.01 specialized doctors per 1,000 people, compared to 0.20 in Java-Bali [72]. These figures highlight the severe shortage of medical professionals in the Maluku-NTT-Papua region, which significantly hampers the ability to provide adequate healthcare services, including vaccination campaigns. This shortage underscores the critical challenges in maintaining healthcare initiatives, such as cold chain management for vaccines, in these under-resourced and geographically isolated areas.

In terms of health development, the Papua region lags significantly behind other parts of Indonesia. This disparity is highlighted by the Public Health Development Index (PHDI), which includes indicators such as child health, reproductive health, healthcare services, health behaviors, as well as the prevalence of infectious and non-communicable diseases, and environmental health [73]. According to the 2018 PHDI report by the Research and Development Agency of the Ministry of Health, Papua and West Papua provinces rank the lowest among the 34 provinces in Indonesia, with West

Papua ranked 33rd and Papua 34th. Over a five-year period from 2013 to 2018, there was no improvement in the PHDI ranking for the Papua region. The persistently low PHDI in Papua signals the need for the Indonesian government to prioritize and enhance health development in this region. A critical aspect of health development is ensuring that the Papuan population has adequate access to healthcare services, which is a fundamental right of every citizen. To achieve equitable access to health services across the country, it is essential to implement a national social health insurance system that guarantees comprehensive healthcare access for all citizens, regardless of their economic status, race, location, or religion [73].

Cultural beliefs and practices in certain parts of Indonesia contribute to vaccine hesitancy, particularly in indigenous communities where there is a preference for traditional medicine over modern healthcare interventions [74]. Public awareness about malaria vaccines is also generally low, which underscores the need for comprehensive public health education to improve understanding of the vaccine's benefits and to increase acceptance rates [75]. Vaccine hesitancy during the COVID-19 pandemic in Indonesia has been significantly influenced by cultural beliefs and practices, particularly in communities where traditional medicine is preferred over modern healthcare interventions [76]. For instance, in several regions, there was a strong reliance on herbal remedies and traditional healers, which led to skepticism and resistance toward the COVID-19 vaccine, despite widespread government campaigns [77]. This cultural preference for traditional practices has also been observed in other government vaccination programs, such as the national immunization campaigns for diseases like measles [78]. These programs have encountered similar obstacles, where communities, particularly in rural and indigenous areas, were reluctant to participate due to deep-rooted beliefs that favor traditional medicine over vaccines [74]. The persistent influence of cultural beliefs on vaccine acceptance, seen in both routine vaccination programs and emergency responses like the COVID-19 pandemic, underscores a significant challenge in achieving widespread immunization coverage in Indonesia. This consistent pattern of resistance highlights the need for culturally sensitive public health strategies that can effectively address and integrate these beliefs, ensuring that both regular and emergency vaccination efforts can overcome such obstacles and achieve their public health goals.

Financial constraints are another major challenge [79]. Implementing a nationwide malaria vaccination program would require substantial financial resources, with an estimated cost of around \$3 per dose for the R21/Matrix-M vaccine, not including the additional costs associated with delivery and administration in remote areas [61]. Funding for such a program is often limited due to competing public health priorities, and securing sustained financial support from both national and international sources is crucial for the program's success. The cost of delivering the vaccine in remote areas is expected to be higher due to logistical difficulties [80].

Lastly, the successful implementation of a national malaria vaccination program requires strong political commitment and effective coordination across various levels of government. Indonesia's decentralized healthcare system can sometimes lead to inconsistencies in policy implementation, with varying levels of support at the local level. Strengthening collaboration between national and local governments and ensuring alignment with national health policies will be key to overcoming these administrative challenges and achieving the program's objectives.

Table IV. Distribution of Doctors in Indonesia by Geographical Areas [72]

Regions	Doc-tors	% of to-tal	% Popu-lation	% Land mass	Doctors to 1000 population ratio	Specialized doctors to 1000 population ratio
Sumatra	24,595	24.2%	13.6%	24.6%	0.44	0.19
Java-Bali	58,283	57.4%	36.7%	6.9%	0.39	0.20
Kalimantan	5,726	5.6%	3.8%	27.9%	0.37	0.13
Sulawesi	8,302	8.2%	4.6%	11.8%	0.44	0.19
Maluku-NTT-Papua	4,709	4.6%	41.4%	28.8%	0.03	0.01
<b>Total</b>	<b>101,615</b>	<b>100%</b>	<b>100%</b>	<b>100%</b>	<b>0.25</b>	<b>0.12</b>

## 7. Future Prospects of the Malaria Vaccine

While the WHO currently prioritizes Africa for the rollout of the RTS,S/AS01 and R21/Matrix-M malaria vaccines due to the continent's disproportionate burden of the disease [38], there's hope for endemic countries like Indonesia. The high efficacy of these vaccines against the dominant *P. falciparum* strain in Africa makes them a powerful tool [59]. However, the presence of other *P.* species in Indonesia, particularly *P. vivax*, necessitates further research to determine their effectiveness in the region. Indonesia is home to all four species of human malaria parasites, with *P. falciparum* and *P. vivax* being the most common [1]. The distinct epidemiological landscape in Indonesia, where *P. vivax* plays a significant role, requires tailored research to assess how well these vaccines can address the country's specific needs.

Currently, there have been no clinical trials or research conducted on the RTS,S/AS01 or R21/Matrix-M malaria vaccines in Indonesia. This absence of data highlights a significant opportunity for future research and development. Indonesia, with its significant malaria burden and unique parasite landscape, could be an ideal candidate for expanded access programs or large-scale clinical trials. These programs would allow researchers to gather data on the vaccines' efficacy against the prevalent plasmodium strains in the region. Positive results could pave the way for wider use of the vaccines in Indonesia and other Southeast Asian countries facing similar challenges. The success of Indonesia's existing malaria control efforts, which have significantly reduced the number of malaria cases over the past decade, can be leveraged alongside these vaccine trials, potentially leading to a more comprehensive approach to malaria prevention in the region.

Moreover, the integration of malaria vaccination into Indonesia's national malaria control strategy could accelerate progress toward the country's goal of malaria elimination by 2030. By contributing to global malaria vaccine research, Indonesia could not only enhance its own public health efforts but also provide valuable insights that could benefit other endemic regions with similar malaria profiles. This collaborative approach would ensure that the global fight against malaria becomes more inclusive and effective, particularly in addressing the needs of diverse malaria-endemic regions like South-east Asia.

## 8. Conclusion

The introduction of WHO-approved malaria vaccines, RTS,S/AS01 and R21, offers a promising avenue for Indonesia to bolster its malaria control efforts, potentially accelerating the country's progress toward its goal of malaria elimination by 2030. However, the effectiveness of these vaccines in Indonesia, where *P. vivax* is prevalent alongside *P. falciparum*, remains uncertain and requires further research. Currently, there have been no clinical trials or research conducted on these vaccines within Indonesia, highlighting a significant opportunity for future studies tailored to the country's unique epidemiological landscape.

## 9. Conflict of Interest

The author(s) declared no conflict of interest.

## 10. Acknowledgment

None declared

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