

Potential of Malaria Vaccine in Eliminating Malaria: a Systematic Literature Review

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ABSTRACT

Introduction: Malaria vaccines show significant potential for disease control but face challenges, including declining efficacy over time and resistance to drugs and insecticides. Despite the initial success of vaccines like RTS,S/AS01, an integrated approach is still needed to address malaria's complex transmission dynamics across endemic regions. This review examines the current status, challenges, and future prospects of malaria vaccine development, focusing on the impact of combining pre-erythrocytic vaccines and transmission-blocking drugs using mathematical modeling to enhance their effectiveness in reducing transmission.

Methods: A systematic literature review was conducted using the PICO framework to evaluate the effectiveness of malaria vaccines in reducing disease transmission. The review included studies involving vulnerable populations, particularly children in African countries. It compared the effectiveness of malaria vaccines with other control strategies, such as insecticide-treated bed nets and antimalarial drugs. Five relevant primary journals were analyzed using databases like PubMed, Scopus, and Google Scholar.

Results: Findings reveal that newly developed malaria vaccines have significant potential to reduce malaria cases. However, large-scale implementation and regular vaccination strategies are required for sustained effectiveness. Genetic studies highlight the emergence of resistance, emphasizing the need for adaptable vaccines and strategies.

Conclusion: Malaria vaccines, while promising, face obstacles such as waning efficacy and resistance. A combined strategy involving vaccines and transmission-blocking treatments is essential for global malaria elimination. Further research and strategic implementation are needed to optimize vaccine effectiveness and overcome these challenges.



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INTRODUCTION

Malaria is an infectious disease transmitted by mosquito vectors. Despite significant advancements in controlling the disease, major challenges remain in the global eradication of malaria. Artemisinin-based combination therapy (ACT) has marked substantial progress in malaria treatment. However, clinical resistance to artemisinin and its derivatives hinders therapy effectiveness and complicates eradication efforts (Handari et al., 2022). Vaccination is often the most effective method for controlling infections of various other diseases. However, malaria poses unique challenges due to the constant polymorphism in the biology of Plasmodium species, which causes the disease (Malino et al., 2023). This variability complicates the identification of suitable vaccine candidates among the thousands of Plasmodium antigens. Currently, no malaria vaccine

has been fully approved and licensed.

Over the years, various interventions have been introduced to control the spread of malaria, including vector control through fumigation, larvicides, and insecticide-treated bed nets. In addition to vector control efforts, malaria prevention involves developing new vaccines to prevent new infections in human populations (White et al., 2015). Malaria vaccines are categorized into three main types: pre-erythrocytic vaccines, blood-stage vaccines, and transmission-blocking vaccines (Greenwood et al., 2017). Pre-erythrocytic vaccines are designed to eliminate sporozoites immediately after mosquitoes inject *Plasmodium* into the human body and to prevent *Plasmodium* from entering the human liver. RTS,S/AS01 is one such pre-erythrocytic vaccine recommended by the WHO to combat *P. falciparum* in children. Blood-stage vaccines target the asexual stage of *Plasmodium* within human red blood cells, while transmission-blocking vaccines aim to prevent further infections (Satyarsa et al., 2020).

Recent advancements in malaria vaccine development have spurred new optimism with the emergence of the R21/Matrix-M vaccine, which received WHO approval in 2023. This vaccine, an improved version of RTS,S/AS01, offers higher efficacy and lower production costs, enabling broader access in malaria-endemic countries. Moreover, ongoing research continues to develop pre-erythrocytic vaccines to enhance resistance to infection and integrates strategies with transmission-blocking vaccines to curb further spread through mosquitoes. This combination-based approach is expected to reduce malaria cases and address the growing challenge of resistance.

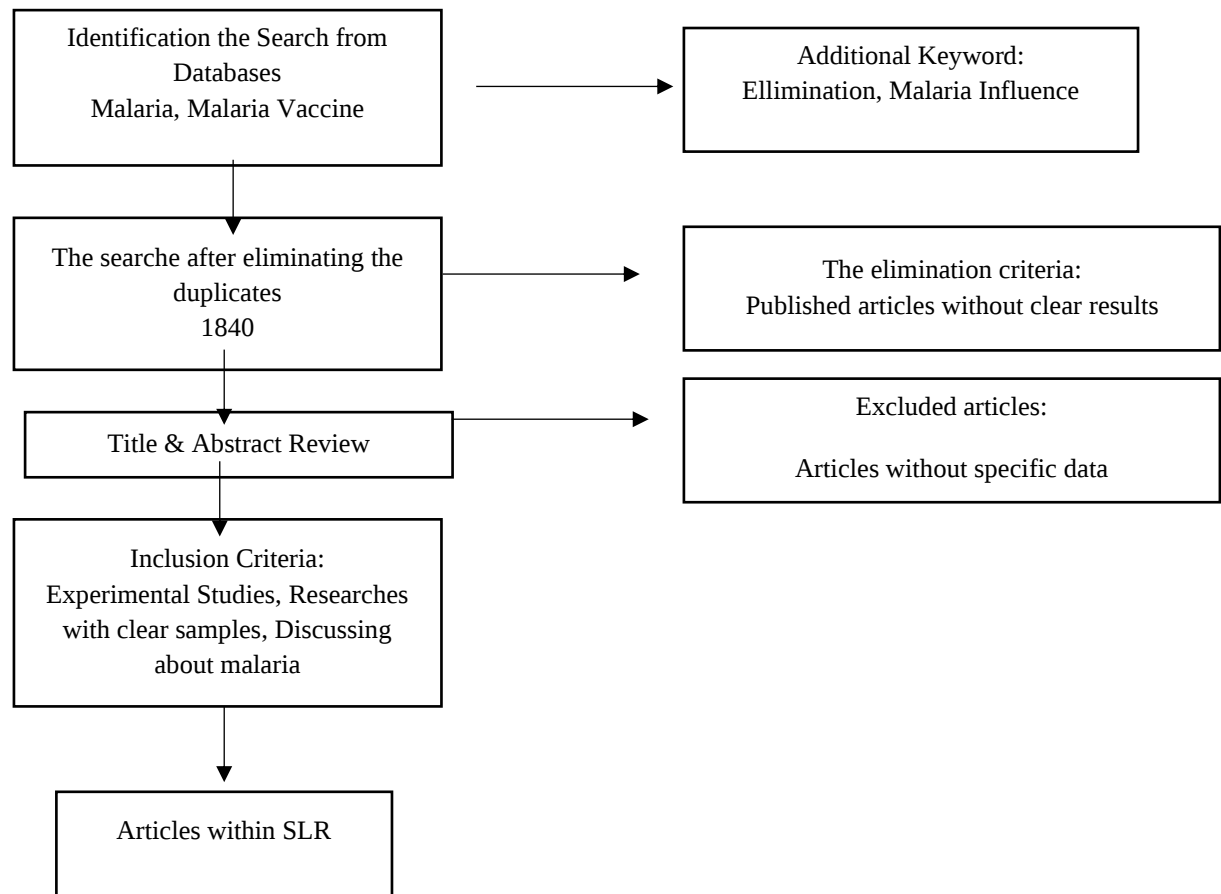
Previous studies have demonstrated that malaria vaccines like RTS,S/AS01 initially show promising efficacy in reducing malaria cases, particularly in children in endemic regions (World Health Organization, 2021). However, their effectiveness tends to decline over time, and challenges such as resistance to antimalarial drugs and insecticides continue to impede disease control efforts (Phillips et al., 2020). Additionally, approaches relying on a single type of vaccine are often insufficient to tackle the complexity of malaria's transmission dynamics, particularly in highly endemic countries (Duffy et al., 2022).

This review examines the current status, explores innovations, and assesses the potential of combining pre-erythrocytic and transmission-blocking vaccines. The study seeks to provide a scientific foundation for developing more comprehensive and sustainable strategies for malaria control. This review aims to investigate the current status, barriers, and prospective advancements in malaria vaccine development. Furthermore, it seeks to analyze the potential impact of combining pre-erythrocytic vaccines and transmission-blocking agents through mathematical approaches to evaluate their effectiveness in reducing malaria transmission.

METHODS

This systematic literature review method, combining a quantitative-descriptive approach with bibliometric analysis. The researchers used bibliometric analysis, a quantitative technique, to analyze bibliographic data in journal articles. The researches applied this technique to investigate references cited in scientific articles, mapping the fields of study discussed in the journal and classifying scientific articles based on relevant research domains.

Various disciplines such as sociology, humanities, communication, marketing, and other social groups can apply the method. Three main stages structure the study: planning (identifying research questions and their boundaries), conducting (searching for and identifying relevant references, followed by data extraction and synthesis), and reporting (translating research findings into article form) (Reuters, 2008).



The research process began by identifying articles from various databases using key terms such as malaria, malaria vaccine, elimination, and the impact of malaria. The researchers used this step to collect relevant literature on malaria vaccine development and disease control strategies. The study utilized platforms such as PubMed, Scopus, and Google Scholar. Identified articles then underwent a deduplication process to ensure the uniqueness of each remaining article, resulting in 1,840 articles for further screening.

The researchers screened the remaining articles using a title and abstract review to evaluate their relevance to the research focus. Then, the researchers eliminated articles lacking clear results or insufficiently specific data at this stage. This selection process ensured that only articles providing significant information were considered. This step was critical in narrowing down articles based on topic relevance, ensuring the efficiency and accuracy of the research process.

The researchers selected articles in the final stage using more specific inclusion criteria, such as experimental studies with well-defined samples and relevant discussions on malaria, including its elimination or the impact of vaccines. The Systematic Literature Review (SLR) analysis included articles that met these criteria. This process **ensured** that the review's findings **were based** on high-quality data, offering valuable insights into the current status, challenges, and progress in malaria vaccine development and more effective disease control strategies.

RESULTS

Titles	Methods	Results
An Optimal Control Model to Understand the Potential Impact of the New Vaccine and Transmission-Blocking Drugs for Malaria: A	A mathematical approach was used in this study to come up with the best way to control malaria by using pre-erythrocytic vaccines and treatments that stop the	Simulation results indicated that combining pre-erythrocytic vaccines and transmission-blocking treatments significantly reduces malaria transmission. The effectiveness of each intervention depends on the number of infected individuals. High-dose pre-erythrocytic vaccines

Titles	Methods	Results
Case Study in Papua and West Papua, Indonesia (Handari et al., 2022)	disease from spreading. The researchers analyzed the model to determine the local stability conditions at the malaria-free equilibrium, based on controlled reproduction numbers. The researchers focused on malaria incidence data from Papua and West Papua Provinces, Indonesia, to estimate model parameters using the non-linear least square fitting method.	were more effective when infection rates were low, whereas transmission-blocking treatments became crucial in scenarios with high infection rates. The combined strategy underscores the importance of large-scale implementation, particularly in areas with high malaria prevalence. These findings highlight the necessity of multifaceted approaches to global malaria control, emphasizing intensive early vaccination and sustained treatment to prevent further transmission, especially in endemic regions like Papua and West Papua.
Seasonal vaccination against malaria: a potential use for an imperfect malaria vaccine (Greenwood et al., 2017)	This research looked at excellence and challenge to use SMC and the compatibility of RTS,S/AS01 malaria vaccine into plans to stop malaria in the Sahel and sub-Sahel parts of Africa, where the disease only comes out during certain times of the year. The analysis included a literature review on SMC implementation and clinical trial results of RTS,S/AS01. The researchers used data on vaccine efficacy and population impact to evaluate the feasibility of annual mass vaccination campaigns before malaria transmission seasons, taking into account changes in vaccine efficacy over time and logistical distribution challenges.	SMC effectively reduced malaria morbidity and mortality in children during high-transmission seasons. However, challenges such as distribution burdens, family acceptance, and drug resistance risks (sulfadoxine-pyrimethamine and amodiaquine) limited its sustainability. Meanwhile, RTS,S/AS01 demonstrated high initial efficacy, although its protection waned rapidly due to challenges in establishing effective immunological memory against malaria antigens. A combined approach—annual mass vaccination campaigns before malaria transmission seasons, complemented by SMC—shows potential for enhanced malaria control in seasonal transmission areas. This strategy could leverage the vaccine's high initial efficacy to protect populations during high-risk periods, with SMC serving as a supplementary measure. These findings emphasize the need for flexible, multifaceted malaria control models tailored to local transmission patterns and implementation challenges.
Analysis of the potential for a malaria vaccine to reduce gaps in malaria intervention coverage (Unwin et al., 2021)	The researchers analyzed household survey data from 20 African countries to assess the overlap in coverage between two malaria interventions: insecticide-treated nets (ITNs) and the DTP3 (diphtheria-tetanus-pertussis, third dose) childhood vaccine. Multilevel logistic regression models explored overlap patterns based on demographic and socioeconomic variables, such as residence location, maternal education level, and wealth status. The researchers projected the	DTP3 coverage consistently surpassed ITN usage in most countries. Among children, 34% did not use ITNs but received DTP3, while 35% used ITNs and received DTP3. Out of 33 million children in 20 countries not using ITNs, 23 million (70%) received DTP3. Providing RTS,S/AS01 to these children could prevent up to 9.7 million (range: 8.5–10.8 million) clinical malaria cases annually. Vaccinating 24 million children who used ITNs and received DTP3 could prevent an additional 10.8 million (range: 9.5–12.0 million) cases. Children using ITNs were 9–13% more likely to reside in rural areas compared to non-users. Maternal education significantly influenced the adoption of malaria interventions and vaccinations, with higher education associated with increased ITN usage and vaccine uptake. Wealth status also strongly predicted intervention coverage.

Titles	Methods	Results
	public health impact of providing the RTS,S/AS01 malaria vaccine to children who received DTP3 but did not use ITNs.	
Future use-cases of vaccines in malaria control and elimination (Penny et al., 2020)	This study used literature reviews and conceptual discussions to explore the development and potential application of malaria vaccines for global burden reduction. Phase 3 trials and ongoing pilot implementation studies provided data on the efficacy of the RTS,S/AS01 vaccine.	The RTS,S/AS01 malaria vaccine showed potential for protecting children in malaria-endemic regions, although further evidence of its safety, impact, and feasibility in pilot studies is required. Future malaria vaccine development is encountered with several key challenges, including: 1. Knowledge gaps: Limited understanding of optimal target antigens and the immune mechanisms necessary for long-term protection. 2. Local adaptation: Local epidemiological conditions influence vaccine efficacy, necessitating region-specific vaccine designs. Future vaccine applications may include: • Improving the current malaria control methods, like vector control. • Targeting vulnerable populations, including children in high-prevalence areas. • Implementing mass vaccination before transmission seasons to maximize the protection impact. These findings underscore the importance of pairing malaria vaccine innovations with better-integrated strategies to achieve global malaria burden reduction.
Hambatan dalam Program Eliminasi Malaria (Karmila et al., 2023)	This qualitative study aimed to identify barriers to malaria elimination in Gelangsar Village, West Lombok Regency. The researchers collected data by conducting in-depth interviews with 11 participants. Data analysis followed an inductive approach, with findings presented narratively.	In-depth interviews have identified several major barriers to the elimination of malaria. 1. The community lacks knowledge about malaria, including its causes and prevention methods. 2. The use of bed nets is not sufficiently monitored to prevent mosquito bites. 3. The proximity of residential areas to livestock enclosures complicates efforts to disrupt mosquito transmission. 4. Traditional practices, such as soaking sugar mold cups (used for making palm sugar) in water for weeks, create breeding grounds for mosquito larvae.

Handari et al. (2022) created and studied the best way to control malaria using a new pre-erythrocytic vaccine and a treatment that stops the disease from spreading. Simulation results indicated that combining these two strategies significantly reduces malaria transmission. High doses of the pre-erythrocytic vaccine are required when the number of infection cases is relatively low, while transmission blocking proves more effective in high-infection scenarios. Large-scale implementation of both strategies is crucial to eradicating malaria, especially in endemic regions worldwide.

In many parts of the Sahel and sub-Saharan regions of Africa, where malaria remains a leading

cause of mortality and morbidity, infection transmission is highly seasonal. Seasonal malaria chemoprevention (SMC), which involves administering a full malaria treatment course to children under five every month during peak transmission seasons, has proven effective in controlling malaria in these areas. However, SMC does not offer complete protection and poses challenges for families and healthcare providers. Additionally, there is a risk of resistance emerging against sulfadoxine-pyrimethamine and amodiaquine, the drugs currently used for SMC ([Greenwood et al., 2017](#)).

The development of malaria vaccines has made significant progress over the past decade. The European Medicines Agency has given the RTS,S/AS01 vaccine a positive opinion, and large-scale projects in sub-Saharan Africa are soon to implement it. This, along with other malaria vaccines under development, demonstrates high efficacy immediately following vaccination. However, this protection quickly wanes, potentially due to difficulties in establishing effective immunological memory against malaria antigens in individuals previously exposed to malaria infection.

[Unwin et al. \(2021\)](#) found a potential strategy for utilizing malaria vaccines that initially demonstrated high efficacy but lack long-term protection was to conduct annual mass vaccination campaigns prior to each malaria transmission season in regions where transmission occurred only during specific months each year.

The malaria burden has undergone substantial changes or reductions in the past two decades. Nonetheless, it continues to pose a significant health challenge necessitating the stringent application of current tools and strategies, alongside the creation and implementation of novel interventions. Malaria vaccines have historically been regarded as a promising intervention to mitigate the malaria burden. Nonetheless, despite extensive development over several decades, only a single vaccine has demonstrated efficacy in safeguarding children through phase 3 trials. These vaccines must exhibit additional safety, efficacy, and practicality in ongoing pilot implementation studies prior to receiving endorsements for extensive application ([Penny et al., 2020](#)).

It is an opportune moment to contemplate the future functions and health objectives of malaria vaccines. These should be considered in relation to potential enhancements in other malaria interventions, such as vector control. We must address significant knowledge deficiencies regarding appropriate antigen targets and the protective immunological responses elicited by vaccines ([Karmila et al., 2023](#)).

[Unwin et al. \(2021\)](#) Indicated that DTP3 vaccine coverage exceeds malaria intervention coverage in the majority of countries. In total, 34% of children neither utilized insecticide-treated nets (ITNs) nor received the DTP3 vaccine, whereas 35% of children employed ITNs and received the DTP3 vaccine, although these statistics differ by country. An estimated 33 million children across 20 countries do not utilize insecticide-treated nets (ITNs). Of these, 23 million (70%) were administered the DTP3 vaccine. Immunizing these 23 million children, provided they have also received all four doses of RTS,S, could avert approximately 9.7 million (range: 8.5–10.8 million) instances of clinical malaria each year. Furthermore, immunizing 24 million children who utilize ITNs and receive the DTP3 vaccine could avert an additional 10.8 million (range: 9.5–12.0 million) cases.

Children utilizing ITNs are 9–13% more likely to live in rural areas compared to those without any interventions, regardless of their vaccination status. Maternal education levels significantly influence intervention adoption, exhibiting a positive correlation with ITN utilization and vaccination rates, while demonstrating a negative correlation with access to unused ITNs. Wealth significantly forecasts intervention coverage.

DISCUSSION

[Suryaningtyas & Arisanti \(2021\)](#) found that malaria vaccines had significant potential in reducing the burden of the disease, though total elimination still encountered challenges. A study that created the best model for controlling malaria using a new pre-erythrocytic vaccine and a treatment that stops the transmission of the disease found that these two collaborated strategies to greatly lower the number of people suffering from malaria ([Satyarsa et al., 2020](#)). The model's

simulation results indicate that a high dose of the pre-erythrocytic vaccine is particularly necessary when the number of infections is relatively low, as it offers robust protection, albeit with a short-lived effect. Transmission blocking is more effective when infection rates are high, as this strategy is more successful at halting disease spread in scenarios with numerous cases (Karunamoorthi, 2014). Large-scale implementation of both strategies is critical for effectively eradicating malaria, particularly in endemic regions worldwide. These findings underline the necessity of a comprehensive approach that integrates vaccines and treatments to address malaria transmission more thoroughly.

In the Sahel and sub-Saharan regions of Africa, where malaria follows a strong seasonal transmission pattern, seasonal malaria chemoprevention (SMC) has proven to be an effective intervention. SMC involves administering complete malaria treatment to children under five every month during periods of high transmission. However, SMC does not provide complete protection and is difficult to implement due to logistical challenges for both families and healthcare providers (Greenwood et al., 2017). Additionally, there is a risk of resistance emerging to the drugs used, such as sulfadoxine-pyrimethamine and amodiaquine. The development of malaria vaccines has made significant progress in recent years, with the RTS,S/AS01 vaccine receiving a positive opinion from the European Medicines Agency and slated for implementation in large-scale projects across sub-Saharan Africa (Khosasih, 2023). This vaccine demonstrates high efficacy shortly after vaccination, but this protection tends to wane quickly. The application of the vaccine through annual mass vaccination campaigns before each malaria transmission season in areas where malaria transmission is limited to just a few months per year could be an effective approach (Hamilton et al., 2023).

Over the past two decades, the malaria burden has significantly decreased due to various interventions, yet malaria vaccines still require further evaluation (Etefia & Etoh, 2023). Before recommending a malaria vaccine for widespread use, ongoing pilot implementation studies must demonstrate its safety, impact, and feasibility (Handari et al., 2022). Karmila et al. (2023) explain the importance about the use of malaria vaccines in conjunction with other innovations in malaria control, such as controlling vectors, and to fill in knowledge gaps about the right target antigens and the immunology of the vaccine's protective effect. In-depth evaluations of vaccine effectiveness under various conditions, as well as its integration with existing malaria control strategies, are essential to achieving global health goals related to malaria.

A study that compared the coverage of DTP3 vaccines with malaria interventions found that, even though the coverage of DTP3 vaccines is higher, a lot more children who don't use insecticide-treated nets (ITNs) could be vaccinated to stop more malaria cases. Of the 33 million children in 20 countries who do not use ITNs, 23 million (70%) have received the DTP3 vaccine (Unwin et al., 2021). Vaccinating these 23 million children could prevent up to approximately 9.7 million (range 8.5–10.8 million) clinical malaria cases annually, assuming all children who receive DTP3 also receive all four doses of RTS,S. Additionally, vaccinating 24 million children who use ITNs and also receive the DTP3 vaccine could prevent another 10.8 million (range 9.5–12.0 million) malaria cases. These data emphasize the importance of integrating malaria vaccines with other interventions, such as ITN usage, to tackle malaria more comprehensively and effectively. Maternal education and wealth are also significant factors influencing intervention coverage, so prevention strategies should take these socio-economic factors into account (White et al., 2015).

CONCLUSION

Vaccines such as RTS,S/AS01 have demonstrated efficacy in alleviating the burden of malaria; however, their effectiveness frequently diminishes over time, particularly in regions with high endemicity. The study concludes that while malaria vaccines can diminish the incidence of cases and fatalities, their efficacy is significantly enhanced when combined with additional interventions such as insecticide-treated bed nets and antimalarial medications. The implementation of pre-erythrocytic vaccines, aimed at the initial phases of Plasmodium infection, alongside transmission-blocking vaccines that inhibit the propagation of malaria, presents significant promise in mitigating the disease's transmission. This study examines the potential effects of combining pre-erythrocytic vaccines with transmission-blocking drugs using a

mathematical model, demonstrating that this combination can enhance efficacy in mitigating malaria transmission. Mathematical modeling suggests that while the vaccine's efficacy may diminish over time, its application alongside other interventions can still substantially decrease the incidence of malaria cases and fatalities, even in regions with low prevalence. Malaria vaccines are essential in the global initiative to eradicate malaria; however, they require support from a flexible and data-informed multifaceted strategy.

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