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Safety and efficacy of R21/Matrix-M vaccine against and eradicate malaria infection

Patricia Valery Rahaded[1], Fauna Herawati[2]
[1,2]Faculty of Pharmacy, Universitas Surabaya, Indonesia

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ABSTRACT

Malaria continues to be a substantial health concern, characterised by elevated rates of illness and death. The development of resistance to existing treatments poses unique obstacles to infection control initiatives. To combat the increasing incidence of malaria, it is imperative to create malaria vaccines such as RTS,S/AS01 and R21/Matrix-M. This study conducted a systematic literature revieew to evaluate the safety and efficacy of malaria vaccines that are currently being developed, with a specific focus on the R21/Matrix-M vaccine. Applying the PRISMA criteria, we identified five studies that specifically examined the efficacy and safety of the R21/Matrix-M vaccination. The findings indicated that the R21/Matrix-M vaccine exhibits favourable tolerability and demonstrates substantial efficacy in clinical studies. Nevertheless, the scarcity of research on the R21/Matrix-M vaccine thus far emphasises the necessity for additional investigation to substantiate its efficacy in malaria treatment.

Corresponding Author:

Fauna Herawati,
Faculty of Pharmacy
Universitas Surabaya
Jl. Raya Kalirungkut, Kali Rungkut, Kec. Rungkut, Surabaya, 60293, Jawa Timur, Indonesia
Email: fauna@staff.ubaya.ac.id

INTRODUCTION

Malaria continues to be a prominent contributor to global morbidity and mortality resulting from infectious diseases(Khambali & ST, 2019)(Shinta & Manalu, 2022)(Melindah, 2023). The predominant form of malaria is attributed to the spread of Plasmodium falciparum by female *Anopheles* spp mosquitoes (Parums, 2023). Plasmodium falciparum is a very intricate pathogen that employs many strategies to evade the host immune response (Datoo, Natama, Somé, Traoré, Rouamba, Bellamy, et al., 2021). Malaria stands as the preeminent parasite ailment in relation to human morbidity and mortality (Handayani et al., 2022). Its impact spans over 84 nations that are endemic to malaria, impacting a staggering 247 million individuals in the year 2021. Tragically, this sickness has resulted in a significant loss of life, claiming the lives of 619,000 individuals. The emergence of resistance to pesticides and medication therapies is a growing challenge in the field of infection control (Parums, 2023). From 2019 to 2020, there was a worldwide rise of 6% in the incidence of malaria cases and a corresponding increase of 12% in malaria-related mortality rates. The majority of these instances transpire inside the African area, wherein 80% of fatalities attributed to malaria are seen in youngsters below the age of 5(Simanjorang, 2020)(Kinansi et al.,

2021)(Ningtyas et al., 2023). The morbidity and mortality targets set out in the World Health Organization's Global Technical Strategy for Malaria 2016-2030 have not been achieved as of yet, as seen by the reported number of 640,000 malaria-related deaths in the year 2020. The use of vaccinations is anticipated to stimulate novel initiatives in combating malaria.(Datoo, Natama, Somé, Bellamy, Traoré, et al., 2022b).

The RTS,S/AS01 malaria vaccine candidate, which is presently in development, demonstrates partial effectiveness by stimulating the production of antibodies against the core repeat (Asn-Ala-Asn-Pro [NANP]) sequence found in the circumsporozoite protein (CSP). The findings of the Malaria Vaccine Implementation Program indicate that the RTS,S/AS01 vaccine had a favorable safety profile and was correlated with a 30% decrease in the incidence of severe malaria cases. In accordance with a preceding phase 3 research, which included a median follow-up duration of 48 months, the vaccine demonstrated a 36% effectiveness against clinical malaria in children aged 5-17 months. Similarly, infants aged 6-12 weeks exhibited a vaccination efficacy of 26% after the administration of four vaccine doses (Datoo, Natama, Somé, Bellamy, Traoré, et al., 2022a). Nevertheless, the RTS,S/AS01 vaccine has not yet met the criteria for approval by the World Health Organization (WHO). Nonetheless, in 2019, a program was initiated to administer a malaria vaccine in three countries. Furthermore, it is imperative to ascertain and cultivate supplementary malaria vaccines in order to enhance the availability of vaccines and ensure comprehensive immunization of the intended demographic. This is crucial for the World Health Organization's objective of attaining a malaria vaccine candidate that exhibits an efficacy rate of 75% or higher against clinical malaria by the year 2030 (Datoo, Natama, Somé, Bellamy, Traoré, et al., 2022a).

Intact sporozoite vaccines include the administration of live sporozoites that have been attenuated by radiation or genetic alteration, as well as the inoculation of sporozoites in conjunction with chemoprophylaxis(Setiarto & Karo, 2021)(Kolik, 2023). The administration of R21 in different adjuvants has been shown to elicit robust anti-CSP antibody titers, while eliciting negligible anti-HBsAg antibody responses. The inclusion of R21 in the adjuvant demonstrated protective effects in a mouse challenge paradigm, wherein transgenic parasites were used (Collins et al., 2017). The R21/Matrix-M malaria vaccine, developed by the Serum Institute of India, consists of the circumsporozoite protein, a secretion of the malaria parasite, fused with the hepatitis B surface antigen. This vaccine is administered alongside Novavax's Matrix-M adjuvant, which enhances the activation of antigen presenting cells (Grant et al., 2023). The R21/Matrix-M vaccine is now undergoing phase III clinical trials, and preliminary (unpublished) trial results and phase II trials have shown high efficacy, similar to that shown with RTS,S/AS01 when administered seasonally. The World Health Organization (WHO) is now engaged in the process of reviewing the efficacy, safety, and suitability of the R21/Matrix-M program. To ensure the successful implementation of the Malaria vaccine, it is crucial to acquire a precise comprehension of the vaccine's safety and efficacy(Burhanuddin et al., 2020)(Khudrotul et al., 2021)(Pujianto, 2022)(Novita, 2023) (Merle et al., 2023).

Based on the aforementioned background, it is necessary to conduct a comprehensive study on the R21/Matrix-M vaccine. Therefore, the objective of this study is to determine the safety and efficacy of the R21/Matrix-M vaccine in combating and eradicating malaria in adults.

RESEARCH METHOD

Study Design

This study used a systematic review or systematic literature review to analyze the safety of R21/Matrix-M vaccination and its effectiveness against malaria infection.

Search Strategy

The identification of literature included in this study is based on the author's predetermined keyword search. The selection of articles included in this study is based on the PRISMA criteria. (Prefered Items of Systematic Review and Meta-Analysis) 8 as seen in Figure 1. The field of literature employs a rigorous evaluation procedure that involves scrutinizing titles and abstracts of relevant scholarly works. The analysis of the whole text of each literary work is performed to ascertain its relevance to the inclusion and exclusion criteria established for this research. Subsequently, a determination is made as to whether the study in question satisfies the requirements for being considered eligible literature.

The literature search conducted for this study included two databases, namely Google Scholar and PubMed, throughout the month of June in the year 2023. All authors were involved in doing the literature search. The method under consideration involves the examination of key terms such as safety, efficacy, R21/Matrix-M vaccination, and its effectiveness against malaria infection. The search columns include a mix of BOOLEAN operators 'AND' and 'OR' to order the keywords. In order to enhance the breadth of data sources used in this study, supplementary literature searches are conducted by exploring studies relevant to the research topic within the bibliographies of the included literature.

In order to optimize the originality of the findings from the included study, there are no restrictions imposed on the year of publication or the kind of the research. In addition, it is imperative that inclusion literature be produced in the English language.

Data Extraction

The authors of this study independently conducted data extraction from the literature contained in this research. A comparison will be made between the outcomes of each. In order to reconcile any discrepancies and uncertainties encountered throughout the data extraction process, a collaborative discussion will be held with the third author to reach a consensus. Table 1 presents the retrieved data from each literature article, including pertinent information such as the author and year of publication, country of origin, study population, research aims, research technique, and research outcomes.

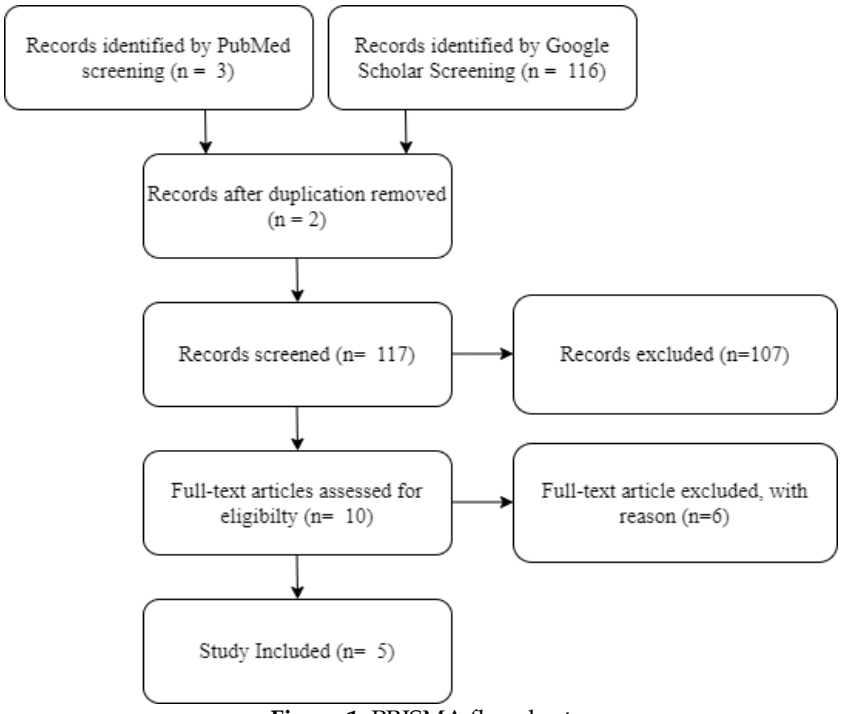

Figure 1. PRISMA flowchart

RESULTS AND DISCUSSIONS

A total of 119 items of literature were acquired from searches conducted on PubMed and Google Scholar. Two instances of duplicated material were removed, and the screening process proceeded. Out of the total sample size of 119 literary works that were examined, it was found that 100 of these works did not correspond to their respective titles, while 9 of them lacked a corresponding abstract. A total of 20 items of literature were considered for examination, with 10 being selected for full-text analysis and the other 10 being eliminated.

The present study effectively included a total of five scholarly works that specifically address the safety and effectiveness of the R21/Matrix-M vaccine in combating Malaria infections.(Collins et al., 2017; Datoo, 2022; Datoo, Natama, Somé, Traoré, Rouamba, & ..., 2021; Nitika et al., 2023; Parums, 2022)

This study demonstrates that the existing body of material pertaining to the efficacy of the R21/Matrix-M vaccine in eliminating malaria remains restricted, mostly due to the vaccine's current status in the third stage of clinical trials under the supervision of the World Health Organization (WHO). Datoo et al. in 2022 showed that a trial study conducted on infants aged 5-7 months in Burkina Faso, R21/MM had a good safety profile and was well tolerated. The majority of side effects that occur are mild, with fever being the most common occurrence. Participants who received R21/MM vaccination showed high specific anti-malarial levels (Datoo, Natama, Somé, Bellamy, & ..., 2022). Meanwhile Collins et al. (2017) demonstrated that the vaccine exhibited noticeable efficiency and effectiveness at low dosages, as shown by in-vivo investigations done on female BALB/c mice within the age range of 6 to 10 weeks. Both Abisco-100 and Matrix-M have been shown to provide sterile protection against transgenic sporozoite challenge in these animal models.

The R21/Matrix-M malaria vaccine, produced by the Serum Institute of India, consists of the circumsporozoite protein, which is released by the malaria parasite, fused with the hepatitis B surface antigen. This vaccine is administered in combination with Novavax's Matrix-M adjuvant, which enhances the recruitment of antigen presenting cells to the site of injection.[14]

The induction of sufficiently high concentrations of antibodies necessary for conferring protection has proven to be a challenging task in the context of malaria. Moreover, even when such concentrations are achieved, the levels of antibodies tend to diminish fast over time. Our study demonstrates that the administration of a solitary booster dosage of R21/Matrix-M has the ability to reinstate elevated levels of antibody concentrations. The administration of the booster dose resulted in the maintenance of long-lasting protective immunity throughout the second year, particularly when the R21 vaccine was administered with a greater dosage of adjuvant. The encouraging potential value of this malaria vaccine candidate is shown by both its degree of protective effectiveness and its ability to maintain this efficacy for a second year. The need of an extra dosage to sustain the observed high effectiveness remains uncertain. To evaluate the potential benefits of supplementary yearly booster vaccination doses, the ongoing experiment has been extended by an additional duration of 2 years. The discovery of immunological correlates of protection has played a crucial role in comprehending the protective immunity elicited by vaccinations designed to target various diseases. Correlates facilitate the evaluation of potential effectiveness across various groups without the need for extra efficacy studies, hence possibly aiding in the attainment of regulatory clearances. The primary objective of several malaria vaccine candidates focused on the P falciparum circumsporozoite protein has been to elicit the production of protective antibodies against the NANP repeat sequence, which is known for its high degree of conservation. The efficacy of both the RTS,S/AS01 malaria vaccine and the R21/Matrix-M vaccine candidate has been assessed via trials, whereby the presence of NANP antibodies has shown a positive correlation with protection in several challenge experiments including non-immune individuals.The numbers 10 and 11 are being referred to. The correlation between these antibodies and vaccination effectiveness was shown in early babies (6-12 weeks old) during the phase 3 study

assessing the RTS,S/AS01 vaccine. However, this correlation was not observed in children aged 5-17 months, which is the current target demographic for this vaccine. During the first and second year of observation, our study examined the relationship between anti-NANP concentrations and vaccination effectiveness in individuals who received R21/Matrix-M with a higher adjuvant dosage. Our findings indicate a strong correlation between anti-NANP concentrations and protection against the first or any malaria episode.[9,13]

The potential of controlling endemic malaria has been revitalized by the promising effectiveness and safety profile of the R21/MM malaria vaccine, as well as the prospect of sustaining immunity with yearly vaccine boosters. Significantly, the R21/MM malaria vaccine stands out due to its remarkable vaccination effectiveness of 77%, making it the first vaccine to successfully meet the efficacy target of 75% set by the World Health Organization (WHO). The next publication, anticipated to be released in early 2023, will provide the findings of an ongoing clinical trial conducted in Thailand (NCT05252845). The study aims to assess the safety and immunogenicity of R21/MM in adult participants. The study scientists, who are affiliated with the University of Oxford, are now engaged in a safety and immunogenicity trial of R21/MM in Thai adults. Additionally, their objective is to ascertain if the concurrent administration of antimalarial medications has any impact on the immunogenicity of the vaccine. This trial includes a pharmacokinetics evaluation of the absorption and pharmacokinetics of the antimalarial drug piperaquine and a single low dose of primaquine (SLDPQ) when administered with the R21/MM vaccine.[12]

Table 1. Summary of study results

Authors and Year	*Country*	Population	Aim of Study	Methodology	Result
(Datoo, Natama, Somé, Traoré, Rouamba, Bellamy, et al., 2021)	Burkina Faso	498 children aged 5–17 months in Nanoro, Burkina Faso. Participants were recruited from the Nanoro health region and received a primary vaccination series consisting of three vaccine doses, 4 weeks apart, before the seasonal peak of malaria transmission (7 May–13 June 2019).	Report safety, immunogenicity, and R21/Matrix-M efficacy, and malaria counts cases could be prevented with this vaccine during 2 years of follow-up, after the first booster dose.	a. Double blind, randomized, controlled phase 2b trial b. This study used R21 vaccine which was based on low-dose circumsporozoite protein, with two different doses of Matrix-M (MM) adjuvant c. Vaccines are administered intramuscularly into the thigh. d. Children were randomly assigned (1:1:1) to groups 1–3	R21/MM has a good safety profile and is well tolerated. The majority of side effects that occur are mild, with fever being the most common occurrence. Vaccine efficacy was 74% (95% CI 63–82) in group 1 and 77% (67–84) in group 2 at 6 months. At 1 year, vaccine efficacy remained high, namely 77% (67–84) in group 1. Participants vaccinated with R21/MM showed high levels of anti-malaria-specific
(Collins et al., 2017)	United Kingdom	The study used female BALB/c (H-2d) mice aged between 6 and 10 weeks, obtained from Harlan in the United Kingdom.	Boosting the effectiveness of the vaccine by creating a CSP-based particle vaccine with increased immunogenicity and, as a result, generating the	a. The R21 fusion protein was produced by CSP from P. falciparum strain NF54 with the N-terminal region of the hepatitis B surface antigen (HBsAg).	The immunogenicity of BALB/c R21 mice is seen even at minimal dosages. When these animals are treated with adjuvants Abisco-100 and Matrix-M, they exhibit sterile protection against transgenic sporozoite challenge.

Authors and Year	*Country*	Population	Aim of Study	Methodology	Result
			R21 vaccine, which is the next generation of RTS,S-like vaccines.	b. This study used several adjuvants were used to manufacture R21. c. Multiple cohorts of BALB/c mice were subjected to immunization using three administrations of 0.5 µg R21 combined with adjuvant.	
(Parums, 2022)	-	-	Provide an overview of the latest discoveries derived from significant clinical studies pertaining to the safety and effectiveness of R21/MM malaria vaccines.	Literature review which included 2 studies	There is an expectation that in the year 2023, there may be regulatory approval, licensing, and implementation initiatives for adjuvanted vaccines designed to prevent malaria. This anticipation is based on the current clinical studies of R21/Matrix-M™ (R21/MM), which have yielded promising results about their safety and efficacy.
(Nitika et al., 2023).	-	-	The objective of this research is to emphasize the significance of implementing a unique R21 vaccination strategy for the purpose of eradicating malaria within a certain period.	Literature review	R21 vaccine prequalification is underway at the WHO. Despite numerous outstanding problems, the R21 vaccine with effectiveness over 75%, the WHO's aim, might revolutionize malaria control, decreasing morbidity and death and eradicating malaria.

CONCLUSION

The study findings indicate that the R21/Matrix-M vaccine has a high level of efficacy in inducing the production of antibodies for the purpose of malaria eradication. The aforementioned study findings provide direct and indirect evidence supporting the clinical testing of the vaccine's safety. Nevertheless, it is essential to validate these findings by conducting several following experiments in other nations, including varied people around the globe.

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