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REVIEW ARTICLE

Efficacy and safety of chemoprophylactic plasmodium falciparum sporozoite vaccines for malaria prevention: a systematic review and meta-analysis

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ABSTRACT

PfSPZ-CVac, an innovative vaccine, aims to combat malaria by using live, weakened Plasmodium falciparum sporozoites in combination with chloroquine. This approach employs the whole parasite, triggering a strong immune response and potentially providing long-term protection. The objective of this study is to assess the efficacy and safety of the PfSPZ-Chemoprophylaxis Vaccine (PfSPZ-CVac) for malaria prevention. A systematic review following PRISMA guidelines was conducted, focusing on randomized controlled trials (RCTs) that assessed the efficacy and safety of the vaccine. Seven eligible studies were selected from eight electronic databases. The quality was assessed using the Cochrane Risk of Bias tool, and data analysis was performed using Review Manager 5.4. PfSPZ-CVac combines live sporozoites with chloroquine, which prevents the parasite from entering the liver and enhance the body's immune response, particularly T-cell activation, to provide long-lasting protection against malaria. The meta-analysis revealed a significant reduction in parasitemia ($P<0.00001$, $I^2=35\%$, MD=0.38). Local solicited adverse events did not show a significant increase (MD=0.73, P=0.45, $I^2=0\%$). Similarly, systemic solicited adverse events and unsolicited adverse events demonstrated minimal risks (MD=0.89, P=0.56, $I^2=23\%$; MD=0.65, P=0.20, $I^2=0\%$). Although PfSPZ-CVac exhibits high efficacy, its administration is complex, and it carries a slight of rare adverse reactions. PfSPZ-CVac demonstrates potential for providing strong, long-term protection against malaria , with a positive safety profile, making it a promising candidate for widespread use in high-transmission regions.

Keyword: Malaria, PsfPZ-CVac, Plasmodium falciparum, Chemoprophylaxis, Malaria vaccine, Efficacy and Safety

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INTRODUCTION

According to the World Health Organization (WHO), malaria is a life-threatening disease responsible for significant global health challenges. In 2022, an estimated 249 million cases and 608,000 deaths were reported across 85 countries.. During the same year, Africa remained the most affected region, bearing approximately 94% of all malaria cases and 95% of the total malaria-related deaths.[1] This highlights the severe impact of malaria in areas with high transmission rates, where healthcare resources are often limited. In Indonesia, the situation is also concerning.[2] According to 2024 data from the Kementerian Kesehatan Republik Indonesia (Kemkes), there were 400,000 confirmed malaria cases, with 110 reported deaths.[3] The burden of malaria in Indonesia is particularly significant due to its tropical climate and environmental conditions that favor mosquito breeding.[4] This makes malaria the third deadliest disease in the world, further emphasizing the need for its elimination, especially since Indonesia has second-highest burden in Asia, after India.[5] Recognizing the urgent need for effective prevention, timely diagnosis, and improved access to treatment, especially for populations in high-risk regions, a promising solution lies in the development of a malaria vaccine.[6] However, the complexities of Plasmodium falciparum biology, including its sophisticated immune evasion mechanisms and variability in host immune responses have posed significant challenges to vaccine development.[7] Previous malaria vaccines, such as RTS,S/AS01 (Mosquirix), have faced limitations in efficacy and durability, providing partial protection with limited longevity. These vaccines require multiple booster doses and show reduced effectiveness in high-transmission regions.[8]

The need for PfSPZ-CVac emerged from the recognition that novel strategies were essential to induce a more robust and durable immune response. PfSPZ-Chemoprophylaxis Vaccine (PfSPZ-CVac) is an innovative experimental malaria vaccine designed to combat the disease by utilizing live Plasmodium falciparum sporozoites (PfSPZ), the infective form of the malaria parasite.[9] Unlike conventional vaccines that rely on fragments or subunits of the parasite, PfSPZ-CVac incorporates the entire parasite with the combination of chemoprophylactic drug.[7] This strategy is designed to elicit a stronger and more comprehensive immune response, thereby enhancing the body's ability to recognize and fight off future malaria infections . The mechanism of PfSPZ-CVac involves the administration of live Plasmodium falciparum sporozoites, the infective stage of the malaria parasite, in combination with chemoprophylaxis.[10] These attenuated sporozoites circulate in the bloodstream, where they are recognized by the immune system, triggering a defensive response against the parasite.[11] To eliminate the risk of actual infection, recipients are administered a chemoprophylactic drug, such as chloroquine, as demonstrated by Bijker, et al. (2013), providing an additional layer of protection.[12] By exposing the immune system to the entire parasite rather than isolated fragments, PfSPZ-CVac aims to stimulate a comprehensive and long-lasting immune response, thereby enhancing the body's ability to recognize and combat future malaria infections.

These chemoprophylactic vaccines offer several notable advantages over traditional malaria vaccines. Early clinical trials have shown that PfSPZ-CVac may provide long-lasting immunity, which is specifically beneficial for regions with high malaria transmission.[13] The vaccine has also demonstrated promising efficacy in malaria-endemic regions, suggesting its potential effectiveness in real-world settings. By inducing immunity against the malaria parasite, it is believed that PfSPZ-CVac could help reduce transmission rates, offering a valuable tool for decreasing the spread of malaria in high-risk populations.[14]

The development and deployment of the PfSPZ-CVac vaccine could represent a major breakthrough in the fight against malaria, addressing many limitations of current prevention and treatment strategies. Its ability to elicit a strong, whole-parasite immune response, coupled with its potential for long-term protection, making it a promising candidate for use in high-transmission regions. As research continues and clinical trials expand, there is hope that PfSPZ-CVac could become a key component of comprehensive malaria control programs, contributing to the reduction of this devastating disease's burden and saving countless lives, particularly among vulnerable populations in endemic regions. Therefore, this review aims to assess the Efficacy and Safety of Plasmodium falciparum sporozoites chemoprophylaxis vaccine (PfSPZ-CVac) for malaria prevention.

METHODS

Study methodology

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Eligibility criteria

The eligibility criteria for this study include the following: study population, type of intervention, outcomes, study design, and reference standards.

Study Population

The Study population consists of healthy individuals with no history of malaria or any other clinical illness. The intervention assessed is PfsPZ-CVac, while the control group received a placebo (normal saline) administered intravenously.

Outcomes

The primary outcomes of the study were the degree of parasitemia and the incidence of adverse events among populations receiving either the intervention or the control.

Type of Studies

Original research articles involving human subjects, with a randomized controlled trial (RCT) design and written in English, were included in this study. Exclusive studies included narrative review, systematic reviews, meta-analysis, non-comparative research, in silico studies, in vivo studies, in vitro studies, technical reports, editor response, scientific poster, study protocol, and conference abstracts. Additionally, articles with unavailable full-text, non-English publications, and irrelevant topics were also excluded.

Reference Standards

The reference standard was experimental research performed by qualified professionals, evaluating the safety and efficacy of PfsPZ-CVac compared to placebo in preventing malaria.

Data Source and Search

The literature search process was carried out with eight electronic databases: PubMed, Wiley, Springer, Scopus, Taylor & Francis, Sage, Proquest, and Cochrane. The literature search covered publications from their inception until November, 6th 2024. The keywords used in electronic databases are detailed in **Appendix 1**. All the studies retrieved from these databases were stored in the authors' library on Rayyan.ai.

Study selection

After removing duplicate articles, the retrieved records were screened based on titles and abstracts by all authors (AINK, ASC, RSD). Potentially eligible full-text articles were thoroughly assessed using the eligibility criteria described above. Any emerging discrepancies were resolved by consensus among the authors. The entire study selection process was documented in the PRISMA flow chart.[10]

From the mentioned database, 86 records were retrieved. After removing 6 duplicates and screening titles and abstracts, 16 potentially relevant articles were selected. Following a full-text review, seven studies met the inclusion criteria and were included in the systematic review and meta-analysis. The study selection process is illustrated in the PRISMA flow diagram (Figure 1)

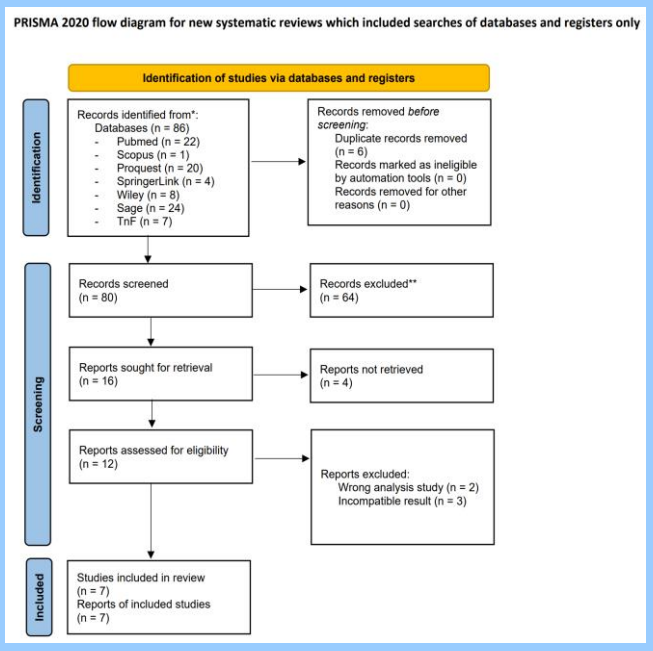

Figure 1. PRISMA flowchart of the study selection

Risk of Bias in Individual Studies (Qualitative Synthesis)

The quality of each included study was assessed by three reviewers (AINK, ASC, RSD) using the Cochrane Risk of Bias (RoB) tool or the RoB 2 tool (revised tools for risk of bias in randomized trials).[11]

Risk-of-bias plots were generated for quality assessment using the 'robvis' software. The summary plot displayed the weighted judgment in a traffic light plot format, illustrating the overall risk of bias and bias risk in each area. The RoB result indicated no potential bias in the included study. Figure 2 illustrates these findings.

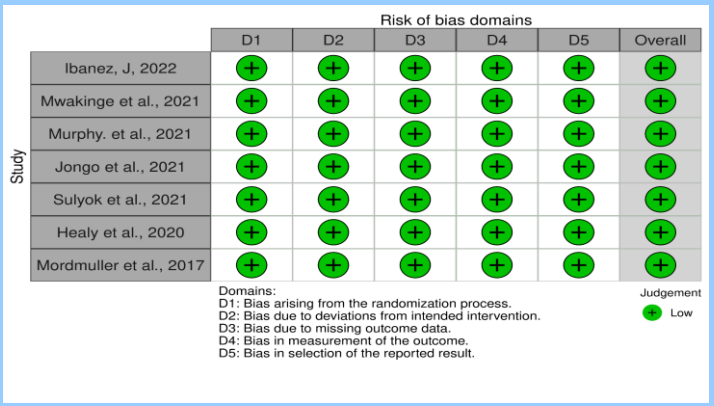

Figure 2. Traffic light plot of the quality assessment of the included studies

Data Extraction and Analysis

Data from the included studies were extracted with Microsoft Excel 2021 (Microsoft Corporation, USA) and Rayyan.ai. The following details were recorded: first author, year of publication, study design, setting, age range, population characteristic, sample size, dosage, and assessment period. All statistical tests for the meta-analysis were conducted using Review Manager (RevMan) v5.4 (Cochrane Collaboration, UK.

This review analyzed data from seven randomized controlled trials (RCT) involving 160 participants across four countries. Published between 2014 and 2024, these studies focused exclusively on the whole Plasmodium falciparum vaccine combined with chemoprophylaxis. As presented in **Appendix 2** and **Appendix 3**, the studies assessed the efficacy (parasitemia degree) and safety (adverse event) Plasmodium falciparum Sporozoites Chemoprophylaxis Vaccine (PfSPZ-CVac).

Quantitative Data Synthesis (Meta-Analysis)

This meta-analysis calculated data in terms of mean and standard deviation (SD), with a 95% confidence interval (CI) . The heterogeneity level was used to determine the effect size, either a Fixed Effect Model (FEM) or Random Effect Model (REM). In this study, the FEM was applied when the included studies were considered homogeneous, as indicated by an I2value less than 50%. The pooled estimates were presented in our forest plot. Subgroup analysis was conducted to explore potential heterogeneity among the included studies.

RESULTS AND DISCUSSION

PfSPZ-CVac Vaccine Mechanism

The PfSPZ-CVac vaccine is a malaria vaccine that combines live Plasmodium falciparum sporozoites and chloroquine.[17,18] This vaccine targets the pre-erythrocytic stage of malaria infection.[18,19,20] Immunization with PfSPZ-CVac introduces a high number of sporozoites into the body.[21] Generally, Plasmodium infection begins when sporozoites invade hepatocytes and replicate exponentially, producing over 100,000 merozoites. These merozoites then enter the bloodstream and infect erythrocytes in the body.[22] However, this process is inhabited by the PfSPZ-CVac vaccine,[21,23] which works by inducing antibodies that block sporozoites from reaching the liver.[24,25] The resulting immunological reaction produces a high level and long-lasting adaptive immunity against malaria parasites.[26,27] As presented in **Appendix 4**, this method is the most effective way to protect against malaria in adults who have never received the vaccine.[28]

The immunological response elicited by PfSPZ-CVac vaccine includes an increase in CD56+ T cells, EMRA, CD8+, CD4+ T cells, and IFN-γ, all of which are associated with protection against malaria.[29,30,31] Repeated administration of the vaccine will induces γδ T cells, which trigger immunity to malaria and reduce the production of proinflammatory cytokines.[29,32,33] CD56 + T cells, EMRA cells, and CD8 + are associated with protection against malaria in individuals without prior malaria exposure.[29] CD56 + and CD8 + T cells are associated with protection, possibly representing NKT cells, by inhibiting parasite proliferation in hepatocytes so that the development of blood stage malaria does not occur.[29,34] These mechanisms are further illustrated in **Appendix 5**.

Efficacy of PfSPZ-CVac againts Malaria

Seven studies involving a total of 160 participants evaluated the efficacy PfSPZ-CVac vaccination, measured by the detection of parasitemia after intervention as Vaccine Efficacy (VE). PfSPZ-CVac intervention was significantly associated with lower detected parasitemia compared to placebo (normal saline) (PfSPZ-CVac=0.38,95% CI:0.28 to 0.53, P<0.00001, I2=35%, fixed-effect model). As shown in Figure 3, these results were statistically significant and demonstrated no heterogenity (I2<50%).[35]

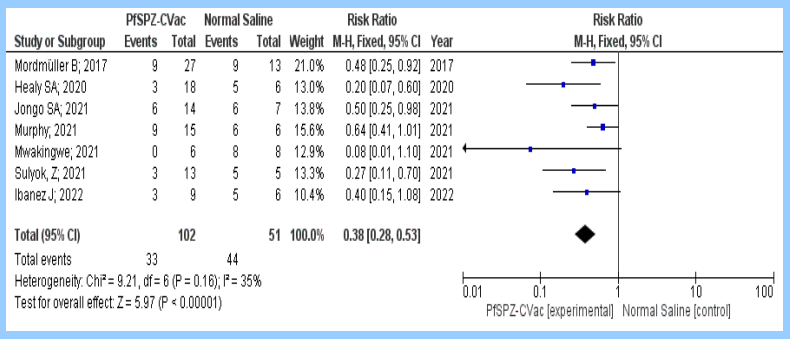

Figure 3. Forest Plot for Detected Parasitemia After PfSPZ-CVac

Detected parasitemia in the blood is a crucial parameter for evaluating malaria vaccine efficacy, as it provides an objective measure of how well the vaccine reduces or prevents the growth of the malaria parasite in the host's bloodstream. Scientificj studies and journals frequently use parasitemia levels as a key outcome to assess the effectiveness of malaria vaccines in both preclinical and clinical trials.[36]

The PfSPZ-CVac vaccine demonstrates good vaccine efficacy (VE). It was significantly more effective in preventing the incidence of parasitaemia against both homologous and heterologous controlled human malaria infection (CHMI). Five of seven included studies supported this result. According to Ibanez et al. the VE was 67% and 63% in subjects immunized at 14-day and 5-day intervals, respectively. Both regimens were safe and well-tolerated, consistent with the previous 56-day regimen using the same PfSPZ dose. Additional VE results included 77% (Sulyok et al.), 80% (Mwakinge et al.), 55% (Jongo et al.), and 75% (Murphy et al.).

Safety of PfSPZ-CVac againts Malaria

Monitoring adverse events (AEs) in assessing the safety of malaria vaccines cannot be overstated, as AEs provide critical information regarding the potential risks associated with vaccine administration. Ensuring the safety of a malaria vaccine is a fundamental aspect of its development and approval, and eventual widespread use in endemic populations.[37] Adverse events are any untoward medical occurrences that may arise following vaccination, ranging from mild reactions such as fever or pain at the injection site to more serious, rare events such as anaphylaxis or autoimmune responses.[38]

Local Solicited Adverse Event

Five studies involving a total of 126 participants analyzed the safety of PfSPZ-CVac vaccination based on local solicited adverse events. Our analysis revealed no significant difference in local solicited adverse event between the PfSPZ-CVac group and the placebo (normal saline) group. (PfSPZ-CVac=0.73,95%CI:0.33 to 1.65, P=0.45,I2=0%, fixed-effect model), as shown in Figure 4. While three studies indicated a positive correlation between PfSPZ-CVac and local solicited adverse event, the studies by Ibanez's and Healy's did not. The I2 value of 0% further confirmed the homogeneity of the study (I2<50%).[39,40]

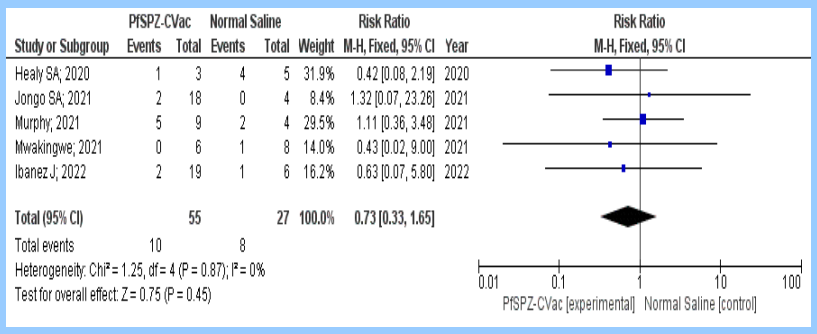

Figure 4. Forest Plot for Local Solicited Adverse Events between PfSPZ-CVac and Placebo

Local solicited adverse events refer to a predefined list of symptoms or events that participants are specifically instructed to monitor or record. For injectable vaccines, solicited local adverse events to be reported usually included, as a minimum pain, erythema, redness, and swelling. Based on the included study, there are some local solicited adverse events include pain, tenderness, pruritus, erythema, swelling, induration, and bruising or extravasated blood. No serious adverse event occurs were reported. The study by Mwakinge et al. noted that no participant in the intervention groups experienced local solicited adverse effects.

Systemic Solicited Adverse Event

Six studies involving a total of 146 participants analyzed the safety of PfSPZ-CVac vaccination based on systemic solicited adverse events. Our analysis revealed no significant difference between systemic solicited adverse event between PfSPZ-CVac group and the placebo (normal saline) group, (PfSPZ-CVac=0.89,95% CI:0.60 to 1.32, P=0.56,I2=23%, fixed-effect model), as shown in Figure 5. While four studies indicated a positive correlation between PfSPZ-CVac and local solicited adverse events, the studies by Healy's and Mwakingwe's did not. The I2 value of 23% confirmed the absence of heterogeneity among the included studies (I2<50%).[40,41]

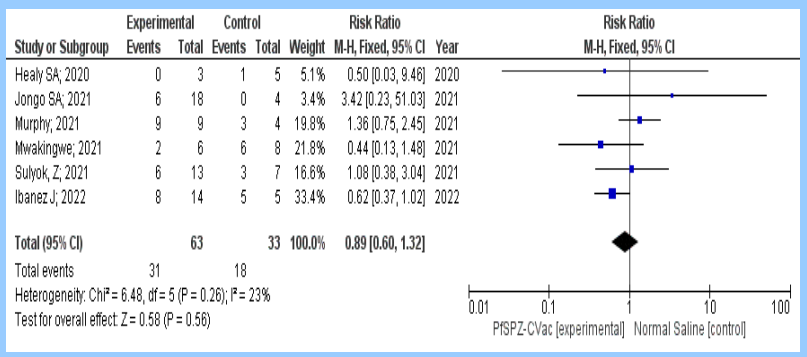

Figure 5. Forest Plot for Systemic Solicited Adverse Events between PfSPZ-CVac and Placebo

A systemic solicited adverse event (SAE) refers to an unintended or undesirable reaction that occurs in response to a medical intervention, like a vaccine. that is both expected and actively monitored (solicited) following administration. This adverse events (AEs) affect broader body systems, including the immune, nervous, or cardiovascular systems.

For the malaria vaccine PfSPZ-CVac, solicited systemic AEs would typically include reactions such as fever, headache, fatigue, muscle aches, chills, and malaise, which are commonly associated with immune responses to vaccination.[40]

All studies [11,36,39,40,41,42,43] included in this analysis reported that the most common systemic solicited adverse events were dizziness and headache. However, the studies by Healy[40] and Mwakingwe[41] differed, showing equal distribution for each adverse event.

Unsolicited Adverse Event

Four studies involving a total of 98 participants analyzed the safety of PfSPZ-CVac vaccination based on unsolicited adverse events. Our analysis revealed no significant difference in unsolicited adverse event between PfSPZ-CVac group and the placebo (normal saline) group, as reported in all included studies.[11,36,39,40,41,42,43] As shown in Figure 6 the results were as follow: PfSPZ-CVac = 0.65, 95%CI:0.34. The I2 value of 23% confirmed the absence heterogeneity among the included studies (I2 < 50%).

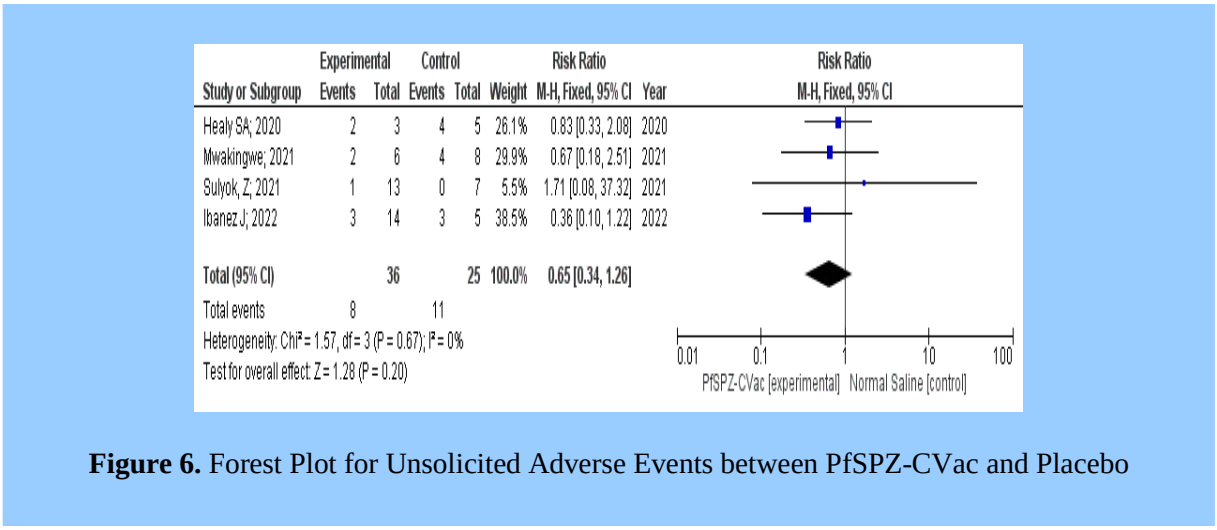

Figure 6. Forest Plot for Unsolicited Adverse Events between PfSPZ-CVac and Placebo

Unsolicited adverse event refers to a local or systemic reactions occurring after vaccination that was not specifically requested or anticipated. Based on the included study, unsolicited adverse evenst were minimal. Examples of such events included pneumothorax and anal fissure.

This comprehensive systematic review and meta-analysis employed a rigorous, systematic approach to assess the efficacy and safety of the *Plasmodium falciparum* Sporozoites Chemoprophylaxis Vaccine (PfSPZ-CVac) against malaria. By synthesizing data from various trials conducted across diverse geographic regions, the study enhances generalizability and reflects the vaccine's performance in varied populations. The findings of this study have significant implications for malaria control and elimination strategies. With emerging drug resistance and a need for novel interventions, the potential of PfSPZ-CVac as an effective and safe prophylactic tool could revolutionize malaria prevention efforts, particularly in high-risk regions.

Despite our results, this meta-analysis has several limitations. Limited long-term safety data: while the study assesses the vaccine's safety based on available trial data, its long-term safety profile remains uncertain. Variability in Malaria transmission settings: the vaccine's efficacy may be influenced by the intensity of malaria transmission in different regions. The study's inclusion of trials conducted in diverse settings may dilute the overall effectiveness if the vaccine performs differently under varying levels of transmission or in different Plasmodium falciparum strains.

CONCLUSION

Malaria remains a critical global health issue, particularly in regions with high transmission rates and limited healthcare resources. The innovative PfSPZ-CVac vaccine, which utilizes live *Plasmodium falciparum* sporozoites combined with chemoprophylaxis, shows promise in providing strong and lasting immunity. Unlike traditional vaccines, its whole-parasite approach stimulates a comprehensive immune response, potentially addressing the limitations of current prevention methods. Evidence suggested that PfSPZ-CVac could effectively reduce malaria transmission, making it a vital tool in combating the disease, especially in endemic regions.

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DECLARATION OF INTERESTS

The authors declare no conflicts of interest related to this research. There are no financial, personal, or professional relationships that could have influence the findings or interpretation of this study.

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ATTACHMENTS

Attachments are provided in the supplementary file.
https://drive.google.com/file/d/1fUSve0brXdWllyh1M-XSi0QZQP3g2LJv/view?usp=sharing