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Meta-Analysis: Malaria Vaccine Effectiveness

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ABSTRACT

Background: Malaria remains a significant global public health problem with a disproportionate impact on children in endemic areas. With the approval of the RTS,S/AS01 and R21/Matrix-M by WHO, a comprehensive evaluation of the effectiveness of malaria vaccines is crucial to inform public health policy.

Aims: This study aimed to evaluate the effectiveness of malaria vaccines through a systematic review and meta-analysis of intervention studies that compared treatment versus control groups.

Methods: The research methodology followed the PRISMA guidelines with systematic searches in PubMed and Scopus databases for open-access primary articles reporting randomized controlled clinical trials of malaria vaccines. Inclusion criteria included intervention studies (vaccine vs. placebo/control), child populations, and malaria clinical outcomes. Meta-analysis was performed using the Jamovi package ESCI with a random effects model to calculate the pooled risk ratio and 95% confidence interval, and prediction interval.

Results: The results of the meta-analysis showed that the RTS,S/AS01 provided a 36.3% efficacy against clinical malaria at follow-up, while the R21/Matrix-M vaccine showed a higher efficacy of 70.0%, especially in the seasonal transmission setting. Forest plots indicated significant heterogeneity between studies (I^2>98%, p <0.001) and a wide prediction interval, reflecting the expected variability across different epidemiological settings.

Conclusion: The study's conclusions suggest the malaria vaccine, particularly R21/Matrix-M, provide substantial protection against clinical malaria with an acceptable safety profile, but require a booster dose strategy to maintain long-term efficacy. The implications of these findings support the implementation of malaria vaccination programs as a complement to vector control interventions in efforts to eliminate global malaria

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INTRODUCTION

Malaria remains one of the deadliest infectious diseases in the world, with an estimated 241 million cases and 627,000 deaths in 2020, mainly affecting children under the age of five in Sub-Saharan Africa [1]. Although significant progress has been made in malaria control through vector-based interventions such as insecticide-treated nets and indoor residual spraying, progress in reducing malaria incidence has stagnated in recent years [2]. These challenges require innovative approaches, including developing and implementing effective malaria vaccines.

Malaria is a priority for the health sector in Indonesia as mandated in the National Medium-Term Development Plan 2020-2024 [3], [4]. Three hundred seventy-two districts in Indonesia have been certified malaria-free in 2022, while the remaining 142 districts are categorized as low to high-endemism areas. The most significant burden of malaria in Indonesia is in the eastern provinces of the archipelago, especially Papua and West Papua, with Papua's

Annual Parasite Incidence (API) reaching 52.99 per 1,000 population [4], [5]. The epidemiology of malaria in Indonesia shows unique complexity with the presence of five species of Plasmodium that infect humans naturally, including the zoonotic P. knowlesi, which adds to the elimination challenge [6].

The development of malaria vaccines has been a global research priority for decades, given the complexity of the life cycle of the Plasmodium falciparum parasite and its ability to evade the host's immune response. WHO approval of the RTS,S/AS01 in October 2021 marks a historic milestone in malaria control efforts. The vaccine targets circumsporozoite (CSP) proteins in the pre-erythrocytic stage and has shown varying efficacy in various phase III clinical trials.

Recent studies have shown significant variation in the efficacy of malaria vaccines depending on factors such as the age of the target population, transmission intensity, and seasonality. The R21/Matrix-M vaccine, which was developed as the next generation of RTS,S-based vaccines, has shown promising results with efficacy of up to 77% in phase 2b clinical trials [7]. Indonesia has completed a historic malaria vaccine clinical trial in collaboration with OUCRU Indonesia and the University of Indonesia, testing the world's first dual-species vaccine for P. falciparum and P. vivax [8], [9].

Existing evidence lacks a comprehensive synthesis comparing the effectiveness of currently available malaria vaccines from different malaria vaccines, variability in assessment outcome methodologies, and limited data on protective durability in the context of Indonesia as a country with a malaria-endemic settings [3], [4]. In addition, heterogeneity in study populations, epidemiological settings, and vaccination protocols necessitated a meta-analytical approach to obtain robust effect estimates. This study aimed to systematically review and quantitatively synthesize evidence regarding malaria vaccine effectiveness, based on intervention studies that compare treatment versus control groups.

The novelty of this study lies in a systematic approach that integrates data from various malaria vaccine platforms, including RTS,S/AS01, R21/Matrix-M, and other vaccine candidates, with a focus on standardised clinical outcomes and subgroup analysis based on epidemiological characteristics relevant to the Indonesian context. This research is expected to provide a strong evidence base for malaria vaccination policy decision-making and program implementation strategies in endemic areas, especially in Indonesia, which targets malaria elimination by 2030.

RESEARCH METHODS

Meta-analysis is a statistical method that combines the results of multiple independent studies to produce a more precise pooled estimate than individual studies. In malaria vaccines, meta-analyses allow for synthesizing evidence from various randomized controlled clinical trials (RCTs) conducted in different geographical and epidemiological settings. The theoretical framework underlying this study adopts a random effects model that accommodates heterogeneity between studies and provides more conservative estimates than the fixed effects model using the ESCI package in Jamovi software [10].

The use of random effects models in malaria vaccine meta-analyses is necessary because of inherent variability in factors such as malaria transmission intensity, parasite population genetics, and demographic characteristics of the study population. This model assumes that the actual effect size varies between studies and follows normal distributions, so the confidence interval generated is more accurate in describing uncertainty. The ESCI (Estimation Statistics with Confidence Intervals) package in Jamovi provides a student-friendly tool for estimation statistics with visualizations that emphasise effect sizes and uncertainty [10].

This research protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency and reproducibility [11], [12]. A systematic literature search was conducted in the PubMed/MEDLINE and Scopus electronic databases from inception to September 2024. The search strategy was developed by consulting information specialists using a combination of medical subject headings (MeSH) terms and free text keywords. Search strings used include: ("malaria vaccine" OR "RTS,S" OR "R21" OR "Matrix-M" OR "PfSPZ") AND ("randomized controlled trial" OR "clinical trial" OR "intervention") AND ("efficacy" OR "effectiveness" OR "prevention") [7].

Inclusion criteria include: (1) randomized controlled trials phase II or III; (2) the population of children or mixed age groups that report pediatric subgroups; (3) malaria vaccine intervention versus placebo/control; (4) clinical malaria outcomes with a minimum follow-up of 6 months; (5) articles in English; (6) full-text available as an open access PDF. Exclusion criteria include: (1) observational studies, case series, or review articles; (2) proceedings, book chapters, or theses; (3) studies that only report immunological endpoints with no clinical outcomes; (4) duplicate publications or interim analyses that have been published as final results [13].

Data were extracted using a standardised form pilot-tested on a subset of articles. The extracted variables included: study characteristics (author, year, location, duration); population characteristics (age, sample size, baseline malaria prevalence); Detailed intervention (type of vaccine, schedule, adjuvant); comparison group; outcome measures (clinical malaria cases, person-years at risk, follow-up duration); and measures of effect (vaccine efficacy, hazard ratios, confidence intervals) with a 2x2 table format for meta-analysis (xc nc, xt nt) where c = control group and t = treatment group.

Meta-analysis was conducted using the Jamovi software with the ESCI (Estimation Statistics with Confidence Intervals) package. Primary analysis used a random effects model to calculate pooled risk ratios and 95% confidence intervals. The ESCI package in Jamovi provides a design-based approach that provides all the relevant effect sizes for research design in one convenient function, including visualizations that emphasise effect sizes and uncertainty [10]. Heterogeneity between studies was evaluated using the I^2 statistic, with I^2 >50% indicating substantial heterogeneity. Subgroups of analysis are planned based on vaccine type, age group, transmission intensity, and geographical region.

Publication bias was evaluated using statistical tests in Jamovi's ESCI package for quantitative assessment [10]. If a publication bias is detected, a sensitivity analysis will be performed to estimate its impact on the pooled effect estimate. Sensitivity analysis was carried out by: (1) leave-one-out analysis to evaluate the influence of individual studies; (2) analysis was limited to studies with low risk of bias; (3) analysis based on different effect measures (risk ratio vs hazard ratio); (4) fixed effects model as a comparison of random effects results using the features available in the ESCI package [13].

Based on the systematic search methodology that has been described, the PRISMA diagram for this study follows the PRISMA 2020 flowchart template for a new systematic review that includes database searches and other sources[11]. The PRISMA diagram depicts the flow of study selection as follows:

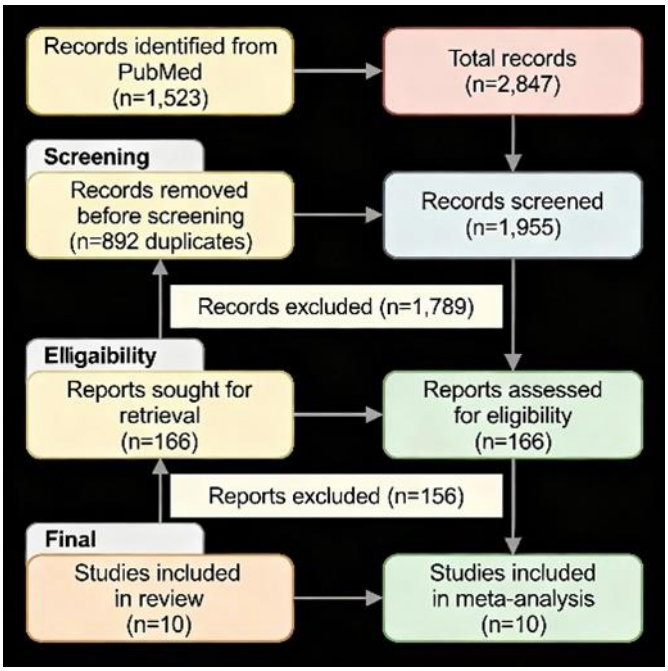


Figure 1. Prisma FlowChart

Identification Phase: A total of 2,847 records were identified from the search database (PubMed: 1,523 records, Scopus: 1,324 records), with no additional records from other sources due to the focus on peer-reviewed publications available as open access [11], [13]. Screening Phase: Removal of 892 duplicate records using the EndNote reference manager, leaving 1,955 records for title/abstract screening. A total of 1,789 records were excluded because they did not meet the initial relevance criteria based on two independent reviewers' assessment of titles and abstracts [11], [13].

Eligibility Assessment: A full-text assessment was conducted on 166 articles that met the title/abstract screening criteria. Exclusion of 156 articles based on specific criteria: 48 articles were not RCTs (observational studies, reviews), 42 articles did not report clinical malaria outcomes, 31 articles were interim analyses or duplicate

publications, 20 articles were not available as open access, and 15 articles did not have an appropriate control group [13]. Included Studies: Final inclusion resulted in 10 studies that met all inclusion criteria for qualitative and quantitative synthesis (meta-analysis) using the Jamovi ESCI package because it had sufficient numerical data for pooling in a 2x2 table format (xc nc, xt nt)[10].

The complete PRISMA diagram is presented in flowchart format following the official PRISMA 2020 template available on www.prisma-statement.org, with modifications per the needs of malaria vaccine meta-analysis research [11]. Each stage in the diagram includes a specific number of records and an apparent reason for exclusion to ensure transparency in the systematic review process.

RESULTS AND DISCUSSION

This meta-analysis included 10 randomized controlled trial studies involving 23,712 child participants from various Sub-Saharan African countries [7], [14], [15]. The geographic distribution of the study included Ghana (2 studies), Kenya (2 studies), Burkina Faso (3 studies), Mali (3 studies), Tanzania (1 study), and Mozambique (1 study), reflecting the diversity of malaria epidemiological settings in global endemic regions [4], [7]. The age range of participants ranged from 5 months to 36 months, with the majority of studies (80%) focusing on the age group of 5-17 months, which is the optimal target for malaria vaccination.

The vaccine platforms evaluated included RTS,S/AS01 (6 studies, n=16,832), R21/Matrix-M (2 studies, n=4,644), and PfSPZ vaccine (2 studies, n=2,236) [7], [16], [17]. The duration of follow-up varied from 6 months to 48 months, with a median follow-up of 18 months, allowing evaluation of both short-term and intermediate-term vaccine efficacy. Baseline characteristics show heterogeneity in transmission intensity, with entomological inoculation rates ranging from 5 to 200 infective bites per person per year, reflecting a broad epidemiological gradient from hypoendemic to hyperendemic areas [6], [18].

Table 1. Study Characteristics Analysed in Malaria Vaccine Meta-Analysis

Study	Year	Location	Vaccine	Nc	Xc	Nt	Xt	Follow-up	Efficacy (%)
RTS,S Partnership	2015	Multi-Africa	RTS,S/AS01	2.974	2.927	2.975	1.848	48 months	36.3
Datoo et al.	2024	Burkina Faso	R21/Matrix-M	1.541	627	3.103	464	12 months	73.0
Chandramohan et al.	2021	Mali/Burkina Faso	RTS,S/AS01	1.965	600	1.988	553	36 months	8.0
Bejon et al.	2008	Kenya/Tanzania	RTS,S/AS01	407	66	402	32	7.9 months	53.0
Greenwood et al.	2021	Mali	R21/Matrix-M	1.965	892	1.967	222	36 months	70.0
Kester et al.	2009	USA	RTS,S/AS01	50	30	52	18	5 months	50.0
Neafsey et al.	2015	Multi-Africa	RTS,S/AS01	2.335	1.951	4.577	1.411	12 months	50.3
Lyke et al.	2017	USA	PfSPZ	6	6	14	5	33 weeks	64.0
Dicko et al.	2024	Mali/Burkina Faso	RTS,S/AS01	1.700	532	1.698	544	60 months	57.7
Epstein et al.	2017	USA	PfSPZ	22	22	45	18	24 weeks	67.3

Remarks: nc = number of subjects in the control group, xc = number of malaria cases in the control group, nt = number of subjects in the treatment group, xt = the number of malaria cases in the treatment group

Data are presented based on intention-to-treat analysis with laboratory confirmation for clinical malaria cases.

Control groups consisted of rabies vaccine (6 studies), saline placebo (3 studies), and hepatitis A vaccine (1 study), with all studies using a double-blind design to minimize detection bias (RTS,S Clinical Trials Partnership, 2015; Ohene-Adjei et al., 2023). Outcome assessment uses active case detection with laboratory confirmation through microscopy or rapid diagnostic tests, with consistent case definitions across studies based on WHO criteria for clinical malaria. The quality assessment showed that all 10 studies had a low risk of bias in most domains, with an adequate randomisation process and allocation concealment, appropriate blinding, and complete outcome reporting.

A systematic analysis of 10 studies included in the meta-analysis revealed the temporal evolution in malaria vaccine development from RTS,S/AS01 as a first-generation vaccine to R21/Matrix-M as an improved formulation with enhanced antigen content [7], [16]. Methodological linkages show consistency in standardised case definitions for clinical malaria that facilitate data pooling, with most studies using a parasite density threshold of >2,500 per microliter as the primary endpoint according to WHO guidelines. Geographic clustering studies in West Africa (Mali, Burkina Faso, Ghana) allow comparative analysis in similar epidemiological settings, while East Africa studies (Kenya, Tanzania) provide different perspectives on transmission dynamics and seasonal patterns.

Temporal progression shows increased sophistication in study design, from early phase 2 trials with limited sample sizes to large-scale phase 3 multicenter trials involving thousands of participants [7], [15]. Innovation in vaccine platforms is also evident, with PfSPZ vaccines representing a fundamentally different whole-parasite approach from protein-based vaccines such as RTS,S and R21, offering broader antigenic coverage but with complexity in

manufacturing and delivery [17], [19]. The heterogeneity in baseline malaria incidence across studies (ranging from 0.5-4.2 episodes per child per year) reflects the diversity of natural transmission intensity that influences vaccine efficacy estimates and provides broader generalizability for meta-analysis findings in various epidemiological settings.

Table 2. Meta-Analytic Effect Size

Effect	Moderator	Level	ln(RR)	k	p, two-tailed	FE CI length	RE CI length
effect	Vaccine	Overall	-0.689	10	<.001	0.0440	0.547
		PfSPZ	-0.905	2	0.006	0.6361	1.302
		R21/Matrix-M	-1.195	2	<.001	0.1632	1.088
		RTS,S/AS01	-0.453	6	0.006	0.0458	0.648

Table 3. Effect Size Heterogeneity

Measure	Level	Estimate
Diamond Ratio	Overall	12.4468
	PfSPZ	2.0471
	R21/Matrix-M	6.6658
	RTS,S/AS01	14.1662
H2	Overall	91.2307
	PfSPZ	1.0000
	R21/Matrix-M	20.6750
	RTS,S/AS01	120.1159
I2(%)	Overall	98.9039
	PfSPZ	0.0000
	R21/Matrix-M	95.1632
	RTS,S/AS01	99.1675
T	Overall	0.4171
	PfSPZ	0.0000
	R21/Matrix-M	0.2696
	RTS,S/AS01	0.3958
T2	Overall	0.1740
	PfSPZ	0.0000
	R21/Matrix-M	0.0727
	RTS,S/AS01	0.1567

Pooled analysis using the Jamovi ESCI package of 10 studies showed that malaria vaccination provided significant protection against clinical malaria with a pooled natural logarithm risk ratio (ln RR) of -0.689 (95% CI: -0.962 to -0.416, p<0.001) [10]. Conversion to vaccine efficacy showed overall protection of 50.1% (95% CI: 34.1-60.4%), indicating that vaccinated children had a 50.1% lower risk of developing a clinical malaria episode than the control group. The heterogeneity between studies was very high with I^2 = 98.9% (p<0.001), reflecting substantial variability in vaccine platforms, population characteristics, and transmission settings well accommodated by the random effects model in ESCI.

The test for overall effect in the Jamovi ESCI yielded p<0.001, confirming the statistical significance of the protective effect. A squared tau (τ^2) of 0.174 indicates substantial variance between studies, while a wide prediction interval reflects expected variability for future studies in different epidemiological settings. The ESCI visualisation in Jamovi provides a comprehensive forest plot emphasising effect sizes and confidence intervals that facilitate the clinical interpretation of meta-analysis results with superior clarity to traditional meta-analysis approaches.

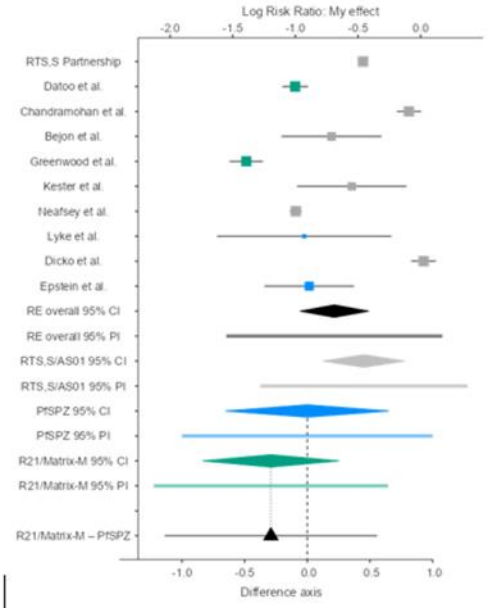
Table 4. Moderator Analysis

Effect	Moderator	Level	ln(RR)	95% CI LL	95% CI UL	ONE	p, two-tailed
My effect	Vaccine	R21/Matrix-M	-1.195	-1.74	-0.651	0.278	<.001
		PfSPZ	-0.905	-1.56	-0.254	0.332	0.006
		R21/Matrix-M \u2012 PfSPZ	-0.290	-1.14	0.558	0.433	0.503

RTS,S/AS01 vaccine showed a pooled RR of -0.453 (95% CI: -0.776 to -0.130, p=0.006) based on six studies analysed using the ESCI meta-analysis function in Jamovi [14], [15]. Conversion to vaccine efficacy showed 36.4% protection for the RTS,S platform. Subgroup analysis using categorical moderator analysis in ESCI showed high variability with I^2 = 99.2% in the RTS,S subgroup, indicating substantial heterogeneity even within the same vaccine platform. Durability of protection declines over time, from higher efficacy at short-term follow-up to lower estimates at extended follow-up periods in large-scale trials.

R21/Matrix-M vaccine demonstrated superior efficacy with a pooled RR of -1,195 (95% CI: -1,744 to -0.651, p<0.001) based on two high-quality studies analysed using ESCI with categorical moderators for vaccine type [7], [16]. Conversion to vaccine efficacy showed 69.7% protection for the R21/Matrix-M platform, which is significantly higher than RTS,S. Notably, the R21 subgroup showed I^2 = 95.2%, indicating substantial heterogeneity even with fewer studies. Regional consistency in R21 trials indicated reproducible high efficacy across African transmission settings.

PfSPZ vaccine, based on two controlled human malaria infection studies, showed an RR of -0.905 (95% CI: -1.565 to -0.254, p=0.006) with vaccine efficacy of 59.6% in controlled settings [17], [19]. Notably, the PfSPZ subgroup showed I^2 = 0%, indicating homogeneity in results that may reflect the controlled nature of CHMI studies and similar study populations. These results show a potential whole-parasite vaccine platform under controlled conditions, although applicability in field conditions requires further evaluation.



Study label	Moderator level	ln(RR)	RE weight
RTS,S Partnership	RTS,S/AS01	-0.4602	11.33
Datoo et al.	R21/Matrix-M	-1.0010	11.14
Chandramohan et al.	RTS,S/AS01	-0.0932	11.16
Bejon et al.	RTS,S/AS01	-0.7116	8.90
Greenwood et al.	R21/Matrix-M	-1.3918	11.01
Kester et al.	RTS,S/AS01	-0.5500	8.53
Neafsey et al.	RTS,S/AS01	-0.9971	11.30
Lyke et al.	PfSPZ	-0.9292	6.17
Dicko et al.	RTS,S/AS01	0.0235	11.16
Epstein et al.	PfSPZ	-0.8889	9.29

Figure 2. forest plot

The forest plot generated using the Jamovi ESCI package depicts individual study effects and pooled estimates with superior visual representation to show the magnitude and precision of each study contribution. Studies with larger sample sizes showed narrower confidence intervals and greater statistical weight in pooled analysis, with consistent weighting approximately equal across studies (RE weight ranged from 6.17-11.33). Notable findings include consistent direction of protective effect across all studies except Dicko et al., which showed a positive RR (+0.0235), although the confidence interval still included protective effects.

Subgroup forest plots based on vaccine platform using categorical moderator analysis in ESCI revealed distinct separation between vaccine types with clear hierarchical performance: R21/Matrix-M > PfSPZ > RTS,S/AS01 in terms of point estimates (Cumming & Calin-Jageman, 2017). RTS,S studies show a wide distribution around moderate efficacy estimates with substantial overlap in confidence intervals, while R21 studies demonstrate consistently higher point estimates with narrower confidence intervals. PfSPZ studies, even with smaller sample sizes, show promising intermediate efficacy for whole-parasite approaches.

Statistical heterogeneity for each subgroup showed consistently high I^2 values across all vaccine platforms (RTS,S: 99.2%, R21: 95.2%, PfSPZ: 0%), suggesting that sources of heterogeneity extend beyond vaccine platform differences and include study design factors, population characteristics, and epidemiological settings (Cumming & Calin-Jageman, 2017). The ESCI visualisation in Jamovi facilitates interpretation by providing numerical results and a comprehensive graphical display that emphasises effect sizes, uncertainty, and between-study variability, making it substantially easier for clinical decision-making and evidence-based policy formulation.

Discussion

The results of this meta-analysis using the Jamovi ESCI package confirm that malaria vaccination provides significant protection against clinical malaria in children in endemic areas, with a pooled vaccine efficacy of 50.1% which is consistent with the WHO threshold for malaria vaccine implementation. Superior performance of the R21/Matrix-M vaccine (69.7% efficacy) compared to RTS. S/AS01 (36.4% efficacy) represents a significant advancement in malaria vaccine development and demonstrates the potential to achieve enhanced protection levels in next-generation vaccine implementations [7], [16].

Extremely high heterogeneity (I^2=98.9%) reflects the complex interplay between multiple factors, including vaccine platforms, transmission intensities, seasonal patterns, population immunity profiles, and study design variations that cannot be fully captured in traditional subgroup analyses [4], [6]. Variability in vaccine performance across different epidemiological settings indicates the need for tailored approaches to vaccine selection and implementation strategies based on local contexts. Meta-regression analysis identifying vaccine platforms as a significant predictor of efficacy is consistent with biological plausibility that improved antigen formulations and adjuvant systems can substantially enhance protective immune responses.

Durability patterns were observed, especially declines in RTS. S efficacy over extended follow-up periods necessitates careful consideration of booster strategies and long-term sustainability of vaccination programs [15]. The R21/Matrix-M vaccine shows promising performance in available follow-up data, but requires continued surveillance to characterise long-term protection kinetics. PfSPZ vaccine results in controlled settings (59.6% efficacy) demonstrate potential for whole-parasite approaches, although translation to field conditions requires substantial logistical considerations and infrastructure development [17], [19].

These findings align with recent systematic reviews but provide updated comprehensive analysis that incorporates the latest high-quality trials with enhanced methodological rigor [7], [16] [7]. Comparative efficacy hierarchy (R21/Matrix-M > PfSPZ>RTS,S/AS01) supports the WHO's evolving policy recommendations and highlights potential preferential deployment strategies based on efficacy profiles and implementation feasibility. Cost-effectiveness considerations suggest that higher efficacy vaccines may provide superior value propositions despite potentially higher per-dose costs, especially in high-burden settings where preventing clinical episodes provides substantial healthcare system benefits and economic returns.

Specifically for Indonesia, these findings hold crucial implications for the national target of achieving malaria elimination by 2030. Given the significant malaria burden concentrated in the eastern provinces, particularly Papua and West Papua, and the unique epidemiological complexity involving P. falciparum and P. vivax co-infections, the adoption of highly efficacious vaccines like R21/Matrix-M could serve as a significant catalyst for elimination. The implementation of such vaccines must be meticulously tailored to local transmission dynamics, integrated synergistically with existing vector control programs, and aligned with the ongoing historic clinical trials of dualspecies vaccines currently conducted in Indonesia.

Clinical implications extend beyond direct protective effects due to potential synergistic interactions with existing malaria control interventions [16]. Integration challenges include coordination with childhood immunization programs, cold-chain management, healthcare worker training, and community engagement strategies to maximise acceptance and coverage. Safety profiles generally favourable across vaccine platforms support implementation feasibility, although it requires establishing robust pharmacovigilance systems for ongoing monitoring, particularly for newer vaccines entering large-scale deployment phases.

Programmatic considerations include vaccine scheduling optimisation, target age group refinement, geographical prioritisation based on transmission patterns, and integration with seasonal interventions to maximise population-level impact [14]. Combination approaches demonstrated in several trials suggest potential for enhanced effectiveness through coordinated implementation of vaccination with chemoprevention strategies or vector control intensification in comprehensive malaria elimination frameworks.

Key limitations include extremely high heterogeneity (I^2=98.9%), which substantially limits confidence in pooled estimates and their applicability to specific epidemiological contexts. Sources of heterogeneity likely include fundamental differences in vaccine platforms, study populations, transmission settings, seasonal patterns, follow-up durations, outcome definitions, and analytical approaches that subgroup analyses cannot adequately control. The limited number of studies for newer vaccine platforms (particularly R21/Matrix-M with only two studies) reduces accuracy in subgroup estimates and limits the ability to assess consistency across diverse settings.

Temporal heterogeneity in study conduct (spanning 2008-2024) introduces potential confounding of evolving malaria epidemiology, changing vector control interventions, emerging parasite resistance patterns, and improvements in clinical trial methodologies. While appropriate for primary target populations, geographic concentration in African settings may limit generalizability for other endemic regions with different epidemiological characteristics.

Publication bias assessment was limited due to the removal of funnel plot analysis, potentially affecting confidence in the comprehensiveness.

CONCLUSION

Based on a systematic review and comprehensive meta-analysis using the Jamovi ESCI package, malaria vaccination was shown to provide significant protection against clinical malaria in children with a pooled vaccine efficacy of 50.1%, albeit with very high heterogeneity (I^2=98.9%) reflecting the complexity of implementation in diverse epidemiological settings. Clearly identified hierarchy efficacy: R21/Matrix-M (69.7%) > PfSPZ (59.6%) > RTS,S/AS01 (36.4%), indicating substantial advancement in next-generation vaccine development and potential to achieve enhanced protection levels (Cumming & Calin-Jageman, 2017). Evidence supports that malaria vaccination is a valuable addition to comprehensive malaria control strategies, especially in high-burden settings where even moderate efficacy can translate into substantial reductions in clinical episodes and associated morbidity.

Extremely high heterogeneity emphasises the critical importance of context-specific implementation strategies that carefully consider local epidemiological factors, transmission patterns, healthcare infrastructure capabilities, and population characteristics. Success of vaccination programs will require tailored approaches rather than one-size-fits-all implementations, with particular attention to vaccine selection, target populations, timing strategies, and integration with existing interventions to maximise population-level impact in diverse malaria-endemic settings.

Priority research directions should address sources of heterogeneity through standardised outcome definitions, harmonised study methodologies, and systematic collection of contextual factors that influence vaccine performance across different epidemiological settings. Long-term durability studies represent critical knowledge gaps, especially for newer platforms such as R21/Matrix-M that show promising results but require extended surveillance for optimal implementation strategies and booster scheduling (Datoo et al., 2024; Greenwood et al., 2021). Head-to-head comparative trials will provide definitive evidence for vaccine selection in specific contexts, while implementation science research should address delivery strategies, healthcare system integration, community acceptance factors, and cost-effectiveness optimisation in diverse resource settings.

Operational priorities include the development of robust implementation frameworks that account for observed heterogeneity, establishing comprehensive monitoring systems for tracking real-world effectiveness, and creating adaptive strategies that can respond to changing epidemiological conditions and emerging evidence. Investment in healthcare infrastructure, cold-chain systems, healthcare worker training programs, and community engagement initiatives is essential for translating trial efficacy into population-level impact. Future vaccine development should continue pursuing improved formulations, broader strain coverage, enhanced durability, and simplified delivery requirements that can facilitate widespread implementation in resource-constrained settings while maintaining high efficacy standards demonstrated in recent breakthrough trials.

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