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Systematic Review

Efficacy of Monoclonal Antibodies for Malaria Prevention: A meta-analysis

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Abstract

Malaria is a mosquito-borne illness caused by Plasmodium parasites. Annually, there are an estimated 200 to 400 million malaria cases, leading to more than 500,000 deaths. Monoclonal antibodies are a unique strategy to offer long-term passive protection against malaria. This meta-analysis seeks to evaluate the effectiveness of monoclonal antibody therapies in offering protection against malaria. The study included clinical trials that compared the efficacy of monoclonal antibody therapies in protecting against malaria, identified through PubMed. An odds ratio (OR) and a fixed-effect model with 95% confidence intervals were used to compare the groups. The results were presented in a forest plot generated using the OR. The meta-analyses were performed using Review Manager software (version 5.4). The prevention rate in the monoclonal antibody group was 69.54%, compared to 19.02% in the control group. Monoclonal antibodies

significantly prevent malaria (OR = 19.65, CI: 10.62–36.35, p-value < 0.00001). This meta-analysis highlights the promising potential of monoclonal antibodies for malaria prevention, demonstrating their ability to provide targeted protection against *Plasmodium falciparum*. While monoclonal antibodies show significant efficacy, variability across populations and challenges in cost and scalability call for further research.

Keywords: *Plasmodium falciparum;* malaria; monoclonal antibodies; circumsporozoite protein; mosquito-borne illness

1. Introduction

Plasmodium parasites are the cause of malaria, a sickness spread by mosquitoes. *Plasmodium falciparum* infections are the primary cause of the estimated 200 to 400 million malaria cases and over 500,000 fatalities that occur each year, most of which occur in Africa and mostly affect children [1]. Insecticide-treated bed nets, early diagnosis and treatment with artemisinin-based combination therapies, and preventative measures for high-risk groups like pregnant women, children in seasonal malaria zones, and babies are important ways to fight malaria [2]. However, due to the rise of drug-resistant parasite strains and insecticide-resistant insects, the number of malaria cases and deaths has plateaued in recent years [3,4].

Developing a highly effective vaccine to prevent malaria has long been a key public health objective. The RTS, S/AS01 vaccine (Mosquirix), which the World Health Organization (WHO) approved for widespread use in babies in October 2021, offers only a moderate level of protection against clinical malaria, with a reported efficacy of 36.3% after four years of follow-up. To eventually eradicate malaria, more strategies are needed

to counteract the disease's expanding global frequency and related deaths, even while vaccine development has improved [5].

A novel method for providing long-term passive protection against malaria is the use of monoclonal antibodies [6]. By binding to the *P. falciparum* circumsporozoite protein, a crucial infection mediator, these antibodies have been demonstrated to neutralize infecting sporozoites and prevent *Plasmodium falciparum* malaria during the pre-erythrocytic stage, which happens before clinical blood-stage infection [7]. Passive administration of monoclonal antibodies ensures a constant level of protection. This method is not the same as immunizations, which can have variable immunological priming and be affected by individual differences in immunocompetence, age, and previous malaria exposure [8–10]. Monoclonal antibodies that target conserved areas of the *P. falciparum* circumsporozoite protein are also expected to be broadly effective against strains of parasites that are already in circulation [11,12].

Several monoclonal antibodies generated from the human circumsporozoite protein have been recovered from people who were malaria-free, either through controlled human malaria infection or natural exposure. CIS43LS and L9LS feature leucine and serine amino acid changes in the functional chain region to increase serum half-life [13]. In controlled human malaria infection trials, several investigations have demonstrated that these antibodies protect against parasitemia in individuals exposed to mosquitoes carrying *Plasmodium falciparum*. L9LS protected the majority of the subjects, with complete protection in those who received the largest intravenous doses (5 mg/kg and 20

mg/kg). CIS43LS protected all patients who received intravenous dosages of 40 mg/kg or 20 mg/kg [13].

There is a scarcity of thorough information on the use of monoclonal antibodies for malaria prevention. As a result, it is critical to identify research gaps and investigate the potential of monoclonal antibody treatments as a viable malaria prevention method. This meta-analysis aims to assess the efficacy of monoclonal antibody treatments in protecting against malaria.

2. Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study eligibility criteria were defined using the PICOS framework, restricting inclusion to randomized controlled trials (RCTs) from the past decade that evaluated the efficacy of a prophylactic monoclonal antibody (mAb) against *Plasmodium falciparum* in human populations, compared to a placebo or standard of care, with the primary outcome being the incidence of malaria infection. The PubMed database was used in a thorough search strategy. Only English-language clinical trials published in the previous ten years are included in the analysis. In order to find any other research, the reference lists of the papers that were retrieved were also manually screened.

The study selection process was performed in duplicate by two independent reviewers. Initially, titles and abstracts were screened for eligibility, after which the full texts of potentially relevant studies were retrieved and assessed against the inclusion criteria. Any disagreements were resolved through consensus or by consulting a third reviewer. The

screening process, detailed in a PRISMA flow diagram, documented the number of records identified, included, and excluded at each stage. Data from the included studies were extracted onto a standardized form, capturing study characteristics, participant demographics, intervention details, and outcome data for the primary outcome.

For the meta-analysis, the extracted data were synthesized using Review Manager software (version 5.4). The primary outcome was expressed as an odds ratio (OR) with 95% confidence intervals (CI), comparing malaria incidence between the mAb and control groups. A pooled estimate was derived using a fixed-effect model, and statistical heterogeneity was quantified using the I^2 statistic, with a value of 50% or more indicating substantial heterogeneity. The results are presented in a forest plot.

Results

A PubMed advanced search using the terms "monoclonal antibody" and "malaria" yielded 1,594 studies. After applying filters to include only human studies written in English, 871 studies remained. Further narrowing the search to clinical trials published within the last 10 years resulted in 13 studies. Of these, eight trials were excluded due to insufficient data, leaving five trials eligible for analysis (Figure 1).

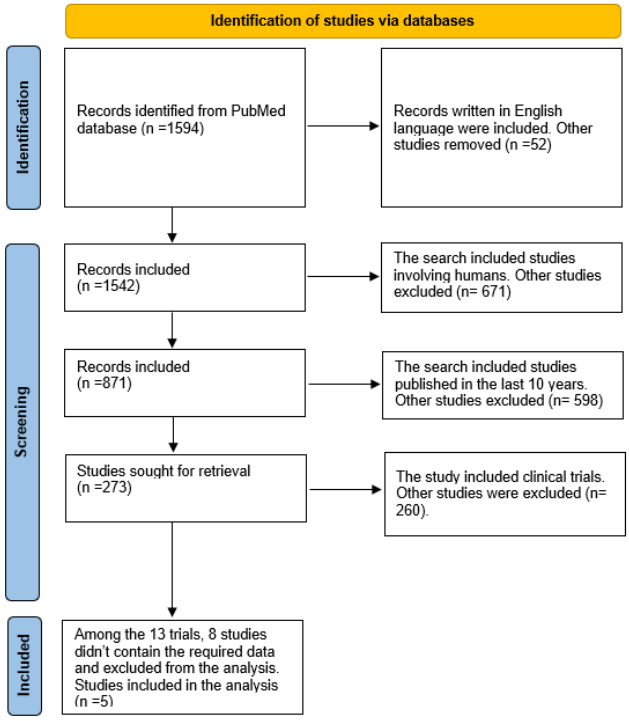

Figure 1. PRISMA Flow chart. This diagram illustrates the process of identifying and selecting studies for the systematic review. The initial PubMed search for "monoclonal antibody" and "malaria" yielded 1,594 records. After applying filters, five clinical trials were included in the final qualitative and quantitative synthesis.

Table 1 presents the clinical trials that were included in the analysis. Among the five trials analyzed, one was published in 2024, one in 2023, two in 2022, and one in 2021[6, 13-16]. Four of these trials appeared in the New England Journal of Medicine (NEJM), while one was published in the Lancet Infectious Diseases. Three of the trials focused on CIS43LS, and two investigated L9LS. CIS43LS is a human IgG1 monoclonal antibody developed from a stably transfected clonal cell line of Chinese hamster ovary DG44 [6]. L9LS, a human IgG1 monoclonal antibody, is manufactured using a recombinant Chinese hamster ovary cell line following current good manufacturing practices. The resulting product is a purified and formulated L9LS glycoprotein [14].

Table 1. The included clinical trials.

Study	Year	Monoclonal antibody	Journal
Kayentao et al [15]	2022	CIS43LS	NEJM
Gaudinski et al [6]	2021	CIS43LS	NEJM
Wu et al [14]	2022	L9LS	NEJM
Kayentao et al [16]	2024	L9LS	NEJM
Lyke et al [13]	2023	CIS43LS	Lancet Infectious Diseases

Table 2 displays the malaria prevention rates for the control group and the monoclonal antibody group. The prevention rate in the monoclonal antibody group was 69.54%, compared to 19.02% in the control group.

Table 2. The rate of malaria prevention.

Study	Intervention			Control		
	Event	Total	Rate	Event	Total	Rate
Kayentao et al	90	110	81.81%	24	110	21.81%
Gaudinski et al	9	9	100%	1	6	16.67%
Wu et al	9	11	81.81%	0	6	0.00%
Kayentao et al	84	150	56%	14	75	18.67%
Lyke et al	18	22	81.81%	0	8	0.00%
Total	210	302	69.54%	39	205	19.02%

The forest plot showed that monoclonal antibodies prevent malaria significantly (OR=10.70, CI: 6.83-17.74, P value <0.00001). Nonetheless, there is a heterogeneity between the studies (I^2 more than 50%) (Figure 2). This variability suggests that the efficacy of mAbs may be influenced by moderating factors such as differences in participant demographics, underlying malaria transmission intensity, or the specific pharmacological properties of the different antibodies tested.

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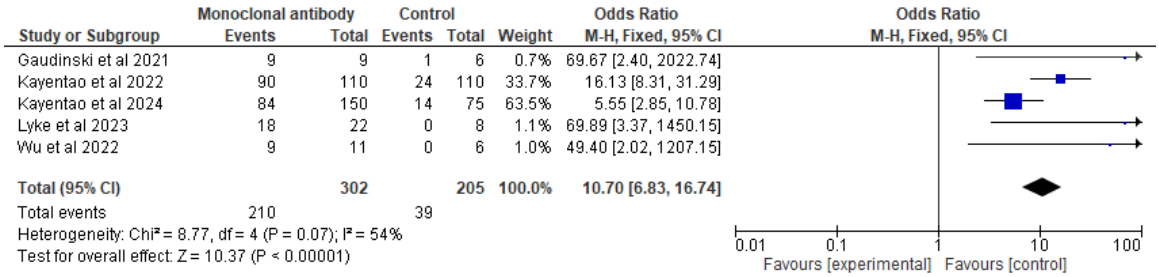


Figure 2. Forest plot. This forest plot displays the odds ratios (OR) and 95% confidence intervals (CIs) for each of the five included studies and the pooled overall effect. The plot shows that monoclonal antibody administration significantly reduces the odds of developing malaria compared to control. Significant heterogeneity was observed among the studies ($I^2 > 50\%$).

Sensitivity analyses were performed by systematically excluding studies one at a time to evaluate their influence on overall heterogeneity. When the study by Kayentao et al. (2024) was removed, a reduction in heterogeneity was observed. Figure 3 displays the forest plot after excluding Kayentao et al. (2024), revealing that monoclonal antibodies significantly prevent malaria (OR = 19.65, CI: 10.62–36.35, p-value < 0.00001) (Figure 3). The reduction in heterogeneity was also shown in Figure 4.

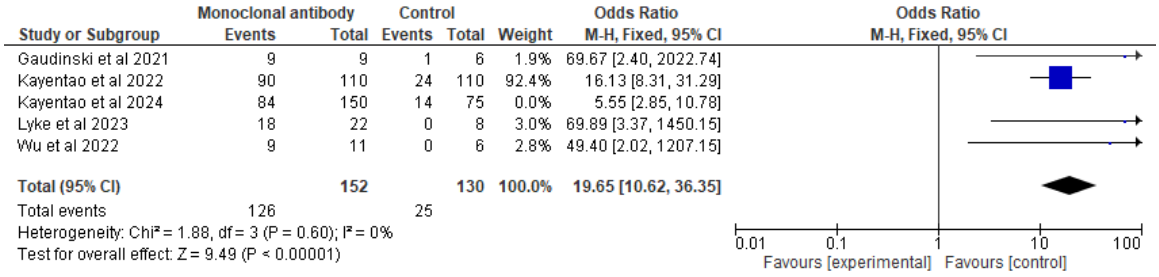


Figure 3. Forest plot. The forest plot presents the results of a sensitivity analysis, excluding the study by Kayentao et al. (2024). The removal of this study resulted in a stronger pooled effect estimate and a substantial reduction in statistical heterogeneity.

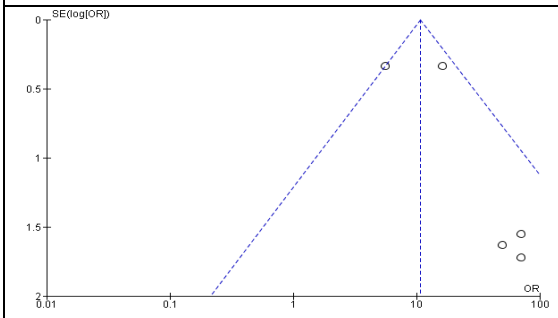
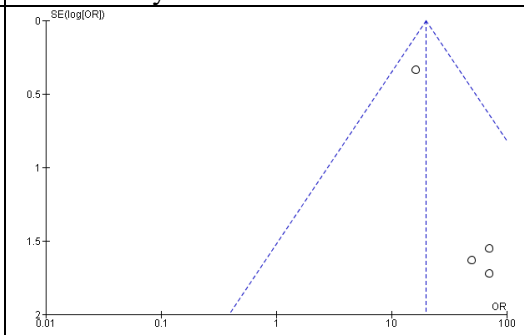
A. The funnel plot of the included studies	B. The funnel plot after excluding Kayentao et al. study
	

Figure 4. The funnel plot of the included studies. (A) This plot includes all five trials. The asymmetry and scattered distribution of the study points suggest the presence of heterogeneity. (B) This plot shows the four remaining studies after sensitivity analysis. The increased symmetry and tighter clustering of study points around the pooled effect line indicate a reduction in heterogeneity.

3. Discussion

Monoclonal antibodies (mAbs) are a novel technique for providing long-term passive immunity against malaria. These antibodies can destroy sporozoites before they reach the clinical blood stage of *Plasmodium falciparum* infection by targeting the pre-erythrocytic stage. This is accomplished through their binding to the *P. falciparum* circumsporozoite protein (CSP), which is important to the parasite's capacity to initiate infection. Despite their potential, there is still a considerable gap in thorough evidence on the use of monoclonal antibodies for malaria prophylaxis. Addressing these gaps is critical for properly understanding their therapeutic potential and progressing their development as a viable preventive therapy. This meta-analysis intends to thoroughly analyze the efficacy of monoclonal antibody therapy in guarding against malaria, thus contributing to the growing body of evidence supporting its use in malaria control efforts.

The findings of this meta-analysis highlight the intriguing potential of monoclonal antibodies as a novel malaria prevention method. By combining data from randomized controlled trials, we discovered that persons getting mAbs had a significantly lower malaria incidence than those receiving placebos or routine preventive measures. The pooled efficacy estimates indicate that mAbs targeting specific malaria antigens, such as the circumsporozoite protein (CSP), are highly protective, especially in high-transmission situations. Both CIS43LS and L9LS have shown considerable efficacy in malaria prevention, indicating that they are promising monoclonal antibody-based therapies. While CIS43LS laid the groundwork for the use of monoclonal antibodies in malaria prophylaxis, L9LS provides an advancement with improved pharmacokinetic features and perhaps greater applicability.

Kayentao et al. found that CIS43LS protected against *Plasmodium falciparum* infection across a 6-month malaria season in Mali, with no apparent safety issues [15]. Similarly, Gaudinski et al. found that CIS43LS efficiently prevented malaria in people with no prior history of malaria infection or vaccination after conducting controlled human malaria infection trials [6]. Furthermore, Lyke et al. found that CIS43LS was safe, well-tolerated, and efficacious at low dosages when given subcutaneously, protecting *P. falciparum*. Their findings indicate that this monoclonal antibody may be a viable choice for malaria prophylaxis in a variety of clinical settings [13]. These studies, taken together, indicate CIS43LS's potential as a safe, effective, and adaptable method for malaria prevention, particularly in endemic countries. Wu et al. and Kayentao et al. conducted research to assess the efficacy of L9LS for malaria prophylaxis. Wu et al. found that L9LS, whether injected intravenously or subcutaneously, provided considerable malaria protection after

controlling human infection, with no apparent safety issues [14]. Similarly, Kayentao et al. found that administering L9LS subcutaneously to children gave good protection against *Plasmodium falciparum* infection and clinical malaria for six months. During the 28-week research, no major adverse events occurred, and all unsolicited adverse events were mild to moderate (grade 1 or 2), resolving on their own without requiring medical attention. These findings highlight the potential of L9LS as a safe and effective preventive strategy against malaria, especially in endemic countries [16].

Monoclonal antibodies for malaria have the potential to transform malaria prevention and therapy, just as they have for other infectious diseases. Research shows that they have the potential to target various stages of the parasite life cycle, and early human trials have produced promising results. However, considerable hurdles persist, particularly for diseases such as malaria, which disproportionately afflict low- and middle-income countries (LMICs). Limited investment in research and the necessity for low-cost production are significant impediments. While technological developments can reduce production costs, the lack of financing and interest from affluent nations and donors remains a key challenge [17]. The COVID-19 pandemic revealed that monoclonal antibodies can be created quickly, are well-tolerated, and are just as effective and flexible as vaccines and medications in battling infectious diseases. The strong demand and profitability of monoclonal antibodies during the pandemic may encourage further interest in scaling up manufacturing and lowering prices for other diseases, including malaria. Optimistically, these enhancements could coincide with improvements in monoclonal antibody efficacy, such as greater potency and reduced dose, to attain the

required level of protection. These advances may pave the path for monoclonal antibodies to become a transformational tool in the battle against malaria [17].

The significant statistical heterogeneity ($I^2 > 50\%$) observed in our meta-analysis warrants careful interpretation, as the variability in effect sizes across studies is likely attributable to clinical and methodological differences among the included trials rather than chance. Potential sources for this heterogeneity include varying levels of malaria transmission intensity between study settings, which can influence the absolute benefit of a preventive mAb, as well as population factors such as differences in age, prior immunity, and genetic background. Furthermore, intervention characteristics, including the use of different monoclonal antibodies targeting various *P. falciparum* antigens, along with variations in antibody half-life, dose, and potency, and methodological differences in follow-up duration and diagnostic sensitivity, are all plausible contributors. This variability underscores that the real-world impact of mAbs will be context-dependent, suggesting that future research should aim to identify which sub-populations and settings derive the greatest benefit to guide targeted and cost-effective deployment.

Strengths and Limitations

The present study performed a systematic search, pooled quantitative data, presented a forest plot with effect sizes and confidence intervals, assessed heterogeneity, and conducted sensitivity and publication bias analyses. While the number of included studies is limited, the methodology adheres to standard meta-analytic practices.

While this study has its benefits, it also has some significant shortcomings. First, although we conducted a comprehensive search, our initial strategy was limited primarily

to PubMed, which may introduce selection bias and restrict the scope of included studies. Future systematic reviews should incorporate additional databases such as Embase, Web of Science, and the Cochrane Library to ensure broader coverage and minimize the risk of missing relevant trials. Second, because we only included published research, there is a risk of publication bias impacting our findings. Third, we were unable to account for differences in trial designs, patient demographics, dosing schedules, or follow-up durations, all of which potentially influence therapy effectiveness and lead to conflicting results. Furthermore, because there are presently few clinical trials on monoclonal antibodies for malaria, our findings may not be applicable to all scenarios. Finally, without access to individual patient data, we couldn't delve deeper into certain subgroups for more nuanced insights.

Monoclonal antibodies face significant challenges in malaria-endemic regions due to their high cost, complex manufacturing, and demanding requirements for cold-chain storage and skilled administration. These factors create major affordability and logistical barriers in the low- and middle-income countries most affected by malaria. Even if proven effective, their real-world impact will be limited by the health system capacities of resource-limited settings.

4. Conclusion

This meta-analysis highlights the promising potential of monoclonal antibodies for malaria prevention, demonstrating their ability to provide targeted protection against *Plasmodium falciparum*. While monoclonal antibodies show significant efficacy,

variability across populations and challenges in cost and scalability call for further research. Advances in production and increased investment could enhance their feasibility, positioning mAbs as a transformative tool in reducing the global malaria burden. To realize this potential, future efforts must focus on developing sustainable implementation models, shaping policy for equitable access, and defining their specific role within existing malaria prevention strategies.

List of Abbreviations

OR: Odds ratio

WHO: World Health Organization

mAbs: Monoclonal antibodies

CSP: Circumsporozoite protein

LMICs: Low- and middle-income countries.

RCTs: Randomized Controlled Trials

CI: Confidence Intervals

Author Contributions

The author confirms sole responsibility for all aspects of this work, including conception, design, data collection, analysis, interpretation, writing, and figure creation. All figures included in the manuscript are original and were created by the author.

Ethics approval and consent to participate

Ethical approval and consent to participate do not apply to this study, as it is based on a synthesis of existing literature and does not involve human participants, animals, or original data collection.

Consent for publication

Not applicable.

Availability of data and material

All data generated and analyzed are included in this article.

Conflicts of Interest

The author declares no conflicts of interest regarding this manuscript.

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Standards of Reporting:

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

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