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The Effect of Malaria on Responses to Unrelated Vaccines in Animals and Humans: A Systematic Review and Meta-Analysis

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Keywords: immunity | malaria | meta-analysis | systematic review | vaccines

ABSTRACT

Vaccine efficacy varies globally, often showing reduced immune responses in low- and middle-income countries, possibly due to the immunomodulatory effects of parasitic infections like malaria. This systematic review evaluates the impact of malaria on immune responses to unrelated vaccines in humans and animals. We systematically searched five databases—MEDLINE, Web of Science, Global Health, Scopus and Embase—up to 5th December 2023. Eligible studies compared immune responses to WHO-approved vaccines between malaria-infected and uninfected groups, or between antimalarial-treated and untreated groups. Meta-analysis was performed using random-effects models with standardised mean differences (SMDs) as summary statistics. The study is registered with PROSPERO (CRD42022298053). Twenty-four articles (17 human, 7 animal) met the inclusion criteria, with 13 human articles contributing data for the meta-analysis. Significant heterogeneity was observed. Vaccine responses were higher in malaria uninfected individuals (SMD 0.34, 95% CI 0.07 to 0.60, $I^2 = 87.15\%$) with weaker differences between antimalarial-treated and untreated groups (SMD 0.07, 95% CI −0.01 to 0.16, $I^2 = 85.01\%$). The overall SMD for malaria uninfected/treated vs. infected/untreated was 0.15, 95% CI 0.05–0.26, $I^2 = 90.91$. Narrative analysis suggested malaria's adverse impact on vaccine responses in animals. Malaria infection may impair vaccines responses; with preventive treatment of malaria partially reversing these effects, highlighting the need for targeted public health interventions.

1 | Introduction

Vaccines are indispensable tools in public health, annually averting an estimated 2–3 million deaths globally [1]. Disparities in both efficacy and immunogenicity across different geographic regions, remain a significant challenge [2]. The response to BCG vaccine, for example, varies from 0% to 80% as one moves from a lower to a higher latitude [3]. Similarly, oral vaccines including rotavirus and polio exhibit poorer responses in low-income compared to high-income settings [4]. One hypothesis for these differences in vaccine responses may be the immunomodulatory effects of parasitic infections such as malaria, prevalent in LMICs, where vaccine specific responses have often been observed to be impaired [5].

Malaria continues to impose a substantial burden globally, with approximately 249 million malaria cases and 608,000 malaria deaths reported in 2022 [6]. Of these, Sub-Saharan Africa (SSA) accounted for 94% cases and 96% deaths [6]. Among the five species of *Plasmodium* (*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium Malariae* and *Plasmodium knowlesi*) known to infect humans, *P. falciparum* causes the greatest morbidity and mortality, predominantly affecting young children in SSA [6].

A previous narrative review suggested that the indirect impact of malaria on child survival extends to vaccine responses, reporting reduced efficacy of both routine and experimental vaccines among the infected compared to the uninfected [5]. A growing body of literature has explored the relationship between malaria and vaccine effectiveness. However, there is still uncertainty regarding the extent of malaria's influence on vaccine responses, fuelling ongoing debate over its true impact. The main objective of this systematic review and meta-analysis was to comprehensively evaluate and synthesise findings from relevant studies on the impact of malaria infection or its treatment on immune responses to unrelated vaccines in human and animal models.

2 | Methods

This systematic review and meta-analysis adhered to PRISMA guidelines (Supporting Information S1) and had a preregistered protocol in PROSPERO (CRD42022298053), also provided in the Supporting Information (Appendix S2).

2.1 | Data Sources and Search Strategy

We searched Ovid MEDLINE, Web of Science, Ovid Global Health, Scopus and Ovid Embase from inception to 5th December 2023. The search focused on papers published in English and encompassed terms related to malaria infection and its treatment, vaccine and immune response (Appendix S3). We included articles reporting on the effect of malaria or of antimalarial treatment on vaccine responses, covering all malaria species and WHO-approved vaccines in both animals and humans. Grey literature, such as dissertations and theses, was also searched, and reference lists of identified papers were screened for further relevant studies. Duplicate publications were identified using Endnote X20 reference manager and verified manually.

2.2 | Inclusion and Exclusion Criteria

We included studies that assessed immune responses to WHO-approved vaccines between malaria-infected and uninfected groups or between malaria-treated and untreated groups. These studies had to evaluate the effect of symptomatic or asymptomatic malaria infection, with participants' malaria status being laboratory-diagnosed at the time of vaccination and subsequent immunological outcomes were measured. We only included randomised controlled trials or observational studies (cohort or longitudinal). The included publications were in English and encompassed both peer-reviewed and grey literature.

We excluded studies investigating the effects of maternal vaccination on newborns or infants under 1 year of age. Additionally, non-primary research articles, including conference proceedings, letters to the editor, review articles and case reports, were not considered. Finally, studies lacking detailed descriptions of the laboratory methods used to assess both malaria exposure and vaccine-associated outcomes were excluded.

2.3 | Data Extraction and Preparation of Data

Two reviewers independently screened titles and abstracts for human studies (L.Z. and E.L.W.) and animal studies (L.Z. and J.N.). Full-text screening and data extraction were conducted independently by the same pair of reviewers for both human and animal studies. All full texts considered eligible by both reviewers were included in the final review, with disagreements resolved through discussion and consensus with a third reviewer (A.M.E.).

A pre-designed Microsoft Excel spreadsheet, covering study characteristics, participant demographics, vaccine details, malaria species, antimalarial treatment and immunological outcomes, facilitated data extraction. Articles were included in the quantitative synthesis if data for meta-analysis were available. Authors were contacted to request for data if the article described that relevant data were collected but not shown.

The antibody outcome measures were extracted for narrative summaries. In the quantitative synthesis, the reported measure (mean [SD], median [IQR], geometric mean [95% CI]) was extracted and categorised by malaria infection or treatment status. When the median (IQR) or geometric mean (95% CI) were presented as the summary measure, they were converted to mean (SD) on the $\log_{10}$ scale for analysis [7, 8].

To obtain an overall effect size, studies reporting results at multiple time points were combined using a weighted average. If a vaccine had multiple reported antibody outcomes, the best correlate of protection was prioritised. Studies examining human immune response to various vaccine serotypes yielded multiple effect sizes. If each serotype had a corresponding effect size, all eligible effect sizes were included in the meta-analysis. A sensitivity analysis, detailed below, assessed the impact of including only one serotype per study.

2.4 | Statistical Analysis

Analysis was conducted using the 'meta' suite for meta-analysis in Stata version 18. The standardised mean difference (SMD) was employed as the summary statistic. Hedges' *g* effect size was calculated to compare the effects of malaria infection or treatment status [9]. A random-effects model (REM), which assumes that true effects vary across studies, was used to estimate pooled effect sizes and their corresponding 95% confidence intervals [10].

The malaria infected or antimalarial-untreated group was used as the reference category, acting as the baseline for comparing antibody responses. In this context, an SMD of 0 indicates no effect of infection or treatment on vaccine responses, SMD > 0 indicates a positive effect (higher response in the uninfected or treated group), and SMD < 0 indicates a negative effect (lower response in the uninfected or treated group).

The I^2 statistic quantified heterogeneity among study specific SMDs [11]. Stratified analysis by malaria infection or treatment status was conducted comparing antibody responses between malaria uninfected and infected, as well as between those who received antimalarial treatment and those who did not. This analysis aimed to assess whether the observed effects were consistent across different groups with respect to malaria infection status and antimalarial treatment; differences between these two groups were quantified by Cochran's *Q* statistic. Stratified analyses by vaccine estimated vaccine-specific SMDs. Meta-regression analysis was further conducted to assess the effect of three factors on effect size: vaccine type, sample size, and whether the study investigated the effect of malaria or its treatment. Additionally, a sensitivity analysis was conducted to assess the effect of including only one vaccine serotype per study (retaining the most prevalent serotype), for those that reported an effect size for each vaccine serotype. Publication bias was assessed using a funnel plot and Egger's test.

2.5 | Quality Assessment

Quality assessment for human studies was conducted using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies [12], while the SYRCLE Risk of Bias (RoB) tool—an adapted version of the Cochrane RoB tool—was employed for animal experiments [13].

2.6 | Participant and Public Involvement

Participants were not involved in designing or executing the systematic review, but our aim is to provide findings that inform public health interventions.

3 | Results

3.1 | Study Selection

We identified 9016 records through electronic database searching, 80 more through screening relevant internet resources to identify grey literature such as unpublished reports, dissertations and theses. After removing duplicates, 6045 unique records remained. Following screening, 129 records were selected for full text review and a total of 24 records met the inclusion criteria (see Figure 1).

3.2 | Characteristics of Included Human Studies

Seventeen eligible articles were included in the systematic review on humans. Of these, 13 (76%) were conducted in children, 2 (12%) in adults and 2 (12%) in both adults and children. Seven (41.2%) were randomised trials and 10 (58.8%) observational studies. These studies spanned various regions including Africa, Asia and South America with publication dates ranging from 1962 to 2022.

Of the 10 articles investigating the effect of malaria infection on vaccine responses, five focused on the impact of acute malaria [14–18], while five examined the influence of asymptomatic parasitaemia [19–23].

Of the seven articles reporting trials involving antimalarial treatment, six investigated whether intervention to prevent malaria influenced immune responses to the vaccines [24–29]. Only one study where antimalarial treatment was administered investigated the effect of treating acute malaria with chloroquine on vaccine response [30].

Articles contributed data on a total of 13 vaccines: tetanus toxoid (9 articles), hepatitis B (1), measles (6), yellow fever (1), *Haemophilus influenzae* type b (2), diphtheria (4), polio (2), cholera (1), typhoid (4), meningococcal (4), Ebola (2), pertussis (3) and pneumococcal (1). Eight articles reported studies administering more than one vaccine [15, 17, 24–29]. In instances where study outcomes were stratified by vaccine serotypes such as polio 1, 2 and 3, meningococcal A and C, 10-valent conjugated pneumococcal antigens, this resulted in separate effect sizes for each vaccine serotype for these studies. Characteristics of the human studies are summarised in Table 1.

Four articles were included in the systematic review but not in the meta-analysis, as two reported proportion of participants seroconverting as the primary outcome [24, 30] and two did not have data for extraction [19, 20]. The remaining 13 articles were included in the meta-analysis. We received raw or study-level summary data for 2 studies directly from study authors [28, 31].

3.3 | Meta-Analysis of Effects of Malaria Infection or Antimalarial Treatment on Vaccine Responses

In this section, we first offer a detailed summary for each vaccine individually. Subsequently, we present a meta-analysis of the combined results across all vaccines. For each of the vaccines included in the meta-analysis, details of the study specific SMDs, their contribution to the overall SMD and heterogeneity measure (I^2) are presented in Appendix S4.

3.4 | Tetanus Toxoid Vaccine

Nine articles investigated the impact of malaria on tetanus toxoid vaccine: four focused on the effect of malaria infection while

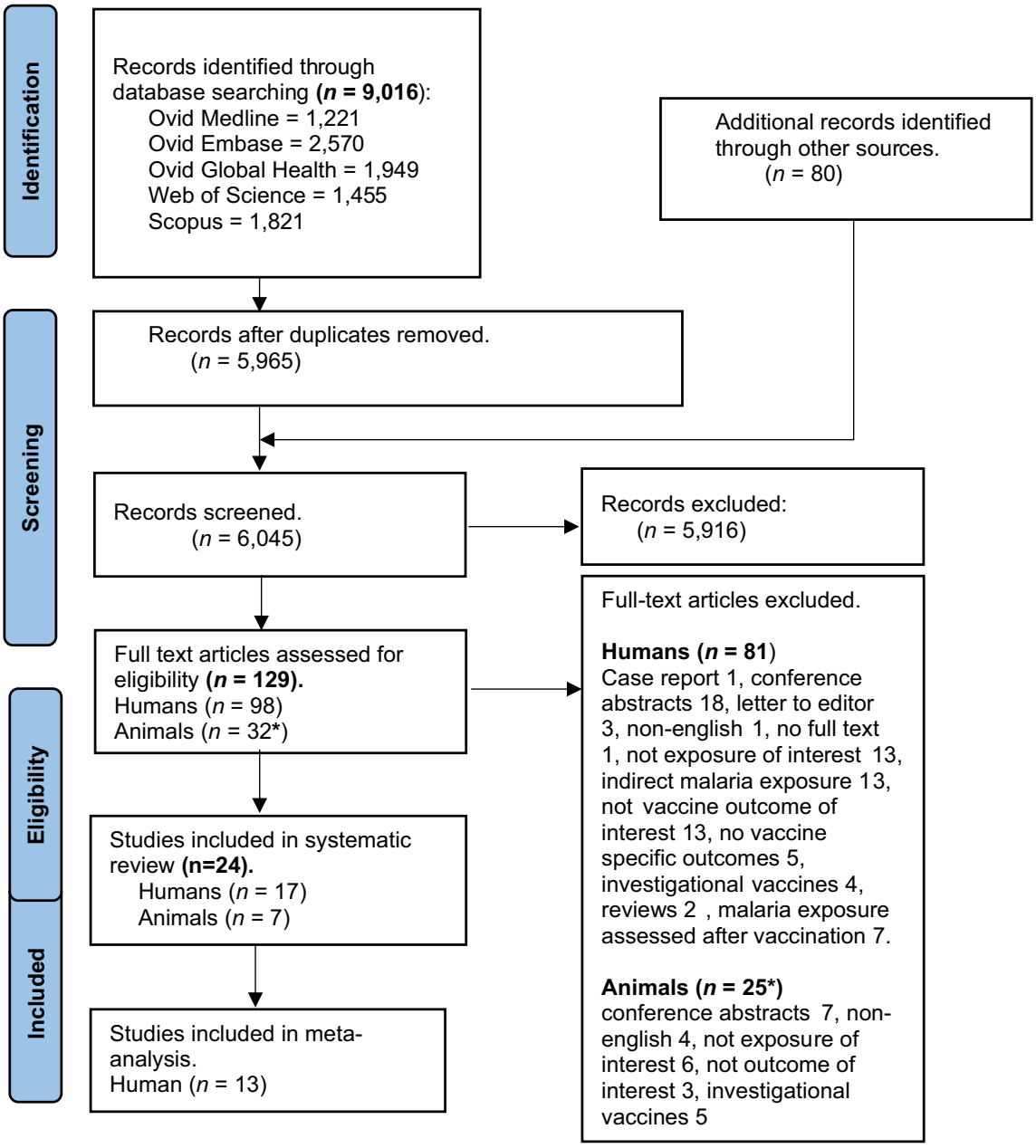

FIGURE 1 | Prism flow diagram of study selection and screening. *Banga et al. [32] record has both human and animal data, so it is considered as two separate articles.

five were on the effect of antimalarial treatment on vaccine responses. Six studies were included in meta-analysis; three were excluded, two because they reported binary outcomes for tetanus toxoid vaccine response [15, 24] and one did not have data for extraction [19]. The meta-analysis indicated no difference in immune response in the malaria uninfected or treated group compared to the infected or untreated group (SMD −0.02, 95% CI −0.46 to 0.43, $I^2 = 96.9\%$) (Figure 2). Of the six studies included in the meta-analysis, two compared vaccine response between malaria infected and non-infected [14, 16], while four assessed vaccine responses in malaria treated vs. untreated participants [25, 26, 28, 29]. Of three articles excluded from meta-analysis, one concluded that antimalarial treatment did not affect tetanus vaccine responses (RR 1.04, 95% CI 0.96 to 1.14) [24], the other observed suppression of tetanus vaccine responses by acute malaria infection ($p < 0.02$) [15] while the third reported no statistically significant differences in vaccine response between the parasitaemic and aparasitaemic participants ($p > 0.16$) [19].

3.5 | Hepatitis B Vaccine

Two articles investigated the impact of malaria on hepatitis B vaccine [25, 28]. Both articles assessed responses in malaria treated vs. untreated. Only one was included in the meta-analysis and showed no significant effect of malaria on vaccine responses (SMD −0.02, 95% CI −0.15 to 0.11) [28]. The second article [25] was excluded because its results were already incorporated in the findings of the included study, which was itself a meta-analysis.

TABLE 1 | Characteristics and findings from human studies.

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Vibrio cholerae CVD103-HgR vaccine: Effect of antimalarial prophylaxis								
Faucher et al. (2002) [27]	RCT	The study took place at the Lalala Public School in Lambarene, Gabon, from January through June 2000. Lambarene is in a tropical rain forest area where *P. falciparum* malaria is hyperendemic	330 Children were enrolled and randomly assigned to a treatment group (165 placebo group and 165 atovaquone/proguanil (A–P) group)	Mean (SD) 8.8 years (2.4) in A–P group, 8.5 years (2.3) in placebo group. Males/females 76/89—A–P, 76/89—placebo	*Plasmodium falciparum*	Vibriocidal antibodies	Strong	The 2 treatment groups did not differ significantly with regard to changes in antibody titres after vaccination. $p = 0.64$ for vibriocidal antibodies
Tetanus toxoid vaccine: Effect of direct malaria exposure								
Brabin et al. (1984) [14]	Cohort	The study was undertaken in western Kenya among women of the Abasamia tribe, in a rural hospital close to the Lake Victoria shoreline, in an area considered holoendemic for malaria	187 Women who attended the antenatal clinic and who had no history of intake of antimalarial drugs during the current pregnancy were included. All participants were administered 310 mg of chloroquine base for malaria prophylaxis. The same dose was given at their subsequent monthly clinic visits; the women were observed to swallow the tablets	Age of women not described	*Plasmodium falciparum*	Tetanus antibody	Weak	There was no apparent influence of either *P. falciparum* infection or gestational age on the immune response to 1 and 2 doses of adsorbed toxoid. The antibody response in pregnant women with and without malaria was comparable to that in non-pregnant healthy adults
Corrigall et al. (1988) [19]	Cohort	Schoolchildren in Papua New Guinea	The subjects for this study were 197 grade one schoolchildren from 9 schools in the Amele region of Madang Province	Mean age 9.78 years, SD 1.13 years	*P. falciparum* 55.9%, *P. vivax* 4.3%, *P. malariae* 1.2% and mixed 7.5%	Tetanus antibodies	Weak	Comparison of the mean rise in antibody between the group of parasitaemic subjects and the aparasitaemic subjects revealed no statistically significant difference in response ($t = 0.797$, $p > 0.1$, 95% confidence limits 0.39 ± -0.96)

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Greenwood et al. (1972) [15]	Cohort	Included participants with parasiteamia in the study and only those without parasiteamia were included in the control group	117	Not indicated	*Plasmodium falciparum*	Tetanus antibodies	Weak	Children with malaria showed a significantly diminished response to tetanus toxoid compared with healthy controls
Tetanus toxoid vaccine: Effect of antimalarial prophylaxis								
Bradley-Moore et al. (1985) [29]	Cohort	The study was carried out in and around the village of Gamzago near Malumfashi in northern Nigeria. Babies were admitted to the project as early as possible after their naming ceremony, usually between the ages of 1 and 2 weeks	383	Exact ages not specifically indicated *N* (%) male: chloroquine group 101 (51%) and control group 85 (45.9%)	*Plasmodium falciparum*	Tetanus antibodies	Weak	At 18 months post-vaccination: there was a statistically significant difference in the tetanus antibody responses in the C/Q group 0.42 ± 0.26 compared to the control group 0.33 ± 0.15 ($p < 0.05$)
Crawley et al. (2012) [28]	Synthesis of data from 5 RCTs	All children presenting for the DTP2 vaccination in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya were eligible	Intermittent preventive treatment for malaria during infancy (IPTi) treated vs. placebo treated groups. The study was done in a subset of 8416 children enrolled in 5 randomised trials of IPTi in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya	2–24 months	*Plasmodium falciparum*	Tetanus antibodies	Strong	Tetanus toxoid vaccine serological responses were not adversely affected by IPTi with various antimalarial drugs

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Greenwood et al. (1981) [26]	RCT	Infants from a malaria endemic area were considered for this study	206 Nigerian infants aged 3–17 months were studied during the course of a trial of a combined meningococcal, measles and tetanus vaccine	The mean age of the children in the group receiving chloroquine (8.7 months ± SD 4.4 months) was similar to the mean age of the group of children who did not (9.2 months ± SD 4.3 months)	*Plasmodium falciparum*	Tetanus antibody	Weak	There were no significant differences in the antibody response to the tetanus toxoid components of the vaccine between children who had received chloroquine and between those who had not (tetanus = 6.6 ± 0.2, $p > 0.05$)
Macete et al. (2006) [25][b]	RCT	Infants were recruited at the EPI clinics of the Manhica Health Center and the Maragra Health Post immediately after they received dose 2 of diphtheria–tetanus toxoid–pertussis (DTP)/ oral polio (OPV) vaccine	1503 Children randomised, 755 in the placebo arm and 248 sulfadoxine–pyrimethamine (SP) arm	Age at first dose, mean ± SD, months 3.3 ± 0.6 (placebo) 3.3 ± 0.6 (SP)	*Plasmodium falciparum*	Tetanus antibody	Strong	No significant difference in GMTs, or in the rates of serological responses to DTP/OPV
Rosen et al. (2005) [24]	Cluster randomised trial	Children, aged 4–74 months ($N = 996$) living in the 6 malarious villages were assigned to 2 groups of 3 villages each, depending on whether they lived in villages east or west of Bobo-Dioulasso	996 Children enrolled and randomly assigned to prophylaxis group (amodiaquine hydrochloride chemoprophylaxis (CH+) $n = 488$) or to the non-prophylaxis group (no chemoprophylaxis (CH−) $n = 508$)	Mean age (SD) of those who received measles 33.7 (15.2), DTP 32.3 (14.9). CH+ male—53% (measles), 48% male (DTP)	*Plasmodium falciparum*	Tetanus antibodies	Moderate	Malaria chemoprophylaxis does not appear to enhance nor impair the antibody response to DTP and measles vaccines
McGregor et al. (1962) [16]	Cohort	African children	66 Children	Children in the third year of life	Not specified	Tetanus antibodies	Weak	GMT were not different between the malarious and non-malarious groups—0.19 units mL^{-1} compared to 0.18 units mL^{-1}

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Hepatitis B vaccine: Effect of antimalarial prophylaxis								
Crawley et al. (2012) [28]	Synthesis of data from 5 RCTs	All children presenting for the DTP2 vaccination in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya were eligible	Intermittent preventive treatment for malaria during infancy (IPTi) treated vs. placebo treated groups. The study was done in a subset of 8416 children enrolled in 5 randomised trials of IPTi in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya	2–24 Months	*Plasmodium falciparum*	Antibodies	Strong	Hepatitis B vaccine serological responses are not adversely affected by IPTi
Macete et al. (2006) [25][b]	RCT	Infants were recruited at the EPI clinics of the Manhica Health Center and the Maragra Health Post immediately after they received dose 2 of diphtheria–tetanus toxoid–pertussis (DTP)/ oral polio (OPV) vaccine	1503 Children randomised, 755 in the placebo arm and 248 SP arm	Age at first dose, mean ± SD, months 3.3 ± 0.6 (placebo) 3.3 ± 0.6 (SP)	*Plasmodium falciparum*	Antibody	Strong	No significant difference in GMTs, or in the rates of serological responses to hepatitis B
Typhoid vaccine: Effect of antimalarial prophylaxis								
Bradley-Moore et al. (1985) [29]	Cohort	The study was carried out in and around the village of Gamzago near Malumfashi in northern Nigeria. Babies were admitted to the project as early as possible after their naming ceremony, usually between the ages of 1 and 2weeks; some infants died before this time	383	Age not indicated *N* (%) male: chloroquine group 101 (51%) and control group 85 (45.9%)	*Plasmodium falciparum*	Tetanus antibodies	Weak	At 18 months post-vaccination, there was no statistically significant difference in the antibody responses in the chloroquine group compared to the control group

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Faucher et al. (2002) [27]	RCT	The study took place at the Lalala Public school in Lambarene, Gabon, from January through June 2000. Lambarene is in a tropical rain forest area where *P. falciparum* malaria is hyperendemic	330 Children were enrolled and randomly assigned to a treatment group (165 placebo group and 165 A–P group)	8.8 Years ± 2.4 (A–P group) 8.5 years ± 2.3 (placebo group). Males/females 76/89—A–P, 76/89—placebo	*Plasmodium falciparum*	Anti-*S. typhi* IgG antibodies	Strong	The 2 treatment groups did not differ significantly with regard to changes in antibody titres after vaccination. ($p = .96$ for anti–*S. typhi* IgG antibodies, $p = .07$ for anti–*S. typhi* IgA antibodies)
Typhoid vaccine: Effect of malaria infection								
Williamson and Greenwood (1978) [17]	Cohort	Children who presented at Ahmadu Bello University Hospital, Malumfashi, Nigeria with acute *P. falciparum* malaria were studied. 40 Healthy afebrile siblings matched for age, sex, and ethnic group acted as a control group—none had detectable malaria parasitaemia	79 Children with acute malaria were randomly allocated to one of the 3 groups. Children in group [28] were immunised at the time of their presentation at hospital with *S. typhi* vaccine, 0.1 mL intradermally, and group-C meningococcal vaccine, 0–5 mL intramuscularly. Group II [25] received the same immunizations 7 days after presentation with acute malaria, and group III [26] were vaccinated 28 days after presentation. All children were treated immediately with chloroquine and any other treatment thought to be necessary	Children but age and sex not specified	*Plasmodium falciparum*	Antibodies to the 0 antigen of *S. typhi*	Weak	The immune response to *S. typhi* vaccine was depressed when given on the day of presentation at hospital. Immune responsiveness to *S. typhi* vaccine was rapidly regained after treatment

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Greenwood et al. (1972) [15]	Cohort	Included participants with parasitaemia in the study and only those without parasiteamia were included in the control group	117	Not indicated	*Plasmodium falciparum*	Tetanus antibodies	Weak	Children with malaria showed a significantly diminished response compared with healthy controls
Meningococcal vaccine: Effect of malaria infection								
Williamson and Greenwood (1978) [17]	Cohort	Children who presented at Ahmadu Bello University Hospital, Malumfashi, Nigeria with acute *P. falciparum* malaria were studied. 40 healthy afebrile siblings matched for age, sex, and ethnic group acted as controls. None had detectable malaria parasitaemia	79 Children with acute malaria were randomly allocated to one of the 3 groups. Children in group [28] were immunised at the time of their presentation at hospital with *S. typhi* vaccine, 0.1 mL intradermally, and group-C meningococcal vaccine, 0–5 mL intramuscularly Group II [25] received the same immunizations 7 days after presentation with acute malaria, and Group III [26] were vaccinated 28 days after presentation. All children were treated immediately with chloroquine and any other treatment thought to be necessary	Children but age and sex not specified	*Plasmodium falciparum*	Antibodies to the meningococcal vaccine	Weak	The immune response to meningococcal vaccines was depressed when they were given on the day of presentation at hospital and a month after the attack, the immune response to meningococcal vaccine was still impaired

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Greenwood et al. (1981) [26]	RCT	Infants from a malaria endemic area were considered for this study	206 Nigerian infants aged 3–17 months were studied during the course of a trial of a combined meningococcal, measles and tetanus vaccine	The mean age of the children in the group receiving chloroquine (8.7 months ± 4.4 months) was similar to the mean age of the group of children who did not (9.2 months ± 4.3 months)	*Plasmodium falciparum*	Group A and group C meningococcal HA antibody titres	Weak	Among the group of children who did not receive chloroquine the rise in both group A and group C meningococcal HA antibody titres following vaccination was significantly less in those with malaria parasitaemia than in those without parasitaemia
Bradley-Moore et al. (1985) [29]	Cohort	The study was carried out in and around the village of Gamzago near Malumfashi in northern Nigeria. Babies were admitted to the project as early as possible after their naming ceremony, usually between the ages of 1 and 2 weeks; some infants died before this time	Chloroquine treated vs. untreated group $N = 383$	Age not indicated Male: chloroquine group 101 (51%) and control group 85 (45.9%)	*Plasmodium falciparum*	Mean rise in antibody level	Weak	At 18 months post-vaccination, there was no statistically significant difference in the antibody responses in the chloroquine group compared to the control group
Greenwood et al. (1980) [20]	Longitudinal study	A full demographic survey of the village was undertaken in 1974. On the basis of this initial survey a 1:5 household sample was selected for the present study, using a system of random numbers	Subjects with eight or more fields positive compared to those with four or fewer fields positive $N = 428$	Both not indicated	*Plasmodium falciparum*	Antibodies	Moderate	It was found that subjects with eight or more fields positive had a significantly lower antibody response than those with four or fewer fields positive ($p \leq 0.02$)

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Ebola vaccine: Effect of asymptomatic malaria infection								
Ishola et al. (2022)[21]	Cohort nested in an RCT	This observational cohort sub-study was nested within the EBOVAC–Salone trial, which evaluated the safety and immunogenicity of the 2-dose Ad26.ZEBOV, MVA–BN–Filo Ebola vaccine regimen in Sierra Leonean adults and children between September 2015 and July 2018. The study was conducted in Kambia District in Sierra Leone, where malaria is a major public health issue	587 Participants were included in the malaria study analysis	188 Participants were adults aged 18 years or older and 399 were children (125 aged 1–3 years, 133 aged 4–11 years, and 141 aged 12–17 years). Overall, 368 participants (63%) were male	*Plasmodium falciparum* accounted for a large majority of the infections; 1 infection with *P. ovale* and 5 with *P. malariae* were detected	EBOV-specific immunoglobulin G (IgG) antibodies	Moderate	The study showed that there is no indication that asymptomatic malaria infection at the time of vaccination has a meaningful impact on the immunogenicity of the 2-dose Ad26.ZEBOV, MVA–BN–Filo Ebola vaccine regimen
Mahon et al. (2021) [22]	RCT	Adult (≥18 years old), non-pregnant healthcare and frontline Ebola response workers were individually randomised to immediate or deferred (18–24 weeks later) vaccination	508 Participants were enrolled in the immunogenicity sub-study from 1 of the 7 STRIVE study sites (Connaught Hospital, Freetown)	A large majority (468 of 506 [92.5%]) were 18–50 years of age and 57.9% were male	*Plasmodium falciparum*	Neutralising antibodies to the rVSVΔG–ZEBOV-GP vaccine strain	Moderate	Asymptomatic malaria infection may reduce robust immune response to rVSVΔG-ZEBOV-GP
Measles vaccine: Effect of antimalarial prophylaxis								
Crawley et al. (2012) [28]	Synthesis of data from 5 RCTs	All children presenting for the DTP2 vaccination in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya were eligible	IPT treated vs. placebo treated groups. The study was done in a subset of 8416 children enrolled in 5 randomised trials of IPTi in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya	2–24 months	*Plasmodium falciparum*	Antibodies	Strong	Measles vaccines's serological responses were not adversely affected by IPTi

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Rosen et al. (2005) [24]	Cluster randomised trial	Children, aged 4–74 months ($N=996$) living in the 6 malarious villages were assigned to 2 groups of 3 villages each, depending on whether they lived in villages east or west of Bobo-Dioulasso	996 Children enrolled and randomly assigned to prophylaxis group (CH+) 488 and 508 to the non-prophylaxis group (CH–)	Mean age (SD) of those who received measles 33.7 (15.2), DTP 32.3 (14.9). CH+ male—53% (measles), 48% male (DTP)	*Plasmodium falciparum*	Proportion with seroconversion or seroresponse	Moderate	Malaria chemoprophylaxis does not appear to enhance nor impair the antibody response to measles vaccine
Greenwood et al. (1981) [26]	RCT	Infants from a malaria endemic area were considered for this study	206 Nigerian infants aged 3–17 months were studied during the course of a trial of a combined meningococcal, measles and tetanus vaccine	The mean age of the children in the group receiving chloroquine (8.7 months ± 4.4 months) was similar to the mean age of the group of children who did not (9.2 months ± 4.3 months)	*Plasmodium falciparum*	Measles specific antibodies	Weak	There were no significant differences in the antibody response to measles components of the vaccine between children who had received chloroquine and between those who had not (mean responses = 4.0 ± 0.2, $p > 0.05$)
Macete et al. (2006) [25][a]	RCT	Infants were recruited at the EPI clinics of the Manhica Health Center and the Maragra Health Post immediately after they received dose 2 of diphtheria–tetanus toxoid–pertussis (DTP)/ oral polio (OPV) vaccine	1503 Children randomised, 755 in the placebo arm and 248 SP arm	Age at first dose, mean ± SD, months 3.3 ± 0.6 (placebo) 3.3 ± 0.6 (SP)	*Plasmodium falciparum*	Antibody	Strong	No significant difference in GMTs, or in the rates of serological responses
Bradley-Moore et al. (1985) [29]	Cohort	The study was carried out in and around the village of Gamzago near Malumfashi in northern Nigeria. Babies were admitted to the project as early as possible after their naming ceremony, usually between the ages of 1 and 2 weeks; some infants died before this time	Chloroquine treated vs. untreated group $N=383$	Age not indicated N (%) male: chloroquine group 101 (51%) and control group 85 (45.9%)	*Plasmodium falciparum*	Mean rise in antibody level	Weak	At 18 months post-vaccination, there was no statistically significant difference the antibody responses in the C/Q group compared to the control group

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Cenac et al. (1988) [30]	RCT	The study was conducted from October to November 1985 in the Baleyara area, Niamey County, Republic of Niger. 10 villages situated within a radius of 10 km of Baleyara were chosen	580 Children, 9–48 months old, were randomly enrolled into 2 groups (289—chloroquine treated and 291—chloroquine untreated)	9–48 Months old, sex not indicated	*Plasmodium falciparum*	Measles antibodies	Weak	The antibody response of children treated with chloroquine was not higher than that of controls, despite the reduction of malarial index: therefore, the efficacy of measles vaccination does not seem seriously impaired by malarial infection
Pertussis vaccine: Effect of antimalarial prophylaxis								
Crawley et al. (2012) [28]	Synthesis of data from 5 RCTs	All children presenting for the DTP2 vaccination in Kisumu, Kenya were eligible	IPT treated vs. placebo treated groups. The study was done in a subset of 893 children enrolled in the randomised trial of IPTi in Kisumu, Kenya	2–24 Months	*Plasmodium falciparum*	Antibodies	Strong	Pertussis vaccine serological responses were not adversely affected by IPTi with various antimalarial drugs
Rosen et al. (2005) [24]	Cluster randomised trial	Children, aged 4–74 months ($N = 996$) living in the 6 malarious villages were assigned to 2 groups of 3 villages each, depending on whether they lived in villages east orwest of Bobo-Dioulasso	996 Children enrolled and randomly assigned to prophylaxis group (CH+) 488 and 508 to the non-prophylaxis group (CH–)	Mean age (SD) of those who received measles 33.7 (15.2), DTP 32.3 (14.9). CH+ male—53% (measles), 48% male (DTP)	*Plasmodium falciparum*	Antibodies	Moderate	Malaria chemoprophylaxis does not appear to enhance nor impair the antibody response to DTP vaccine
Macete et al. (2006) [25][a]	RCT	Infants were recruited at the EPI clinics of the Manhica Health Center and the Maragra Health Post immediately after they received dose 2 of diphtheria–tetanus toxoid–pertussis (DTP)/ oral polio (OPV) vaccine	1503 Children randomised, 755 in the placebo arm and 248 SP arm	Age at first dose, mean ± SD, months 3.3 ± 0.6 (placebo) 3.3 ± 0.6 (SP)	*Plasmodium falciparum*	Antibody	Strong	No significant difference in GMTs, or in the rates of pertussis vaccine serological responses

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Pneumococcal (10-valent conjugated pneumococcal antigen) vaccine: Effect of malaria infection								
Singer et al. (2017) [23]	Cohort SD	Eligible children were enrolled from a maternal–infant study cohort developed in 2006–2010	Malaria infected vs. malaria uninfected group $N = 385$	Mean (SD) 6.1 (0.66), male:female = 1:1	*Plasmodium falciparum*	Anti-pneumococcal immunoglobulin G (IgG)	Weak	Chronic malaria exposure or infection during early life does not appear to have a consistently detrimental effect on IgG response to pneumococcal vaccine antigens in mid-childhood
Yellow fever vaccine: Effect of antimalarial prophylaxis								
Crawley et al. (2012) [28]	Synthesis of data from 5 RCTs	All children presenting for the DTP2 vaccination in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya were eligible	IPT treated vs. placebo treated groups. The study was done in a subset of 8416 children enrolled in 5 randomised trials of IPTi in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya	2–24 Months	*Plasmodium falciparum*	Antibodies	Strong	The proportions unprotected following yellow fever vaccination were similar in both groups; 3 of 72 (4.2%; 95% CI 0.9 to 12) in the sulfadoxine pyrimethamine group and none of 64 (0.0–5.6) in the placebo group, a difference of 4.2% (95% CI −0.1 to 8.5)
Haemophilus influenza B vaccine: Effect of antimalarial prophylaxis								
Crawley et al. (2012) [28]	Synthesis of data from 5 RCTs	All children presenting for the DTP2 vaccination in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya were eligible	IPT treated vs. placebo treated groups. The study was done in a subset of 8416 children enrolled in 5 randomised trials of IPTi in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya	2–24 Months	*Plasmodium falciparum*	Antibodies	Strong	*Haemophilus influenza* B vaccine serological responses was not adversely affected by IPTi with various antimalarial drugs

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Haemophilus influenza B vaccine: Effect of malaria infection								
Usen et al. (2000) [18]	Cohort	Children were eligible for the study if they were aged 12–30 months, weighed > 70% of the expected weight for age and were not enrolled in the efficacy trial of a conjugate vaccine against Hib that was ongoing. Children were enrolled into the malaria group if they had fever (rectal temperature > 37.5°C) or a history of fever and parasitaemia. Siblings of children enrolled into the study were not eligible	Malaria infected vs. uninfected group. $N = 174$	Age (months): (malaria group)—22.8 ± 5.4, (febrile no malaria groupp)—20.3 ± 5.7, health group)—20.7 ± 3.9 Sex (F/M) (malaria group)—26/18, (febrile no malaria group)—21/25, and (healthy group)—23/24	*Plasmodium falciparum*	Antibodies	Moderate	After vaccination the median antibody titre was substantially higher in the healthy controls (23 μg mL^{-1}) than either the malaria group (6.3 μg mL^{-1}) or the febrile group (7.5 μg mL^{-1}) (Kruskal–Wallis test chi square 11.6, 2 df, $p = .0002$). The median postvaccination titre in the febrile control group was similar to that in the malaria group (chi-square 0.725, 1 df, P 5 0.395)
Diphtheria vaccine: Effect of antimalarial prophylaxis								
Bradley-Moore et al. (1985) [29]	Cohort	The study was carried out in and around the village of Gamzago near Malumfashi in northern Nigeria. Babies were admitted to the project as early as possible after their naming ceremony, usually between the ages of 1 and 2 weeks; some infants died before this time	Chloroquine treated vs. untreated group $N = 383$	Age not indicated N (%) male: chloroquine group 101 (51%) and control group 85 (45.9%)	*Plasmodium falciparum*	Antibodies	Weak	At 18 months post-vaccination, there was no statistically significant difference in the diphtheria vaccine antibody responses in the C/Q group compared to the control group
Crawley et al. (2012) [28]	Synthesis of data from 5 RCTs	All children presenting for the DTP2 vaccination in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya were eligible	IPT treated vs. placebo treated groups. The study was done in a subset of 8416 children enrolled in 5 randomised trials of IPTi in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya	2–24 Months	*Plasmodium falciparum*	Antibodies	Strong	Diphtheria vaccine serological responses are not adversely affected by IPTi with various antimalarial drugs

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Rosen et al. (2005) [24]	Cluster randomised trial	Children, aged 4–74 months ($N=996$) living in the 6 malarious villages were assigned to 2 groups of 3 villages each, depending on whether they lived in villages east or west of Bobo-Dioulasso	996 Children enrolled and randomly assigned to prophylaxis group (CH+) 488 and 508 to the non-prophylaxis group (CH−)	Mean age (SD) of those who received measles 33.7 (15.2), DTP 32.3 (14.9). CH+ male—53% (measles), 48% male (DTP)	*Plasmodium falciparum*	Proportion with seroconversion or seroresponse	Moderate	Malaria chemoprophylaxis does not appear to enhance nor impair the antibody response to DTP vaccine
Macete et al. (2006) [25][b]	RCT	Infants were recruited at the EPI clinics of the Manhica Health Center and the Maragra Health Post immediately after they received dose 2 of diphtheria–tetanus toxoid–pertussis (DTP)/ oral polio (OPV) vaccine	1503 Children randomised, 755 in the placebo arm and 248 SP arm	Age at first dose, mean ± SD, months 3.3 ± 0.6 (placebo) 3.3 ± 0.6 (SP)	*Plasmodium falciparum*	Antibody	Strong	No significant difference in GMTs, in the rates of diphtheria vaccine serological responses
Polio vaccine: Effect of antimalarial prophylaxis								
Bradley-Moore et al. (1985) [29]	Cohort	The study was carried out in and around the village of Gamzago near Malumfashi in northern Nigeria. Babies were admitted to the project as early as possible after their naming ceremony, usually between the ages of 1 and 2 weeks; some infants died before this time	Chloroquine treated vs. untreated group $N=383$	Age not indicated Male: chloroquine group 101 (51%) and control group 85 (45.9%)	*Plasmodium falciparum*	Antibodies	Weak	At 18 months post-vaccination, there was no statistically significant difference in the polio vaccine antibody responses in the C/Q group compared to the control group

(Continues)

TABLE 1 | (Continued)

Author (year)	Study design	Population description	Compared groups (sample size)	Age, gender	Type of malaria	Outcome	Quality assessment[a]	Finding
Crawley et al. (2012) [28]	Synthesis of data from 5 RCTs	All children presenting for the DTP2 vaccination in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya were eligible	IPT treated vs. placebo treated groups. The study was done in a subset of 8416 children enrolled in 5 randomised trials of IPTi in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya	2–24 Months	*Plasmodium falciparum*	Antibodies	Strong	Polio vaccine serological responses were not adversely affected by IPTi with various antimalarial drugs

[a]Quality assessment based on EPHPP (Effective Public Health Practice Project) tool.
[b]Some results from Macete et al. [25] are included in the results of Crawley et al. [28]. To avoid duplicate counting, data from Macete et al. [25] was excluded from the meta-analysis when this overlap occurred.

3.6 | Measles Vaccine

Six articles investigated the impact of malaria on measles vaccine responses [24–26, 28–30]. All six studies assessed responses in malaria treated vs. untreated groups but only three were included in the meta-analysis. The meta-analysis results suggest no significant effect of malaria on measles vaccine responses (SMD 0.004, 95% CI −0.14 to 0.15 and $I^2 = 41.45\%$). One article [25] was excluded because its results were already incorporated in the findings of one of the included articles [28]. Two other articles were excluded from the meta-analysis because their outcome data were binary [24, 30]. Both studies showed that treatment of malaria does not affect vaccine responses.

3.7 | Yellow Fever Vaccine

One article assessed the effect of malaria on immune response to yellow fever vaccine [28]. It compared vaccine responses between treated and untreated groups. This article was excluded from the meta-analysis because its outcome data were binary. It showed that antimalarial treatment compared to no treatment does not affect vaccine responses.

3.8 | *H. Influenza* Type b Vaccine

The impact of malaria on immune responses to *H. Influenzae* type b vaccine was investigated in two articles [18, 28]. One focused on the effect of malaria infection [18] while the second focused on the effect of antimalarial treatment [28]. Both studies were included in the meta-analysis which showed no significant effect of malaria on vaccine responses (SMD 0.47, 95% CI −0.47 to 1.41, $I^2 = 93.72\%$).

3.9 | Diphtheria Vaccine

Four articles assessed the effect of malaria on diphtheria vaccine responses [24, 25, 28, 29]. All compared vaccine responses between treated and untreated groups. Only two were eligible for meta-analysis and showed no significant effect of antimalarial treatment on vaccine responses (SMD 0.04, 95% CI −0.04 to 0.13, $I^2 = 0\%$). One was excluded from the meta-analysis as its results were binary in nature [24] and that antimalarial treatment had no effect on vaccine responses (RR 0.86, 95% CI 0.76 to 0.96). The second article [25] was excluded from the meta-analysis because its results were already incorporated in the findings of one of the included papers [28].

3.10 | Polio Vaccine

Two articles reported on the impact of malaria on polio vaccine responses, providing effect sizes for different polio vaccine serotypes [28, 29]. Both studies compared vaccine responses in the treated and untreated groups but only one article that provided data for polio vaccine serotypes 1, 2 and 3 was included in the meta-analysis [29]. The results showed no difference in immune response in the malaria treated group compared to the untreated group (SMD −0.25, 95% CI −0.69

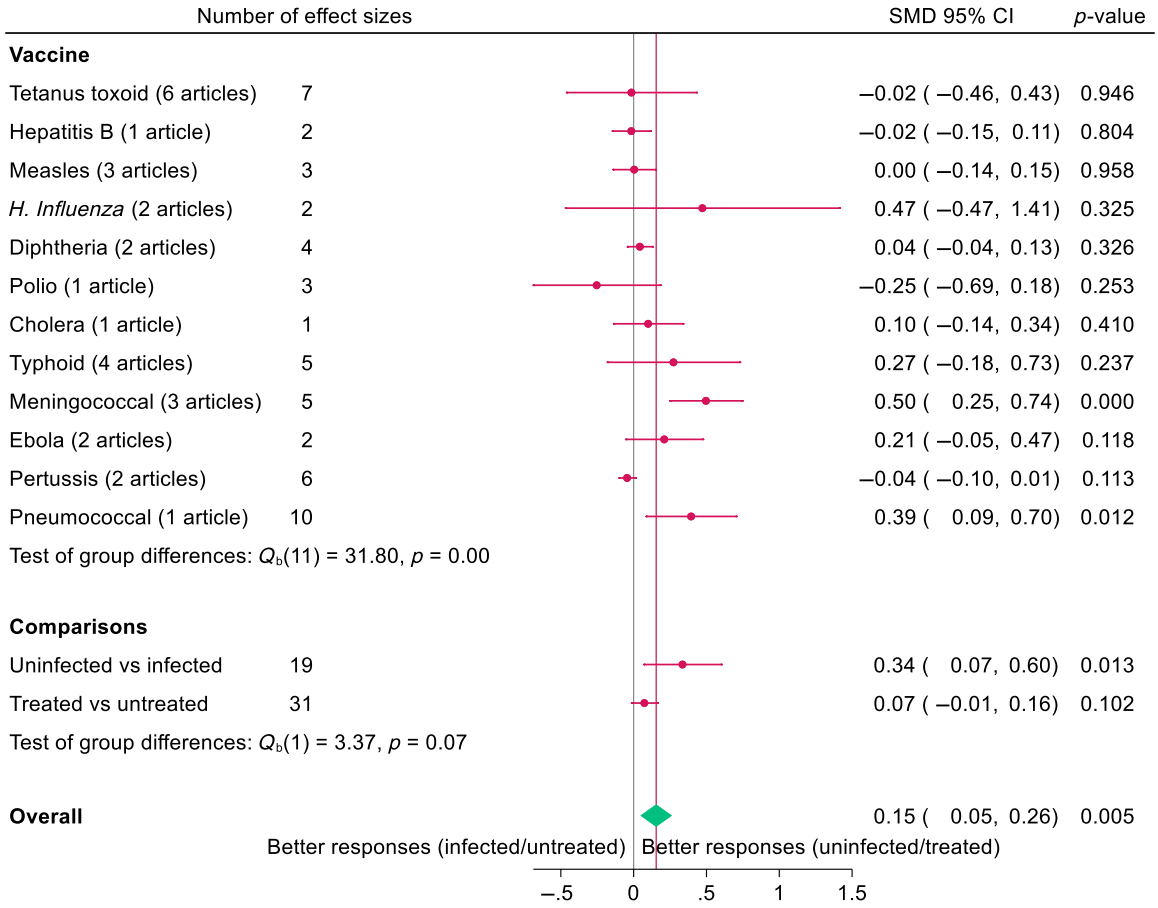

FIGURE 2 | Forest plot of the effect of malaria infection or treatment on vaccine responses. References and study specific standardised mean differences are presented in Appendix S4.

to 0.18, $I^2 = 41.85\%$). The excluded article reported binary outcomes and did not show any effect of antimalarial treatment on vaccine responses [28].

3.11 | Cholera Vaccine

One article examined the effect of malaria on responses to cholera vaccine comparing responses between treated and untreated participants [27]. Its results showed slightly higher vaccine response in the treated group compared to the untreated group (SMD 0.10, 95% CI −0.14 to 0.34).

3.12 | Typhoid Vaccine

Four articles assessed the effect of malaria on typhoid vaccine responses, and all were included in the meta-analysis [15, 17, 27, 29]. Two articles reported more than one effect size. One article reported effect sizes for both *Salmonella typhi* H and *S. typhi* S IgG antibody outcomes, comparing vaccine responses between malaria infected and non-infected groups [15] while the other reported effect sizes for both *S. typhi* IgG and IgA antibody outcomes [27]. One additional article also compared vaccine responses between malaria infected and uninfected groups [17]. Two articles compared responses between malaria treated and untreated groups [27, 29]. The meta-analysis results indicated a slightly higher vaccine response in the uninfected or treated groups compared to the infected or untreated groups, although not statistically significant (SMD 0.27, 95% CI −0.18 to 0.73, $I^2 = 85.63\%$).

3.13 | Meningococcal Vaccine

Four articles investigated the impact of malaria on meningococcal vaccine responses [17, 20, 26, 29]. Three articles were included in the meta-analysis, and all compared vaccine responses between the treated and untreated groups [17, 26, 29]. Two studies contributed two effect sizes for both meningococcal group A and C antibody outcomes [26, 29] and one study only provided an effect size for meningococcal group C antibody outcome [17]. The results indicated a statistically significant higher vaccine response in the treated group compared to the untreated group (SMD 0.50, 95% CI 0.25 to 0.74, $I^2 = 57.99\%$). The excluded article did not have data suitable for meta-analysis, however, it reported that parasitaemia negatively affected vaccine responses [20].

3.14 | Ebola Vaccine

Two articles assessed the effect of malaria on Ebola vaccine responses, and both compared vaccine responses between malaria

TABLE 2 | Characteristics and findings from animal experiments.

Author (year)	Vaccine	Animal species	Compared groups (sample size)	Age, gender	Type of malaria parasite	Outcome	Finding
BCG							
Tangie et al. (2022) [33]	BCG	Wild type C57BL/6 mice	Malaria infected and non-infected	6–8 Weeks, females	Virulent *P. berghei* and non-virulent *P. chabaudi*	Pulmonary bacterial burden	Malaria co-infection modulates both B- and T-cell immune responses but does not significantly alter the ability of the BCG vaccine to inhibit the growth of *M. tuberculosis* irrespective of parasite virulence
Parra et al. (2011) [34]	BCG	C57BL/6 mice	BCG vaccinated [5] vs. unvaccinated [5]	6–8 Weeks, females	*Plasmodium yoelii* NL	Lung colony forming units (CFU) levels	At 8 months after BCG immunisation, statistically equivalent lung CFU levels were detected in the BCG (5.5960.11 $\log_{10}$ CFU) and BCG/*P. yoelii* (5.5860.22) groups as well as the naive (6.4060.30) and naive/*P. yoelii* (6.1160.15) animals
Pneumococcal polysaccharide (SSSIII) vaccine							
Morges and Weindanz (1980) [35]	Pneumococcal polysaccharide (SSSIII)	Nude mice (nu/nu) and mice heterozygous for the nude gene (nu/+) having a BALB/c	Malaria infected vs. uninfected	8–12 Weeks, both males and females	*Plasmodium yoelii*	Hemolytic antibody titres to SSSIII-coated SRBC	Both the serum antibody and splenic PFC responses to SSSIII were severely depressed euthymic nu/+ mice immunised 10 days after infection with *P. yoelii*. In contrast, athymic nu/nu mice infected with this parasite responded normally to immunisation with SSSIII
McBride et al. (1977) [36]	Pneumococcal polysaccharide (SIII)	CBA/Lac mice	Malaria infected vs. uninfected	3 Months, females	*P. yoelii*, strain 17X, and *P. berghei*, strain NK 65	Anti-SIII haemagglutination titres	These experiments show that the antibody response to SIII administered during acute malaria was severely reduced and, perhaps more important, that some immunodepression persisted for several weeks after apparent recovery from the infection

(Continues)

TABLE 2 | (Continued)

Author (year)	Vaccine	Animal species	Compared groups (sample size)	Age, gender	Type of malaria parasite	Outcome	Finding
Meningococcal (groups A and C combined) polysaccharide vaccine							
Oyeyinka (1982) [37]	Meningococcal (groups A and C combined) polysaccharide vaccine	BALB/c mice	Malaria infected vs. uninfected	6–8 Weeks, sex not reported	*Plasmodium berghei*	Antibodies to the meningococcal vaccine	Mean meningococcal haemagglutinating antibody titres obtained in malaria infected mice showed lower values, than those obtained in uninfected mice, 7 days ($p < .05$) and 14 days ($p > .05$) after vaccination
Pertussis vaccine							
Viens et al. (1974) [39]	Pertussis vaccine	Albino mice(Canadian breeding farm)	Malaria infected vs. uninfected	Age not reported, males	*Plasmodium berghei yoelii*	Antibodies to pertussis	Infected mice with *Plasmodium berghei yoelii* responded poorly to pertussis vaccine when administered at peak parasitaemia and there was a lack of protection against intracerebral challenge with virulent *Bordetella pertussis*
Tetanus toxoid vaccine							
Tarzaali et al. (1977) [38]	Tetanus toxoid vaccine	White CF 1 mice	Malaria infected vs. uninfected	Age not reported, females	*Plasmodium yoelii*	Response to challenge dose of tetanus toxoid 16 days after vaccination	Non-parasitised mice were protected with dilutions 1/320 and 1/2560 of tetanus vaccine following the challenge exposure whereas mice previously infected with *P. yoelii* parasites were more affected by the tetanus toxin challenge. This difference is statistically highly significant
Diphtheria vaccine							
Tarzaali et al. (1977) [38]	Diphtheria vaccine	White CF 1 mice	Malaria infected vs. uninfected	Age not reported, males	*Plasmodium yoelii*	Anti-diphtheria antibodies	Antibody titres were higher in non-parasitised mice than in parasitised ones. It was also noted that the antibody response of parasitised mice was better among those immunised with the diphtheria–pertussis mixture than in those given diphtheria toxoid alon

infected and uninfected groups [21, 22]. One article investigated the recombinant vesicular stomatitis virus–Zaire Ebola virus envelope glycoprotein vaccine (rVSVΔG–ZEBOV-GP). The second article evaluated a two-dose regimen: Adenovector expressing Zaire Ebola (Ad26.ZEBOV) followed by modified vaccinia Ankara viral construct (MVA–BN–Filo). Both articles were included in the meta-analysis. The results suggested that vaccine response is higher in the malaria-uninfected group compared to the infected group, though not statistically significant. (SMD 0.21, 95% CI −0.05 to 0.47, $I^2 = 62.08\%$).

3.15 | Pertussis Vaccine

Three articles investigated the impact of malaria on pertussis vaccine response, and all compared vaccine responses between treated and untreated groups [24, 25, 28]. Two studies reported outcome measures for both filamentous haemagglutinin antibodies (FHA) and toxin antibodies, both of which were included in the meta-analysis [25, 28]. The results suggested a trend towards a lower immune response in the treated group compared to the untreated group, however, not statistically significant (SMD −0.05, 95% CI −0.10 to 0.01). One article was excluded from the meta-analysis because its results were reported as a binary outcome [24]. It showed that antimalarial treatment significantly improved pertussis vaccine responses (RR 0.57, 95% CI 0.39 to 0.85).

3.16 | Pneumococcal Vaccine

One article investigated the impact of malaria on the immune response to a 10-valent conjugated pneumococcal antigen vaccine [31]. It compared vaccine responses between malaria infected and uninfected groups and contributed 10 effect sizes, one for each of the *Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F. All were included in the meta-analysis, the results showed statistically significant higher immune response in the malaria uninfected group compared to the infected group (SMD 0.40, 95% CI 0.09 to 0.7, $I^2 = 74.4\%$).

3.17 | Primary Combined Meta-Analysis

Overall, pooling the results from all vaccines, we observed statistically significant higher responses in the malaria uninfected or treated groups compared to the malaria infected or untreated groups (SMD 0.15, 95% CI 0.05 to 0.26, $I^2 = 90.91\%$, p 0.005) (Figure 2).

3.18 | Stratified and Exploratory Analysis

We calculated overall SMDs separately for articles reporting on the impact of malaria infection and those reporting on the effect of antimalarial treatment. We found significantly higher vaccine responses among individuals without malaria compared to those who were infected (SMD 0.34, 95% CI 0.07 to 0.60). Comparing those who received antimalarial treatment with those who did not, the effect estimate favoured treatment, although the confidence intervals included 0 (SMD 0.07, 95% CI −0.01 to 0.16). The overall SMD between studies reporting on the impact of malaria infection and those reporting on the effect of antimalarial treatment using Cochran's Q statistic, there was weak evidence of a difference in effect sizes between the two ($p = 0.07$) (Figure 2).

Meta-regression analysis was conducted on three major variables: vaccine type, sample size and whether effect of malaria infection or treatment was reported. For the latter, there was a significant difference in effect sizes between malaria infection/uninfected and treated/untreated groups ($p = 0.03$), similar to the results generated using Cochran's Q statistic. Meta-regression found no evidence of differences by vaccine type or sample size. We conducted a sensitivity analysis by including only the outcome for the most common vaccine serotype from papers reporting multiple antibody outcomes for the same vaccine. This analysis was performed for the pneumococcal, pertussis, meningococcal, typhoid and polio vaccines. An average SMD of 0.11 (95% CI −0.01 to 0.24), suggesting a slightly higher vaccine response in the uninfected or treated group compared to the infected or untreated group. This result was broadly consistent with the overall findings but with a wider confidence interval (Appendix S6).

3.19 | Quality Assessment and Publication Bias

Quality assessment, guided by the EPHPP, was conducted on 17 articles. Of these, 9 (53%) were rated as weak, 5 (29%) as moderate, and 3 (18%) as strong. Publication bias assessed using funnel plots and Egger's test indicated its presence (Appendix S5).

3.20 | Characteristics of Included Animal Studies

One article [32] presented outcomes for both human and animal studies. We treated each as a separate study, resulting in a total of 32 animal articles selected for full text review. After thorough evaluation based on inclusion criteria, only seven were suitable for inclusion (Figure 1). All the studies were conducted in mice and were published between 1974 and 2022.

Two articles assessed the impact of malaria on BCG vaccine responses [33, 34], two focused on pneumococcal vaccine [35, 36], one examined meningococcal vaccine responses [37], another assessed both diphtheria and tetanus toxoid vaccine responses [38] and one investigated the impact on pertussis vaccine responses [39].

The malaria strains utilised in the studies varied, with 3 studies using the *Plasmodium yoelii* species [34, 35, 38], one using *Plasmodium berghei* [37], one using both *P. berghei* and *Plasmodium chabaudi* [33] and two using both *P. yoelii* and *P. berghei* [36, 39].

Given the diverse nature of outcomes in vaccine responses observed in the animal studies, pooling the results was deemed inappropriate. Instead, we provide a narrative summary of the findings, including study characteristics and references for each animal experiment (Table 2).

3.21 | Effect of Malaria on Vaccine Responses in Animal Models

Among the two articles [33, 34] that investigated the impact of malaria on BCG vaccine responses, both studies utilised C57BL/6 female mice aged between 6 and 8 weeks. Tangie et al. [33] demonstrated that BCG provided protection against *Mycobacterium tuberculosis* irrespective of malaria infection whether induced by virulent *P. berghei* or non-virulent *P. chabaudi*. Likewise, Parra et al. [34] found that BCG conferred protection in the presence of *P. yoelii NL*. Notably, both malaria-infected and uninfected BCG-vaccinated mice exhibited significant anti-tuberculosis protection 4 weeks after the *M. tuberculosis* challenge ($p < 0.01$).

In the two articles investigating the impact of malaria on immune response to the pneumococcal polysaccharide (SSSIII) vaccine, Morges and Weidanz [35], used both male and female BALB/c mice aged between 6 and 8 weeks while McBride et al. [36] employed 3-month-old female inbred CBA/Lac mice. The study by Morges and Weidanz [35] had a sample size of five mice per group, whereas McBride et al. [36] had four to five mice per group. The Morges and Weidanz [35] study demonstrated that malaria significantly suppressed the immune response, resulting in a notable decrease in both serum antibody levels and splenic plaque-forming cell (PFC) responses to the vaccine. Specifically, euthymic nu/+ mice immunised 10 days after infection with *P. yoelii* exhibited markedly depressed responses, whereas athymic nu/nu mice infected with the same parasite showed normal vaccine responses. This could suggest possible role of T cells in malaria immunosuppression. Similarly, McBride et al. [36] reported a severe reduction in antibody response during acute malaria induced by both *P. yoelii*, and *P. berghei*, with some degree of immunosuppression persisting for several weeks following infection resolution.

The study by Oyeyinka, investigated the effects of malaria on the immune response to meningococcal (groups A and C combined) polysaccharide vaccine using BALB/c mice aged 6–10 weeks [37]. Mean meningococcal haemagglutinating antibody titres were lower in *P. berghei* malaria infected mice compared to uninfected mice. Specifically, 7 days after vaccination, the antibody titres were significantly lower in the malaria-infected group ($p < 0.05$). Although the difference was not statistically significant at 14 days post-vaccination ($p > 0.05$), a trend towards lower antibody titres persisted in the infected mice.

The study conducted by Tarzaali et al. investigated the impact of malaria on the immune response to both tetanus and diphtheria toxoid vaccines [38]. For the tetanus vaccine experiment, white CF 1 mice (Canadian Breeding Farm) were used, consisting of female mice weighing 17–22 g, while for the diphtheria vaccine experiment, male mice weighing 20–25 g were utilised. The results from the tetanus vaccine experiment revealed that *P. yoelii* malaria infection suppressed antibody titres in parasitised mice compared to non-parasitised ones across all dilutions. Similarly, in the diphtheria vaccine experiment, lower antibody titres were observed in the *P. yoelii* malaria infected mice compared to uninfected mice.

The study by Viens et al. investigated the impact of malaria on pertussis vaccine responses using 244 male albino mice from the Canadian Breeding Farm weighing between 12 and 20 g [39]. The study found that mice infected with *Plasmodium berghei yoelii* exhibited a diminished antibody response to the pertussis vaccine. Furthermore, the study observed a notable lack of protection against intracerebral challenge with virulent *Bordetella pertussis* in the infected mice indicating compromised vaccine efficacy in the presence of malaria infection.

We conducted quality assessment using the SYRCLE Risk of Bias (RoB) tool. All seven papers included in the systematic review were scored as 'unclear' on domains such as incomplete outcome data, selective outcome reporting and other potential sources of bias. Consequently, all papers were deemed to have a high risk of bias overall.

4 | Discussion

Our systematic review and meta-analysis aimed to elucidate the impact of malaria on immune responses to unrelated vaccines in humans and animals. Overall, we found that malaria infection may attenuate vaccine responses, with infected individuals exhibiting lower antibody responses compared to non-infected individuals. Antimalarial treatment did not exhibit a statistically significant effect on vaccine responses in our analysis, but it is noteworthy that there appeared to be a positive trend in the treatment effect.

To our knowledge, this is the first systematic review with a meta-analysis to explore whether malaria affects immune responses to unrelated vaccines in humans. Our results align with a previous systematic review on parasite–vaccine interactions, that concluded that parasite infections, including those caused by *Plasmodium* spp., detrimentally impact immunisation outcomes [40]. Additionally, our findings are consistent with the conclusions drawn in an earlier review which reported impairment of vaccine responses in individuals with clinical malaria and asymptomatic parasitaemia [5]. The observed decrease in vaccine responses among malaria-infected individuals carries significant implications for public health, especially in regions where malaria is endemic. Reduced vaccine responses may compromise efforts to control infectious diseases in these areas, highlighting the importance of understanding and addressing contributing factors.

We observed variability in the effect of malaria or its treatment on vaccine responses across different vaccine types. Specifically, we noted higher antibody responses, for pneumococcal, meningococcal, and *Haemophilus* B conjugate vaccines among uninfected or treated groups. However, for other vaccine responses, we found no difference. These findings suggest that malaria may have a more pronounced impact on vaccines targeting encapsulated bacteria, which often utilise polysaccharide antigens. This aligns with a previous review which showed that malaria impairs immune responses to heterologous polysaccharide antigens, further emphasising the need for targeted interventions for vaccines against this particular group of organism in malaria-endemic regions [5].

Several hypothesised mechanisms underlie the observed impairment of vaccine responses in malaria-infected individuals. Continuous exposure to malaria antigens may lead to the development of atypical memory B cells (aMBCs), which negatively

impact long-term B cell responses [41]. A positive correlation has been shown between aMBCs and *P. falciparum* transmission [42]. These aMBCs are associated with the upregulation of T-cell inhibitory markers. Specifically, an increase of PD1+ and TIM3+ T-cell subsets (CD4+, CD8+, and DN) has been observed in the malaria-exposed individuals, leading to T-cell exhaustion and senescence [43, 44]. Additionally, the inflammatory nature of malaria blood-stage infection can induce regulatory T cell (Treg) responses, which suppress both malaria-specific and vaccine-induced immunity [45, 46]. This increased Treg response may cause T cell exhaustion, resulting in poor vaccine response [47].

It is essential to recognise potential confounding factors, such as the timing of treatment relative to vaccination and variations in treatment efficacy, as well as the potential impact of co-infections like helminths, which are prevalent in malaria-endemic regions. A systematic review and meta-analysis on malaria-helminth co-infections in SSA found a comorbidity prevalence rate of 69% [48]. Studies have demonstrated that helminth infections have immunomodulatory effects, which may impair vaccine responses [49]. Additionally, helminths have been associated with impairment of vaccine responses in humans and animals [50]. Therefore, caution is warranted when interpreting the observed association between malaria and reduced vaccine responses due to the complex interplay of multiple pathogens and other uncontrolled confounders. These confounders, such as prior exposure to malaria, nutritional status and socioeconomic status, can influence the association between malaria and vaccine responses, and were rarely controlled for in the analyses reported in the included papers. Furthermore, there is a possibility that some participants in the preventive treatment trials were not exposed to malaria, which could further complicate the interpretation of the results.

In animal studies, consistent with findings in human studies, malaria infection preceding vaccination generally dampened vaccine responses across a range of vaccines, including pneumococcal, meningococcal, pertussis, tetanus and diphtheria vaccines. One possible explanation for this greater consistency is that malaria induces similar immunosuppressive effects across different species. However, there were notable exceptions such as the BCG vaccine, where malaria infection did not significantly alter vaccine responses. This discrepancy suggests potential variability in the impact of malaria on different types of vaccines.

The strength of our review lies in its rigorous methodology, which synthesises available evidence from both human and animal studies. By utilising the SMD as a summary statistic in the meta-analysis, we provided a comprehensive synthesis of the literature. One major limitation is the significant heterogeneity among the included studies, both human and animal. This heterogeneity can stem from differences in study design, populations and methodologies. Additionally, most of the included human studies were assessed to have a weak quality rating, which may affect the reliability and generalizability of the findings. We assessed all animal studies to have a high risk of bias overall. Additionally, there was evidence of publication bias in the human studies upon assessment. To enhance the reliability and validity of our findings, we conducted a comprehensive literature search, to include grey literature. Furthermore, we performed meta-regression to explore factors contributing to heterogeneity and conducted sensitivity analyses by focusing on the response to the most common strain in studies with vaccines targeting multiple strains to evaluate the robustness of our conclusions (Supporting Information S6). While the meta-regression suggests that some of the heterogeneity is due to different effect sizes when comparing malaria-infected vs. uninfected and malaria-treated vs. untreated groups, the sensitivity analysis indicated that overall, malaria infection or treatment does not significantly affect vaccine responses of 0.11 (95% CI −0.01 to 0.24). Therefore, caution is warranted when interpreting and generalising these results.

5 | Conclusion

Our systematic review highlights the potential detrimental effect of malaria on responses to unrelated vaccines in humans and animals. Despite significant progress in understanding this phenomenon, several key questions remain unanswered regarding the underlying mechanisms and optimal strategies for intervention. The observed impairment of vaccine responses in malaria-endemic regions underscores the urgent need for public health interventions to mitigate this negative impact. A possible approach would be to undertake implementation research to assess the benefits of treatment for malaria on vaccine responses on a larger scale beyond traditional treatment trials. In summary, while malaria presents an obstacle to vaccine effectiveness, strategic interventions and ongoing research endeavours offer promising avenues to enhance immunisation outcomes in malaria-endemic regions.

Author Contributions

A.M.E. and L.Z. conceived the idea. L.Z. conducted the literature searches. L.Z., J.N. and E.L.W. screened articles for relevance and conducted the subsequent data extraction. A.M.E. was the third reviewer in case of disagreement between the two reviewers each for human and animal studies, respectively. L.Z. conducted data analysis. A.N., J.K., G.N., L.Z., E.L.W. and A.M.E. contributed to data interpretation. L.Z. drafted the manuscript. All authors reviewed, provided input and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Peer Review

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.