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ORIGINAL ARTICLE

Effectiveness of Non-Artemisinin Antimalarial Drugs in Pregnancy: A Meta-Analysis Approach

Jeetu Gangil[1], Gunjan Agarwal[2], Shakti Singhal[3], Leena Gangil[4], Bhaswat Chakraborty[5], Girendra Gautam[6]

Abstract

Background: Malaria is a deadly disease with a high prevalence of morbidity and mortality, causing a significant economic crisis in many countries. Although several malaria control programs have been implemented, this research aimed to compare the effectiveness of antimalarial drug regimens and analyze the comparative effectiveness of all the derivatives used for the management of malaria. This study also aimed to compare the safety and tolerability of antimalarial drug regimens and the relative efficacy of all the derivatives in the treatment of malaria in pregnant women. **Methods:** Electronic databases such as PubMed/Medline, Web of Science, Global Health, Scopus, and the Cochrane Library were searched for published records and literature. Additionally, a bibliographic search of the reference lists of included studies and a random Google search were performed to identify any additional studies that may have been missed during the database search. Randomized controlled trials with an active treatment comparator, either as monotherapy or in combination, or placebo for the treatment of malaria in pregnant women, without any other restrictions, were included in our study. All the required data were extracted into a standardized data extraction sheet. Review Manager Software (RevMan, version 5.3 for Windows; The Cochrane Collaboration, Oxford, UK) was used to conduct the meta-analysis. **Results:** In total, 1077 records were identified, of which 379 were considered for full-text screening, resulting in the final inclusion of 18 studies for the meta-analysis. We evaluated a total of thirteen clinical trials involving 9,070 participants to assess parasitaemia outcomes in pregnant women. We compared Non-ACT (Chemoprophylaxis), the intervention group, with Placebo/No treatment (Control group). Among subjects who received chloroquine, there was no statistically significant reduction in parasitaemia (RR 0.86, 95% CI 0.49, 1.49; P=0.59). However, subjects who received Proguanil showed a decreased risk of parasitaemia compared to placebo (RR 0.08, 95% CI 0.02, 0.40; P<0.002). Overall, the Forest plot meta-analysis demonstrated a statistically significant decrease in parasitaemia with the Non-ACT group compared to the control group (RR 0.42, 95% CI 0.37, 0.48; P<0.00001). The Forest plot confirmed that although adverse effects were found in both arms, there was no significant difference in the decrease of adverse effects between the treatment arms (RR: 0.97; 95% CI: 0.85 to 1.12; P=0.68). Subjects who received Chloroquine showed a statistically significant increase in mean birth weight compared to placebo (MD 81.02, 95% CI 33.84, 128.21, P=0.008). However, the overall Forest plot meta-analysis revealed a statistically significant increase in mean birth weight in the intervention group compared to placebo (MD 32.89, 95% CI 12.82, 52.97, P=0.001). Sensitivity analysis indicated that our findings were robust, as they were similar to the original analysis. A symmetrical presentation in the funnel plot indicated the absence of publication bias in the included studies. **Conclusion:** The current evidence indicates that antimalarials were effective in terms of fever clearance, parasitic clearance, mortality, and adverse events when compared to placebo in pregnant patients with malaria.

Keywords: Malaria, Pregnant, Quinine, Parasitaemia, Chemoprophylaxis

[1]PhD Scholar, K.B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwavidyalaya, Gh/6, Sector-23, Gandhinagar, Gujarat 382023, India

[2]Max Healthcare, ITM Hospital and Research Centre, Sithouli, Gwalior, Madhya Pradesh 475001, India

[3]Department of Anesthesia, Gajra Raja Medical College, Veer Savarkar Marg Gwalior, Madhya Pradesh 474009, India

[4]Institute of Dental Education & Advance Studies (IDEAS), Near Toll Plaza, Etawah Road NH-92, Gwalior, Madhya Pradesh 474020, India

[5]Shree S.K.Patel College of Pharmaceutical Education and Research, Ganpat University, Ganpat Vidyanagar, Mehsana-Gozaria Highway, PO - 384012, India

[6]Shri Ram College of Pharmacy, Indraprasth Colony, Laxman Vihar Colony, Civil Lines South, Muzaffarnagar, Uttar Pradesh 251001, India

Corresponding Author: PhD Scholar, K.B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwavidyalaya, Gh/6, Sector-23, Gandhinagar, Gujarat 382023, India **Email**: drjeetugangil@gmail.com

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Introduction

The disease burden, including mortality, remains high even in this era of highly sophisticated medical science and highly precious malaria control programs over the decades.[1] Approximately 95% of the population resides in malarial-prone areas, with 80% of recorded malarial cases. According to published information, malaria cases and deaths due to malaria have decreased considerably over the past decades. Between 2010 and 2018, the incidence of malaria fell from 71 to 57 cases per 1,000 populations at risk. However, in

2018 alone, more than 400,000 people died from malaria, and 93% of those deaths occurred in sub-Saharan Africa. Pregnant or lactating women and newborns living in malaria-endemic areas are especially vulnerable, and malaria in pregnancy (MiP) continues to play a significant role in worldwide maternal deaths. In 2015, malaria was the third most common cause of death among women of reproductive age in Africa, and MiP was responsible for more than 400,000 cases of maternal anemia and approximately 15-18% of maternal deaths worldwide. Unfortunately, the women who are most vulnerable to malaria are often the least protected against it, even though MiP also poses a significant threat to newborns as it can cause spontaneous abortion, stillbirth, premature delivery, low birth weight, and neonatal mortality [2].Top of Form

To combat MiP, intermittent preventive treatment in pregnancy (IPTp) should commence early in the second trimester of pregnancy with three or more doses of the antimalarial sulfadoxine-pyrimethamine and continue monthly throughout the pregnancy until delivery. Based on available data, the percentage of eligible women receiving three or more doses of IPTp in 36 African countries increased from 2% in 2010 to 31% in 2018. However, there is still much work needed to ensure that pregnant women and newborns across the globe are protected against malaria [2].

According to a published study in the journal 'The Lancet' in 2004, they proposed active involvement and coordination by the WHO and the Special Programme in Research and Training in Tropical Diseases (WHO/TDR) in trials emphasizing the clinical benefits and harmful effects of antimalarials. Moreover, multinational and multicenter placebo-controlled trials on various antimalarial drug combinations are required to determine the use of these agents as first-line management in different settings. This systematic and standardized approach will facilitate better analysis, including individual patient data analysis. These analyses, including meta-analyses, will enable the evaluation of the trials with respect to their quality of randomization, allocation, assessment of data uniformity, follow-up information, and handling of missing data. Furthermore, this approach will also facilitate better data analysis, more robust findings, and subgroup analysis. Additionally, this process of meta-analysis will lead to better conclusions, wider generalizability of results, clearer identification of information gaps, and a call for further research and incorporation of new results [3-4].

We have conducted a systematic review of the literature, which traditionally has been largely narrative. The purpose of this meta-analysis is to critically evaluate available literature and statistically analyze comparable studies or trial findings to derive more robust conclusions. Its primary objectives were to increase the number of observations, enhance statistical power, and improve the assessment of effect measures for an intervention or etiological factor. The reason for choosing this approach was that healthcare professionals and researchers often conduct a series of studies, including pre-clinical and clinical studies, to evaluate the safety and effectiveness of a drug. However, the strength of these studies, especially clinical ones, may sometimes be limited due to sample size, study quality, and other factors. We employed a meta-analysis approach to collect and synthesize data from numerous clinical studies, which is a proven method for arriving at valid and more powerful conclusions regarding a drug's effects. Furthermore, meta-analysis provides a framework for assessing and combining a series of study findings, rather than viewing each set of findings in isolation. These analyses are frequently used in internal research, government agency submissions, and marketing. In addition to assessing efficacy, meta-analyses are also applied to generate evidence on adverse effects, as many of these events are typically rare. Therefore, collecting information through multiple studies to calculate the risk of these rare events may be the only practical approach.

Objectives

Primary Objective

To compare the effectiveness of anti-malarial drug regimens and analyze the comparative effectiveness of chemoprophylaxis used for the management of malaria. Efficacy Evaluation Criteria (based on available information); Parasite Clearance or parasitaemia.

Secondary Objective

To compare the safety and tolerability of antimalarial drug regimens and the relative efficacy of each derivative in treating malaria. Insight of Safety and Tolerability: Adverse drug reactions (ADR/AE), serious adverse events (SAE), mortality, and treatment failure based on available published information.

Study Design

Criteria for Studies to Be Included: Types of participants

The study participants consisted of pregnant or breastfeeding women who were affected by malaria. All individuals had a confirmed diagnosis of malaria either through Rapid Diagnostic Testing (RDT) or by examination of blood slides using microscopy.

Types of Studies for Inclusion/Exclusion

Randomized controlled trials with an active treatment comparator; Abstracts or full article, available published information or data.

Study Code

Every study is provided with a coding containing of: 'Author name, code of the Country by mentioning first three alphabet of country name, study year published'

Criteria for considering excluded studies

Duplicate studies**,** Inadequate information**,** Article not found; Title or abstract available with no information of data**,** PK-PD Studies or Pharmacogenomics or Non RCT**,** Observational studies**,** ACT based regimens**,** Review articles.

Study Outcomes

Primary Outcomes: Clinical

Parasitic clearance or Parasitic clearance time taken to clear the parasite; rate of 50% (fifty) or 90% (Ninety) parasitic clearance (PC50, PC90), as reported; in vivo sensitivity as S (parasite clearance within 7 days of drug therapy initiation and till 28 days), RI (parasite clearance by 7 days after that reactivation by 28 days), RII (temporary striking decrease in parasitaemia), RIII (no significant decrease in parasitaemia).

Secondary Outcomes

Adverse drug reactions; nausea, vomiting, diarrhoea, lightheaded, other

Results

Evaluation of identified articles

Around 1077 articles were identified (Year 1983 – Year 2021) out

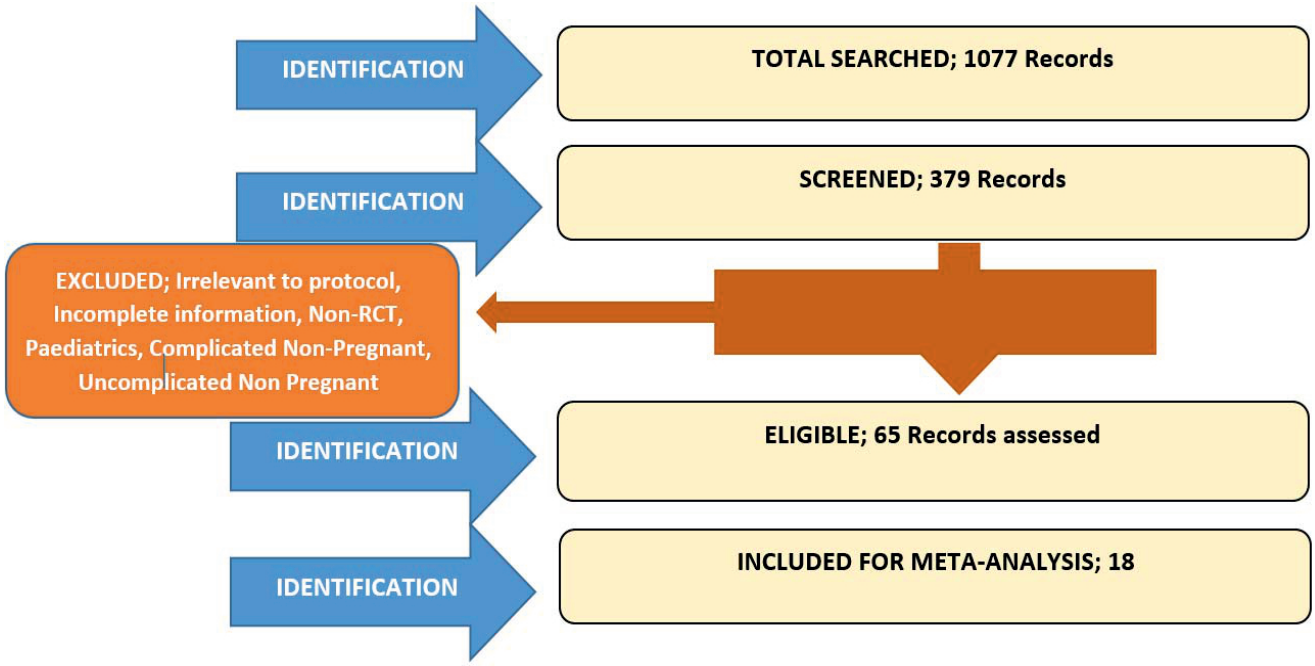

Figure 1: Flow Diagram For Literature Search

of which 379 were screened among which 65 were eligible records assessed and 18 were included for meta-analysis (figure 1, Flow Diagram for Literature Search)

Description of included studies

Each trial was given a coding which consists of: Name of Investigator, country name, year the trial conducted was performed. These studies conducted in several countries; Mozambique (Two study), Nigeria (Two studies), Thailand (Two studies), Uganda (Two studies), Burkina Faso (One study), Gambia (Three studies), Cameroon (One study), Kenya (Five studies). We included RCT studies; Pyrimethamine-Dapsone (GreenwoodGAM1989[5], Menendez GAM1994 [6]), SP(Challis MOZ2004 [7], Mbaye GAM2006 [8], Menendez MOZ2008 [9], Ndyomugyenyi UGA2011[10], NjagiKEN2003A [11], NjagiKEN2003B [11], PariseKEN1998A [12], PariseKEN1998B [12], ShulmanKEN1999 [13]), Pyrimethamine (NahlenNIG1989 [14] and Mefloquine (NostenTHA1994 [15]), Chloroquine (VillegasTHA2007 [16], CotBUR1992 [17], CotCAM1995[18], NdyomugyenyiUGA2000 [19]), Proguanil (FlemingNIG1986 [20]).

Primary Outcome: Parasitaemia

We evaluated a total of thirteen clinical trials involving 9,070 participants to assess parasitaemia outcomes in pregnant women. We compared the Non-ACT (Chemoprophylaxis) intervention group to the Placebo/No treatment control group. The total number of subjects in the Non-ACT group was 4,771, while in the Control group, there were 4,299 participants. An overall summary of the forest plot revealed that subjects who received Pyrimethamine-Dapsone showed a statistically significant decrease in parasites in their blood (RR 0.41, 95% CI 0.22, 0.76, P=0.005). However, subjects who received Pyrimethamine 25mg weekly did not show a statistically significant decrease in parasites in their blood compared to the control group (RR 0.79, 95% CI 0.36, 1.73, P=0.56). On the other hand, subjects who received Sulfadoxine-pyrimethamine demonstrated a decreased risk of parasitaemia compared to the placebo group and exhibited a statistically significant reduction in the number of parasites (RR 0.40, 95% CI 0.35, 0.46, P<0.00001). Conversely, subjects who received chloroquine did not show a statistically significant reduction in parasitaemia (RR 0.86, 95% CI 0.49, 1.49, P=0.59). Furthermore, subjects who received Proguanil showed a decreased risk of parasitaemia compared to the placebo group (RR 0.08, 95% CI 0.02, 0.40, P<0.002). Overall, the forest plot meta-analysis indicated a statistically significant reduction in parasitaemia with the Non-ACT group when compared to the control group (RR 0.42, 95% CI 0.37, 0.48; P<0.00001) (Figure 2: Forest Plot – Parasitaemia).

Secondary Outcome

i. **Adverse Events:** We evaluated six trials (ChallisMOZ2004, Menendez MOZ20085582, Nosten THA1994, Parise KEN1988A, Parrise KEN1988B, and Shulman KEN1999-7,006 Participants) for the adverse events in pregnant women. We evaluated Non-ACT (Chemoprophylaxis)that is the intervention group vs Placebo/No treatment (Control group). Adverse events reported were skin reaction, nausea/vomiting, dizziness, vertigo, visual abnormalities and other. Forest plot confirmed that although adverse effects were found in both arms, there was no overall difference in the decrease of adverse effects in both the treatment arms (RR: 0.97; 95% CI: 0.85 to 1.12; P=0.68). (figure 3, Forest Plot: Adverse Events)

ii. **Mean Birthweight:** We evaluated total fourteen clinical trials (8889 participants) for mean birth weight outcomes in pregnant women. We evaluated Non-ACT (Chemoprophylaxis) that is the intervention group vs Placebo (Control group). Total numbers of subjects in Non-ACT group were 4667 whereas in Control group were found to be 4222. Overall summary of this forest plot found that in subjects who received Proguanil 100 mg daily did not showed a statistically significant increase in mean birth weight compared to placebo (MD 132.00 95%CL -61.69, 325.60. P=0.18). In subjects who received

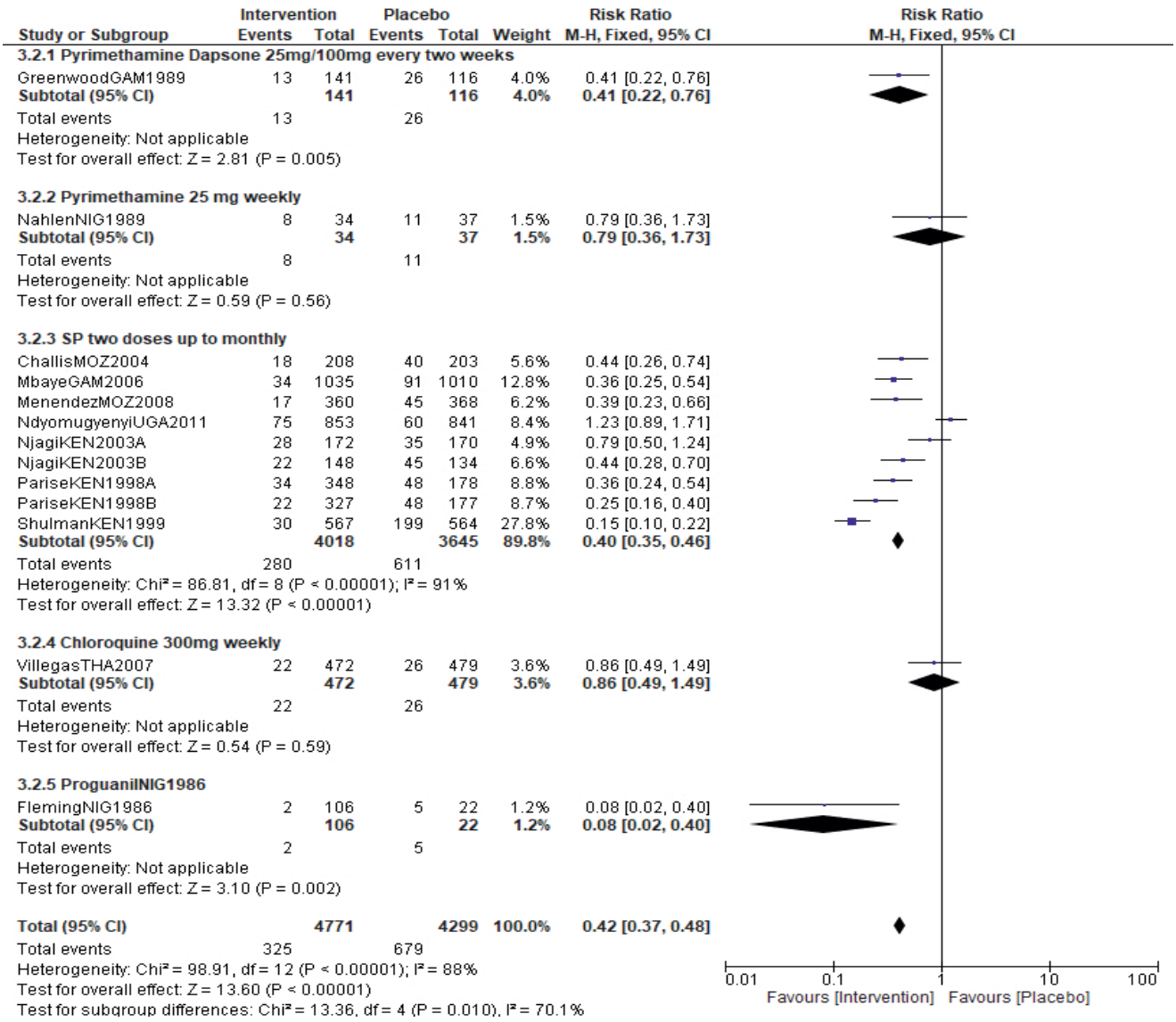

Figure 2: Forest Plot: Parasitaemia

Pyrimethamine-Dapsone (GreenwoodGAM1989) although no statistically significant result was obtained, Intervention group showed increased mean birth weight compared to placebo (MD 146.00, 95% CI -5.18, 297.18, one trials, 117 participants P=0.06). In subjects who received Pyrimethamine-Dapsone(MenendezGAM1994) statistically significant result was obtained with Intervention group and it showed increased mean birth weight compared to placebo (MD 132.00, 95% CI -61.69, 325.69, one trials, 182 participants P=0.01). In subjects who received Sulfadoxine pyrimethamine no statistically significant result was obtained, Intervention group showed increased mean birth weight compared to placebo (MD 18.85, 95% CI -4.79, 42.49, one trials, 6255 participants P=0.12). In subjects who received Mefloquine did not show a statistically significant increase in mean birth weight and benefit shifted towards placebo (MD -80.00 95%CL 176.77 16.77 P=0.11). In subjects who received Chloroquine showed a statistically significant increase in mean birth weight compared to placebo (MD 81.02 95%CL 33.84, 128.21. P=0.008). But overall Forest plot metaanalysis showed a statistically significant result and resulted in increased mean birth weight with intervention group compared to placebo (MD 32.89, 95% CI 12.82 ,52.97 P=0.001). (figure 4, Mean Birth weight)

Senstivity Analysis

The sensitivity analysis was conducted by removing the RCT with least weight (FlemingNIG 1986), which yielded a significantly lesser occurrence of parasitaemia in interventional arm (OR: 0.46; 95% CI: 0.46 to 0.68; P<0.0001) in comparison to the control arm among the in pregnant women, Figure 5, which was similar to the original analysis (OR: 0.42; 95% CI 0.37 to 0.48; P<0.0001), which specifies that, our findings was robust. (figure 5, Sensitivity analysis of parasitaemia outcome in pregnant women)

A sensitivity analysis was performed by removing the study with least weight [0.2%; MenendezMOZ2008], revealed a non-significantly lesser occurrence of adverse events in intervention group (OR: 0.97; 95% CI 0.84 to 1.11; P-0.65) than control among the pregnant women, figure 6. This was similar to the original analysis (OR: 0.97; 95% CI 0.85 to 1.12; P=0.68), which indicates that, our findings were robust, figure 6, Sensitivity analysis of

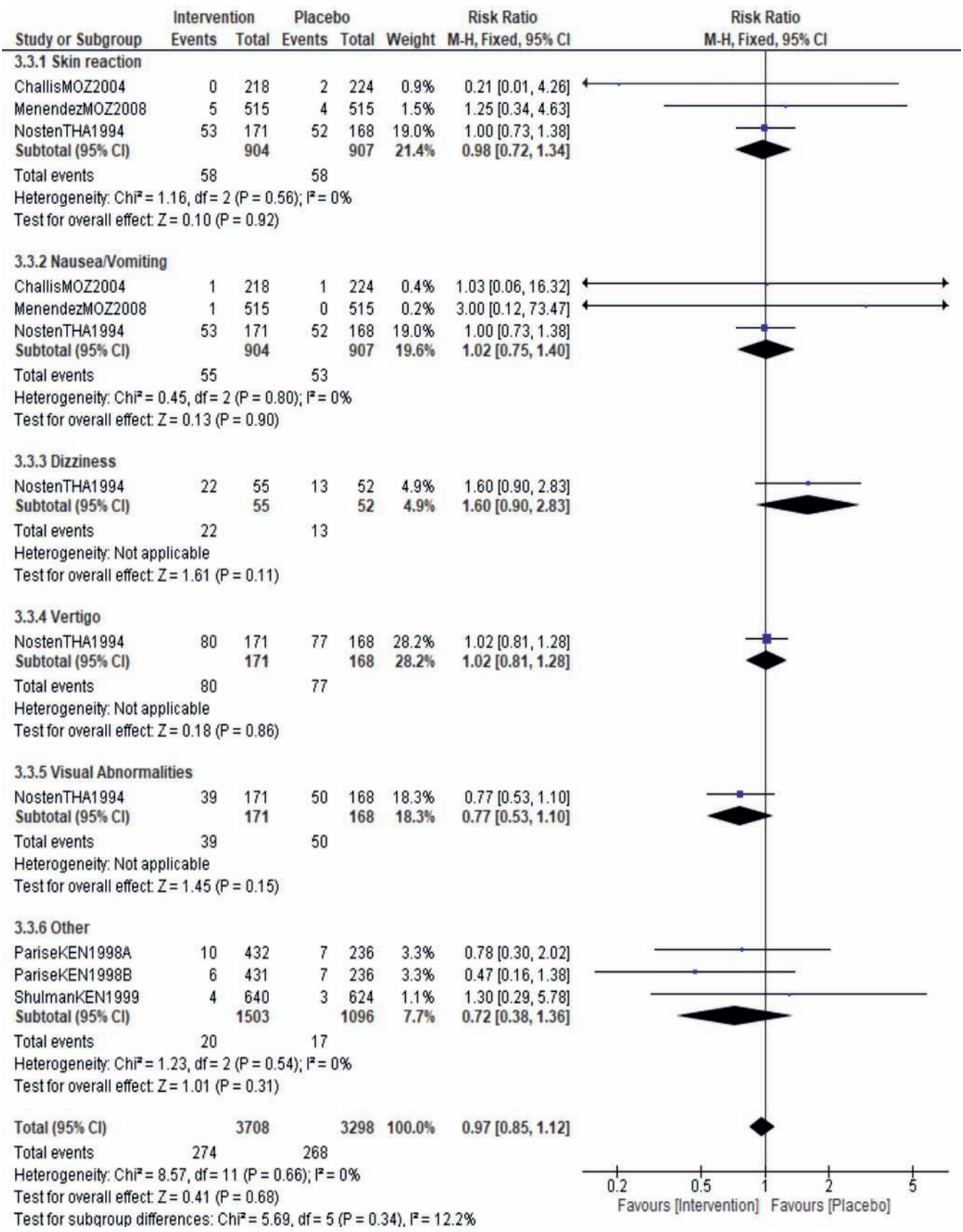

Figure 3: Forest Plot: Adverse Events

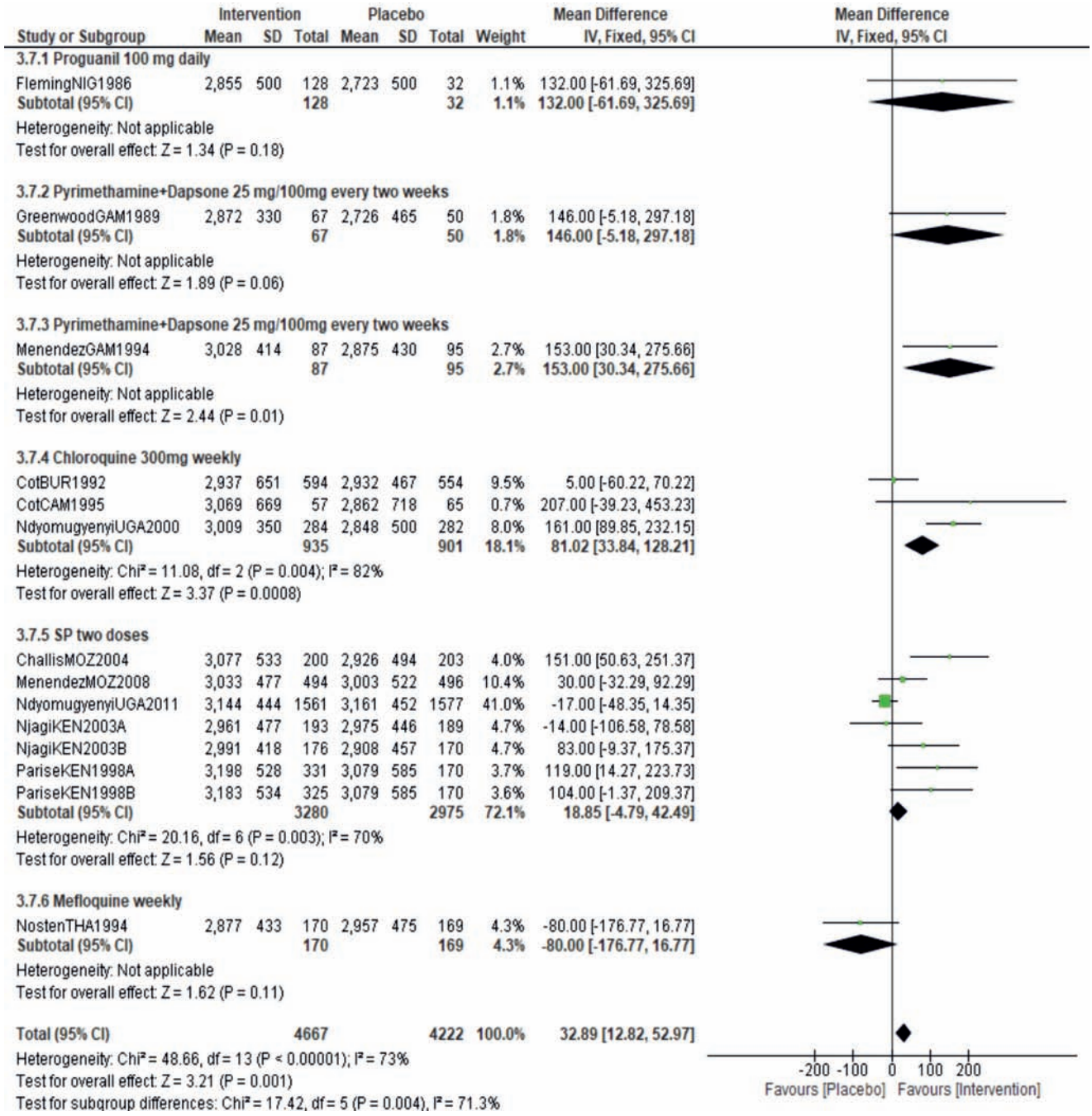

Figure 4: Mean Birth weight

adverse events outcome in pregnant women

b. PUBLICATION BIAS

A funnel plot was generated by considering the parasitemia in pregnant women in the X-axis and standard error in the Y-axis. There was a symmetrical presentation in the funnel plot, which indicates the absence of publication bias in the included studies. (Figure 7, Funnel plot of parasitaemia in Pregnant women)

Discussion

Malaria has historically been a deadly disease with no exact treatment approach promising 100% cure or assurance of control. Over time, numerous programs and approaches have been developed and implemented worldwide to control this disease. While many of these efforts have been effective to a certain extent, they haven't achieved maximum control. Nonetheless, these successes have fueled hope for the development of new medicines and treatment strategies for managing the disease. Anti-malarial agents are used to treat malaria, and there are many such agents in medical science. However, each drug has its own advantages and disadvantages in terms of efficacy and safety profiles. Moreover, the efficacy of these agents in pregnant women remains a subject of debate, with no consensus reached based on existing studies. The findings to date have inconsistencies in various outcomes, populations, drug choices, routes of administration, and other factors. Given the lack of consensus on the efficacy and safety of anti-malarial agents based on available evidence, there is a need for comprehensive systematic reviews that can gather all existing literature, collect the

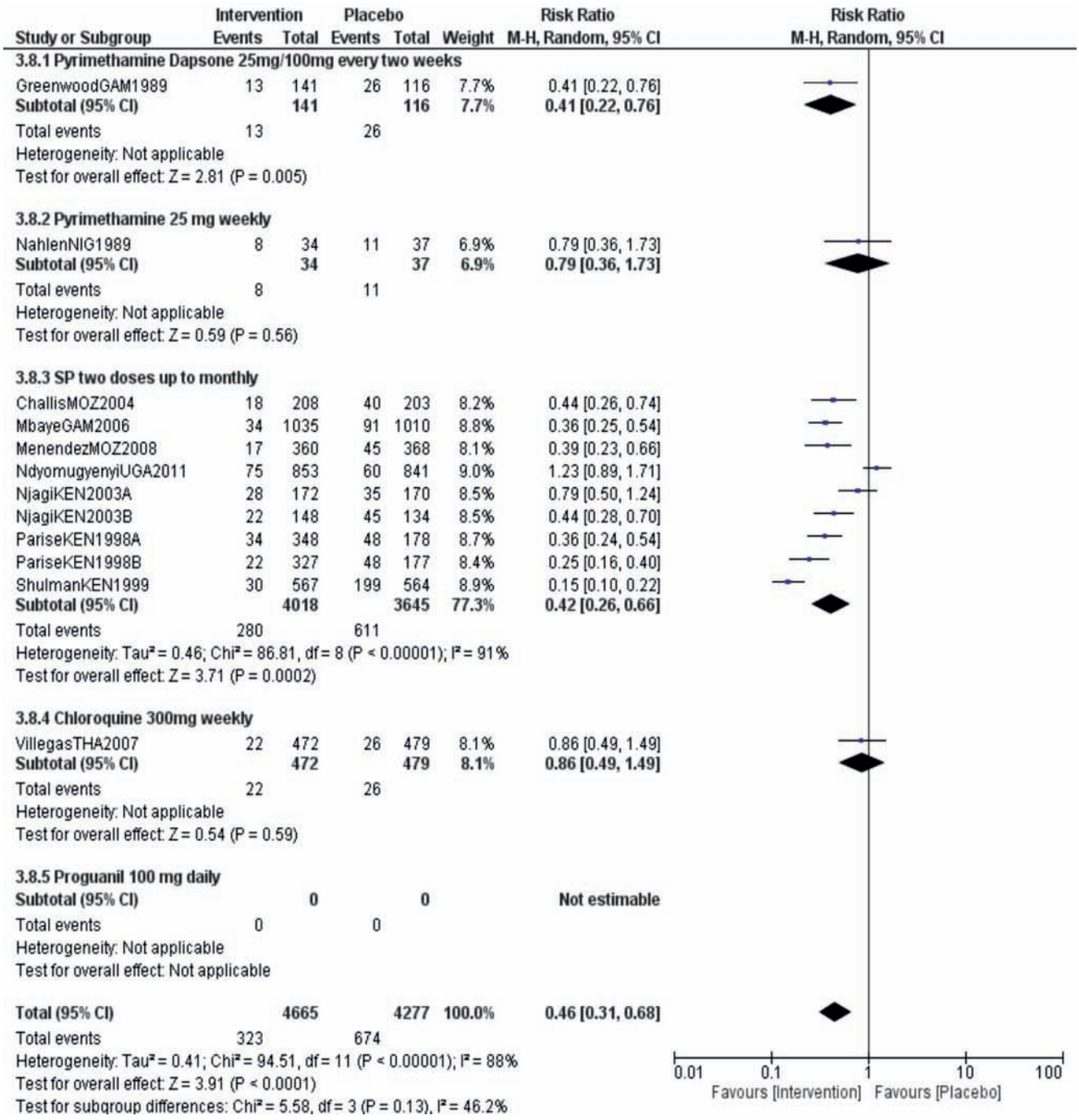

Figure 5: Sensitivity analysis of parasitaemia outcome in pregnant women

necessary information, and perform meta-analyses to provide accurate statistical findings from different studies. Therefore, we conducted a systematic review and meta-analysis to assess the efficacy and safety of antimalarial agents.

Malaria infection during pregnancy increases the risk of maternal anemia, mortality, abortion, prematurity, and low birth weight, which is the greatest risk factor for neonatal mortality [21]. This overview is based on maternal and birth outcomes in the largest series of randomized antimalarial pregnancy trials. Meta-analyses of clinical trials suggest that successful prevention of these infections decreases in Non-ACT vs. Placebo/No Treatment for treating malaria in pregnant women. Outcomes such as parasitaemia, mortality, and adverse events were evaluated for the comparison of Non-ACT vs. Placebo/No Treatment. We assessed a total of thirteen clinical trials (9,070 participants) for parasitaemia outcomes in pregnant women, and the overall Forest plot meta-analysis showed a significant decrease in parasitaemia with the Non-ACT group compared to placebo (RR 0.42, 95% CI 0.37, 0.48; P<0.00001). A study conducted by Challis et al. showed that placental malarial parasitaemia was lower in the SP group, resulting in the placenta remaining aparasitaemic for a longer duration in the SP-treated group. Due to this decrease in placental malarial parasitaemia, the average birth weight was significantly higher in the SP group [22].

We evaluated a total of nine clinical trials (10,362 participants) for

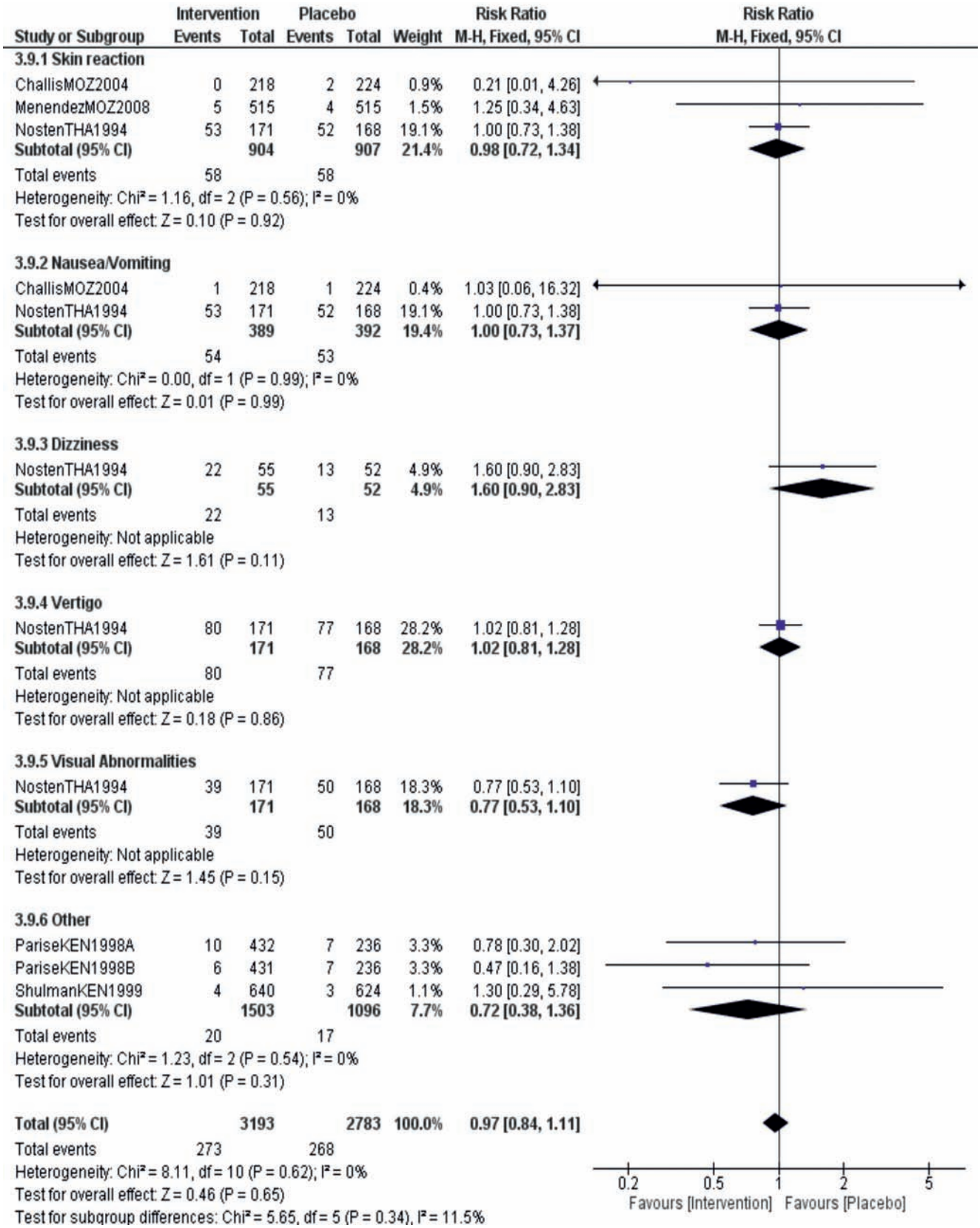

Figure 6: Sensitivity analysis of adverse events outcome in pregnant women

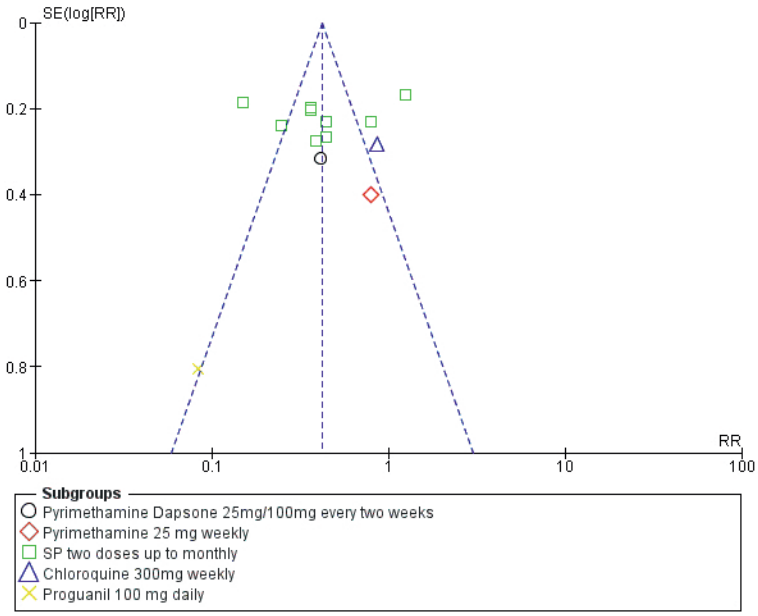

Figure 7: Funnel plot of parasitaemia in Pregnant women

mortality outcomes in pregnant women, and the overall Forest plot meta-analysis did not show a significant reduction in mortality with either intervention (RR 1.12, 95% CI 0.59, 2.13; P=0.73). We assessed six trials for adverse events in pregnant women, and the Forest plot meta-analysis confirmed that although adverse events were found in both arms, there was no overall difference between the two groups (RR: 0.97; 95% CI: 0.85 to 1.12; P=0.68).

We evaluated a total of fourteen clinical trials (8,889 participants) for mean birth weight outcomes in pregnant women. The overall Forest plot meta-analysis showed a statistically significant increase in mean birth weight in the intervention group compared to placebo (MD 32.89, 95% CI: 12.82 to 52.97; P=0.001). A study conducted by Cot et al. showed that in the CQ group, the mean birth weight was significantly greater (P=0.02) and the rate of low birth weight newborns was lower (10.5% compared to 27.7%; P=0.02) compared to the control group [23].

Conclusion:

The current meta-analysis reveals that pregnant women experienced a significant decrease in parasitaemia with the Non-ACT group compared to placebo, although there were no significant changes between the treatment and control groups in terms of mortality outcomes and the occurrence of adverse events. However, a significant increase in mean birth weight was observed in pregnant women treated with the Non-ACT group compared to placebo. Overall, the current evidence suggests that treatment with anti-malarial agents is more effective in managing malaria in pregnant women with a good safety profile and a lower occurrence of adverse events. Even though sensitivity analysis did not show an impact on the overall outcome analysis.

Conflict of Interest:	All authors declare no COI
Ethics:	There is no ethical violation as it is based on voluntary anonymous interviews
Funding:	No external funding
Guarantor:	Dr Jeetu Gangil will act as guarantor of this article on behalf of all co-authors.

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