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Mefloquine for preventing malaria in pregnant women (Review)

González R, Pons-Duran C, Piqueras M, Aponte JJ, ter Kuile FO, Menéndez C

González R, Pons-Duran C, Piqueras M, Aponte JJ, ter Kuile FO, Menéndez C.
Mefloquine for preventing malaria in pregnant women.
Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD011444.
DOI: 10.1002/14651858.CD011444.pub3.

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[Intervention Review]

Mefloquine for preventing malaria in pregnant women

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Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: Unchanged, published in Issue 11, 2018.

Citation: González R, Pons-Duran C, Piqueras M, Aponte JJ, ter Kuile FO, Menéndez C. Mefloquine for preventing malaria in pregnant women. *Cochrane Database of Systematic Reviews* 2018, Issue 11. Art. No.: CD011444. DOI: 10.1002/14651858.CD011444.pub3.

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ABSTRACT

Background

The World Health Organization recommends intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine for malaria for all women who live in moderate to high malaria transmission areas in Africa. However, parasite resistance to sulfadoxine-pyrimethamine has been increasing steadily in some areas of the region. Moreover, HIV-infected women on cotrimoxazole prophylaxis cannot receive sulfadoxine-pyrimethamine because of potential drug interactions. Thus, there is an urgent need to identify alternative drugs for prevention of malaria in pregnancy. One such candidate is mefloquine.

Objectives

To assess the effects of mefloquine for preventing malaria in pregnant women, specifically, to evaluate:

- the efficacy, safety, and tolerability of mefloquine for preventing malaria in pregnant women; and
- the impact of HIV status, gravidity, and use of insecticide-treated nets on the effects of mefloquine.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, Embase, Latin American Caribbean Health Sciences Literature (LILACS), the Malaria in Pregnancy Library, and two trial registers up to 31 January 2018. In addition, we checked references and contacted study authors to identify additional studies, unpublished data, confidential reports, and raw data from published trials.

Selection criteria

Randomized and quasi-randomized controlled trials comparing mefloquine IPT or mefloquine prophylaxis against placebo, no treatment, or an alternative drug regimen.

Data collection and analysis

Two review authors independently screened all records identified by the search strategy, applied inclusion criteria, assessed risk of bias, and extracted data. We contacted trial authors to ask for additional information when required. Dichotomous outcomes were compared using risk ratios (RRs), count outcomes as incidence rate ratios (IRRs), and continuous outcomes using mean differences (MDs). We have presented all measures of effect with 95% confidence intervals (CIs). We assessed the certainty of evidence using the GRADE approach for the following main outcomes of analysis: maternal peripheral parasitaemia at delivery, clinical malaria episodes during pregnancy, placental malaria, maternal anaemia at delivery, low birth weight, spontaneous abortions and stillbirths, dizziness, and vomiting.

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Main results

Six trials conducted between 1987 and 2013 from Thailand (1), Benin (3), Gabon (1), Tanzania (1), Mozambique (2), and Kenya (1) that included 8192 pregnant women met our inclusion criteria.

Two trials (with 6350 HIV-uninfected pregnant women) compared two IPTp doses of mefloquine with two IPTp doses of sulfadoxine-pyrimethamine. Two other trials involving 1363 HIV-infected women compared three IPTp doses of mefloquine plus cotrimoxazole with cotrimoxazole. One trial in 140 HIV-infected women compared three doses of IPTp-mefloquine with cotrimoxazole. Finally, one trial enrolling 339 of unknown HIV status compared mefloquine prophylaxis with placebo.

Study participants included women of all gravidities and of all ages (four trials) or > 18 years (two trials). Gestational age at recruitment was > 20 weeks (one trial), between 16 and 28 weeks (three trials), or ≤ 28 weeks (two trials). Two of the six trials blinded participants and personnel, and only one had low risk of detection bias for safety outcomes.

When compared with sulfadoxine-pyrimethamine, IPTp-mefloquine results in a 35% reduction in maternal peripheral parasitaemia at delivery (RR 0.65, 95% CI 0.48 to 0.86; 5455 participants, 2 studies; high-certainty evidence) but may have little or no effect on placental malaria infections (RR 1.04, 95% CI 0.58 to 1.86; 4668 participants, 2 studies; low-certainty evidence). Mefloquine results in little or no difference in the incidence of clinical malaria episodes during pregnancy (incidence rate ratio (IRR) 0.83, 95% CI 0.65 to 1.05, 2 studies; high-certainty evidence). Mefloquine decreased maternal anaemia at delivery (RR 0.84, 95% CI 0.76 to 0.94; 5469 participants, 2 studies; moderate-certainty evidence). Data show little or no difference in the proportions of low birth weight infants (RR 0.95, 95% CI 0.78 to 1.17; 5641 participants, 2 studies; high-certainty evidence) and in stillbirth and spontaneous abortion rates (RR 1.20, 95% CI 0.91 to 1.58; 6219 participants, 2 studies; I^2 statistic = 0%; moderate-certainty evidence). IPTp-mefloquine increased drug-related vomiting (RR 4.76, 95% CI 4.13 to 5.49; 6272 participants, 2 studies; high-certainty evidence) and dizziness (RR 4.21, 95% CI 3.36 to 5.27; participants = 6272, 2 studies; moderate-certainty evidence).

When compared with cotrimoxazole, IPTp-mefloquine plus cotrimoxazole probably results in a 48% reduction in maternal peripheral parasitaemia at delivery (RR 0.52, 95% CI 0.30 to 0.93; 989 participants, 2 studies; moderate-certainty evidence) and a 72% reduction in placental malaria (RR 0.28, 95% CI 0.14 to 0.57; 977 participants, 2 studies; moderate-certainty evidence) but has little or no effect on the incidence of clinical malaria episodes during pregnancy (IRR 0.76, 95% CI 0.33 to 1.76, 1 study; high-certainty evidence) and probably no effect on maternal anaemia at delivery (RR 0.94, 95% CI 0.73 to 1.20; 1197 participants, 2 studies; moderate-certainty evidence), low birth weight rates (RR 1.20, 95% CI 0.89 to 1.60; 1220 participants, 2 studies; moderate-certainty evidence), and rates of spontaneous abortion and stillbirth (RR 1.12, 95% CI 0.42 to 2.98; 1347 participants, 2 studies; very low-certainty evidence). Mefloquine was associated with higher risks of drug-related vomiting (RR 7.95, 95% CI 4.79 to 13.18; 1055 participants, one study; high-certainty evidence) and dizziness (RR 3.94, 95% CI 2.85 to 5.46; 1055 participants, 1 study; high-certainty evidence).

Authors' conclusions

Mefloquine was more efficacious than sulfadoxine-pyrimethamine in HIV-uninfected women or daily cotrimoxazole prophylaxis in HIV-infected pregnant women for prevention of malaria infection and was associated with lower risk of maternal anaemia, no adverse effects on pregnancy outcomes (such as stillbirths and abortions), and no effects on low birth weight and prematurity. However, the high proportion of mefloquine-related adverse events constitutes an important barrier to its effectiveness for malaria preventive treatment in pregnant women.

2 April 2019

Up to date

All studies incorporated from most recent search

All eligible published studies found in the last search (31 Jan, 2018) were included and one ongoing study was identified (see 'Characteristics of ongoing studies' section)

PLAIN LANGUAGE SUMMARY

Mefloquine for preventing malaria in pregnant women

What is the aim of this review?

The aim of this Cochrane Review was to find out whether the antimalarial drug mefloquine is efficacious and safe for prevention of malaria in pregnant women living in stable transmission areas. We found six relevant studies to help us answer this question.

Key messages

The antimalarial drug mefloquine is efficacious for malaria prevention in pregnant women. The drug has been found to be safe in terms of adverse pregnancy outcomes, such as low birth weight, prematurity, stillbirths and abortions, and congenital malformations. However, it is worse tolerated than other antimalarial drugs.

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What was studied in the review?

Pregnant women are vulnerable to malaria infection, especially if they are living with HIV. The consequences of malaria during pregnancy can be severe and include poor health outcomes for both women and their children. For this reason, in malaria-endemic areas of stable transmission, women are recommended to prevent malaria infection by sleeping under mosquito bed-nets and by taking effective drugs (such as sulphadoxine-pyrimethamine or cotrimoxazole in case of HIV infection) as chemoprevention against malaria throughout pregnancy.

This Cochrane Review looked at the effects of mefloquine for prevention of malaria in both HIV-uninfected and HIV-infected pregnant women.

What are the main results of the review?

We found five relevant studies conducted in sub-Saharan Africa and one in Thailand between 1987 and 2013. These studies compared mefloquine with placebo or other antimalarial drugs currently recommended for prevention of malaria in pregnant women. The review shows the following:

• Compared with sulfadoxine-pyrimethamine, mefloquine chemoprevention in HIV-uninfected women:

◦reduces risks of maternal peripheral parasitaemia (presence of malaria parasites in the blood of women) and anaemia at delivery;
◦ makes no difference in the prevalence of adverse maternal outcomes (such as low birth weight, prematurity, stillbirths and abortions, and congenital malformations) and in the incidence of clinical malaria episodes during pregnancy; and
◦ increases risks of drug-related adverse events including vomiting, fatigue/weakness, and dizziness.

• Compared with cotrimoxale prophylaxis alone, mefloquine chemoprevention plus cotrimoxazole in HIV-infected women:

◦ reduces the risk of maternal peripheral parasitaemia at delivery and the risk of placental malaria;
◦ makes no difference in the prevalence of adverse pregnancy outcomes (such as low birth weight, prematurity, stillbirths and abortions, and congenital malformations) and in the incidence of clinical malaria episodes during pregnancy; and
◦ increases the risk of drug-related adverse events such as vomiting and dizziness.

Overall, the high proportion of mefloquine-related adverse events constitutes an important barrier to its effectiveness for malaria preventive treatment in pregnant women.

How up-to-date is this review?

The review authors searched for studies up to 31 January 2018.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Mefloquine compared with sulfadoxine-pyrimethamine for preventing malaria in pregnant women

Mefloquine compared with sulfadoxine-pyrimethamine for preventing malaria in pregnant women

Patient or population: HIV-uninfected pregnant women
Setting: Benin, Gabon, Mozambique, and Tanzania
Intervention: mefloquine
Comparison: sulfadoxine-pyrimethamine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments (compared with sulfadoxine-pyrimethamine)
	Risk with sulfadoxine-pyrimethar	Risk with mefloquine				
Clinical malaria episodes during pregnancy	-	-	IRR 0.83 (0.65 to 1.05)	- (2 RCTs)	⊕⊕⊕⊕ HIGH[a]	Mefloquine results in little or no difference in the incidence of clinical malaria episodes during pregnancy
Maternal peripheral parasitaemia at delivery	43 per 1000	28 per 1000 (20 to 37)	RR 0.65 (0.48 to 0.86)	5455 (2 RCTs)	⊕⊕⊕⊕ HIGH[a]	Mefloquine results in lower maternal peripheral parasitaemia at delivery
Placental malaria	52 per 1000	54 per 1000 (30 to 97)	RR 1.04 (0.58 to 1.86)	4668 (2 RCTs)	⊕⊕⊖⊖ LOW[a,b,c] Due to imprecision and heterogeneity	Mefloquine may result in little or no difference in placental parasitaemia
Maternal anaemia at delivery	219 per 1000	184 per 1000 (166 to 206)	RR 0.84 (0.76 to 0.94)	5469 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a,d] Due to imprecision	Mefloquine probably results in fewer women anaemic at delivery
Low birth weight	117 per 1000	111 per 1000 (91 to 137)	RR 0.95 (0.78 to 1.17)	5641 (2 RCTs)	⊕⊕⊕⊕ HIGH[a,e]	Mefloquine results in little or no difference in low birth weight
Stillbirths and abortions	31 per 1000	37 per 1000 (28 to 49)	RR 1.20 (0.91 to 1.58)	6219 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a,b]	Mefloquine probably results in little or no difference in stillbirths or abortions

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					Due to imprecision	
AEs: vomiting	82 per 1000	390 per 1000 (338 to 449)	RR 4.76 (4.13 to 5.49)	6272 (2 RCTs)	⊕⊕⊕⊕ HIGH[a]	Mefloquine results in a four-fold increase in vomiting
AEs: dizziness	94 per 1000	396 per 1000 (316 to 496)	RR 4.21 (3.36 to 5.27)	6272 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a,f] Due to risk of bias	Mefloquine probably results in a four-fold increase in dizziness

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; IRR: incidence rate ratio; RCT: randomized controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Not downgraded for risk of bias: although one trial has serious risk of bias, the other is of good quality and exclusion of the smaller trial has little effect on the estimate of effect.
[b]Downgraded by 1 for imprecision: confidence intervals range from considerable benefit to considerable harm.
[c]Downgraded by 1 for heterogeneity: substantive qualitative heterogeneity is evident in the meta-analysis.
[d]Downgraded by 1 for imprecision: CIs include little or no important difference to a 24% reduction in anaemic women.
[e]Not downgraded for imprecision: we consider that a 22% reduction or 17% increase in birth weight is not a clinically significant change.
[f]Downgraded by 1 for performance bias: both trials are unblinded.

Summary of findings 2. Mefloquine plus cotrimoxazole compared with cotrimoxazole for preventing malaria in pregnant women

Mefloquine plus cotrimoxazole compared with cotrimoxazole for preventing malaria in pregnant women

Patient or population: HIV-infected pregnant women
Setting: Benin, Kenya, Mozambique, and Tanzania
Intervention: mefloquine plus cotrimoxazole
Comparison: cotrimoxazole

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments (compared with cotrimoxazole)
	Risk with cotrimoxazole	Risk with mefloquine plus cotrimoxazole				

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Clinical malaria episodes during pregnancy	-	-	IRR 0.76 (0.33 to 1.76)	- (1 RCT)	⊕⊕⊕⊕ HIGH	Mefloquine results in little or no difference in the incidence of clinical malaria episodes during pregnancy
Maternal peripheral parasitaemia at delivery (PCR)	66 per 1000	34 per 1000 (20 to 62)	RR 0.52 (0.30 to 0.93)	989 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a] Due to risk of bias	Mefloquine probably results in lower maternal peripheral parasitaemia at delivery
Placental malaria (PCR)	68 per 1000	19 per 1000 (10 to 39)	RR 0.28 (0.14 to 0.57)	977 (2 RCTs)	⊕⊕⊕⊕ MODERATE[a]	Mefloquine plus cotrimoxazole results in fewer women with placental malaria at delivery
Maternal anaemia at delivery	178 per 1000	168 per 1000 (130 to 214)	RR 0.94 (0.73 to 1.20)	1197 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a] Due to risk of bias	Mefloquine plus cotrimoxazole probably results in little or no difference in maternal anaemia cases at delivery
Low birth weight	118 per 1000	141 per 1000 (105 to 188)	RR 1.20 (0.89 to 1.60)	1220 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a] Due to risk of bias	Mefloquine plus cotrimoxazole probably results in little or no difference in the proportion of births that are low birth weight
Spontaneous abortions and stillbirths	50 per 1000	56 per 1000 (21 to 149)	RR 1.12 (0.42 to 2.98)	1347 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[a,b,c]	We do not know if mefloquine plus cotrimoxazole results in a difference in spontaneous abortions and stillbirths
AEs: vomiting	30 per 1000	239 per 1000 (144 to 396)	RR 7.95 (4.79 to 13.18)	1055 (1 RCT)[d]	⊕⊕⊕⊕ HIGH	Mefloquine plus cotrimoxazole results in an eight-fold increase in vomiting
AEs: dizziness	75 per 1000	296 per 1000 (214 to 411)	RR 3.94 (2.85 to 5.46)	1055 (1 RCT)[e]	⊕⊕⊕⊕ HIGH	Mefloquine plus cotrimoxazole results in a four-fold increase in dizziness

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; IRR: incidence rate ratio; RCT: randomized controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

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Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by 1 for risk of bias: one of the included trials is at serious risk of bias.

[b]Downgraded by 1 for inconsistency: trials showed substantial heterogeneity.

[c]Downgraded by 1 for imprecision: confidence intervals range from considerable benefit to considerable harm.

[d]A second RCT, Denoeud-Ndam 2014a BEN, reported 50 events in the mefloquine+cotrimoxazole group and 0 in the control group (cotrimoxazole), with RR 101 (95% CI 6.29 to 1621.68). This trial was open and participants knew to which group they were allocated. Meta-analysis causes a paradoxically very wide CI. Because of this distortion, we have used the results from Gonzalez 2014b KEN MOZ TAN in the grade table.

[e]A second RCT, Denoeud-Ndam 2014a BEN, reported 52 events in the mefloquine+cotrimoxazole group and 0 in the control group (cotrimoxazole), with RR 105 (95% CI 6.54 to 1685.03). This trial was open and participants knew to which group they were allocated. Meta-analysis causes a paradoxically very wide CI with the lower 95% CI. Because of this distortion, we have used the results from Gonzalez 2014b KEN MOZ TAN in this ‘Summary of findings' table.

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BACKGROUND

Description of the condition

Malaria is the most important parasitic disease worldwide and is endemic in parts of Africa, Asia, and South America. Pregnant women are at higher risk of malaria infection than non-pregnant women in the same age group, and are at higher risk of severe illness (Brabin 1983; Desai 2007). Malaria infection during pregnancy, particularly the first or second pregnancy, is also associated with adverse outcomes for both mother (severe anaemia) and infant (low birth weight, neonatal mortality; Ataíde 2014; Guyatt 2004; Menendez 2010; Radeva-Petrova 2014; Schwarz 2008; Steketee 2001). Symptoms most commonly reported by semi-immune pregnant women with clinical malaria include headache, arthromyalgias, and fever (Bardaji 2008). In areas of low transmission, pregnant women with malaria parasitaemia frequently present with symptoms and signs such as fever, malaise, headache, and vomiting. The infection may develop into severe complications such as cerebral malaria and pulmonary oedema if untreated, and may be a cause of maternal mortality (Bardaji 2008).

To reduce the burden and consequences of malaria in pregnancy, the World Health Organization (WHO) currently recommends that pregnant women who live in moderate to high malaria transmission areas in Africa sleep under an insecticide-treated net (ITN), as described in Gamble 2006, and receive intermittent preventive treatment (IPT) with sulfadoxine-pyrimethamine at each scheduled antenatal care visit (provided that doses are at least one month apart) (WHO 2013). IPT is a form of malaria chemoprevention that was tested and adopted as policy in response to both malaria parasites developing resistance to weekly prophylaxis with chloroquine and low compliance with the weekly regimen (WHO 2004). The long elimination half-life of sulfadoxine-pyrimethamine allows intermittent dosing while still providing prophylactic cover for the intervening weeks (White 2005). IPT is therefore defined as "administration of a curative treatment dose of an effective antimalarial drug at predefined intervals during pregnancy" regardless of the presence or absence of current infection (White 2005).

Sulfadoxine-pyrimethamine remains the drug used for IPT in pregnancy, even though resistance has spread in many parts of southern and eastern Africa (ter Kuile 2007; WHO 2012a), which is spurring researchers and policy makers to seek safe and effective alternatives to sulfadoxine-pyrimethamine (Desai 2018).

Description of the intervention

Mefloquine is a 4-methanolquinoline that is related to quinine. It was originally developed by the US military for preventing malaria in soldiers and has been widely used for preventing malaria in travellers (Schlagenhauf 2010). Like sulfadoxine-pyrimethamine, mefloquine has a long elimination half-life of two to four weeks; in travellers, weekly dosing consists of 250 mg (FDA 2004), and in pregnant women monthly dosing at treatment doses is feasible (Briand 2009).

Mefloquine was first investigated in the 1990s as prophylactic treatment for pregnant women. An observational study raised concerns that mefloquine may be associated with increased risk of stillbirth (Nosten 1999); however other trials did not confirm this finding (Pekyi 2016; Steketee 1996). A systematic review considered the safety of mefloquine in pregnancy and concluded that no evidence indicates that mefloquine use in pregnancy carries increased risk for the foetus (Gonzalez 2014). The drug is known to be associated with a range of mild dose-related transient side effects, such as vomiting, nausea, and dizziness (Bardaji 2012; Lee 2017; Sevene 2010; ter Kuile 1995). Researchers have described severe neuropsychiatric side effects that occur in about one in 10,000 travellers taking mefloquine as chemoprophylaxis (Phillips-Howard 1995; Steffen 1993). Studies conducted in Beninese pregnant women found that dizziness and vomiting are the most frequent adverse effects related to use of mefloquine as IPT in pregnancy (Briand 2009; Denoeud-Ndam 2012).

Data show resistance to mefloquine in multi-drug resistance areas of Thailand (Carrara 2009; Nosten 2000), but it remains rare in Africa (Aubouy 2007; MacArthur 2001; Oduola 1987).

How the intervention might work

Malaria chemoprevention is thought to work through clearance or suppression of asymptomatic malaria infection in the peripheral blood of the mother and the placenta (White 2005). This reduction in malaria parasitaemia may, however, be insufficient to justify recommendations for widespread prophylactic prescriptions that do not provide subsequent benefit for clinically important outcomes for mother and baby. These outcomes may include a reduction in episodes of maternal malaria, reduced risk of anaemia, and improved birth weight, as well as more substantive outcomes such as a reduction in severe maternal illness or lower rates of spontaneous pregnancy loss and maternal, neonatal, and infant mortality (see Figure 1).

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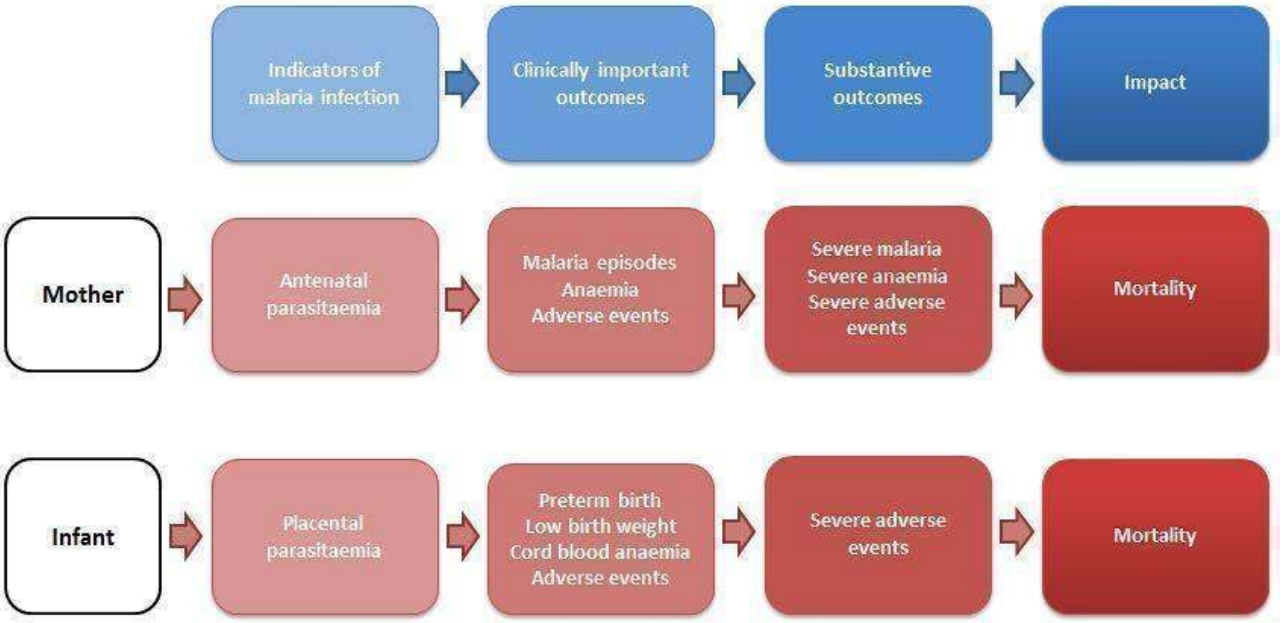
Figure 1. Indicators and impact of malaria infection in mothers and infants.



Effects of malaria chemoprevention may depend on the local malaria epidemiology and thus the level of acquired immunity against malaria in pregnant women. In stable transmission areas, women of reproductive age may be partially immune to malaria, presenting parasitaemia without clinical disease; however, asymptomatic infections may have detrimental effects, such as anaemia and low birth weight. In contrast, in unstable malaria transmission areas, naturally acquired malaria immunity is usually low among adults and malaria infection may be associated with clinical episodes and severe illness.

Primigravidae women are at higher risk of adverse effects of malaria infection than multigravidae women. This is thought to result from women developing antibodies specific to placental-type parasites when exposed to *Plasmodium falciparum* during their first pregnancy. These antibodies are then present in subsequent pregnancies (Ataíde 2014). This is seen in multigravidae women as a more specific and efficient immune response and clearing the infection at an earlier stage than in primigravidae women (Walker 2013).

Another potential effect modifier of the susceptibility to malaria infection is HIV status (Menéndez 2011). In many malaria-endemic areas, data show that the prevalence of HIV infection, which has been observed to increase the risk of malaria infection, is high among pregnant women (Gonzalez 2012; van Eijk 2003). Compared with HIV-uninfected women, HIV-infected women are more likely to carry malaria parasites in their blood, to have higher parasite densities, and to develop placental parasitaemia, anaemia, and malaria symptoms (Ayisi 2003; van Eijk 2002; van Eijk 2003). This increased risk of malaria is the same in multigravidae (women in their third pregnancy or higher) and in women in their first or second pregnancy (ter Kuile 2004; van Eijk 2003). Placental malaria infection may also increase the risk of perinatal mother-to-child transmission of HIV (Ayisi 2003).

Use of ITNs during pregnancy has been shown to have a beneficial impact on pregnancy outcomes (reduced prevalence of low birth weight, miscarriage, and placental parasitaemia) in malaria-endemic Africa (Gamble 2007), and this approach could modify the effect of IPT (Menéndez 2008).

Why it is important to do this review

The WHO recommends IPT with sulfadoxine-pyrimethamine for all pregnant women who live in moderate to high malaria transmission areas in Africa (WHO 2004; WHO 2013). However, studies have shown that resistance to sulfadoxine-pyrimethamine in some regions of Eastern Africa has been increasing steadily during the past two decades (Iriemenam 2012; Mockenhaupt 2008). Thus, there is an urgent need for more effective antimalarials to prevent malaria during pregnancy.

This review aims to evaluate the efficacy and safety of mefloquine for preventing malaria in pregnant women. These findings could serve as the basis for future guidelines on preventive agents for malaria in pregnant women.

OBJECTIVES

To assess the effects of mefloquine for preventing malaria in pregnant women - specifically, to evaluate:

- the efficacy, safety, and tolerability of mefloquine for preventing malaria in pregnant women; and
- the impact of HIV status, gravidity, and use of insect-treated nets (ITNs) on the effects of mefloquine.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs.

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Types of participants

Pregnant women of any gravidity regardless of HIV status, living in malaria-endemic areas (CDC 2017).

Types of interventions

Interventions

Mefloquine given to pregnant women as intermittent preventive treatment or as chemoprophylaxis.

Controls

Placebo, no intervention, or an alternative drug regimen.

Types of outcome measures

Maternal

- Maternal peripheral parasitaemia during pregnancy
- Maternal peripheral parasitaemia at delivery
- Placental malaria[1]
- Mean haemoglobin and maternal anaemia (moderate and severe) at delivery
- Clinical malaria episodes during pregnancy

Foetal/infant

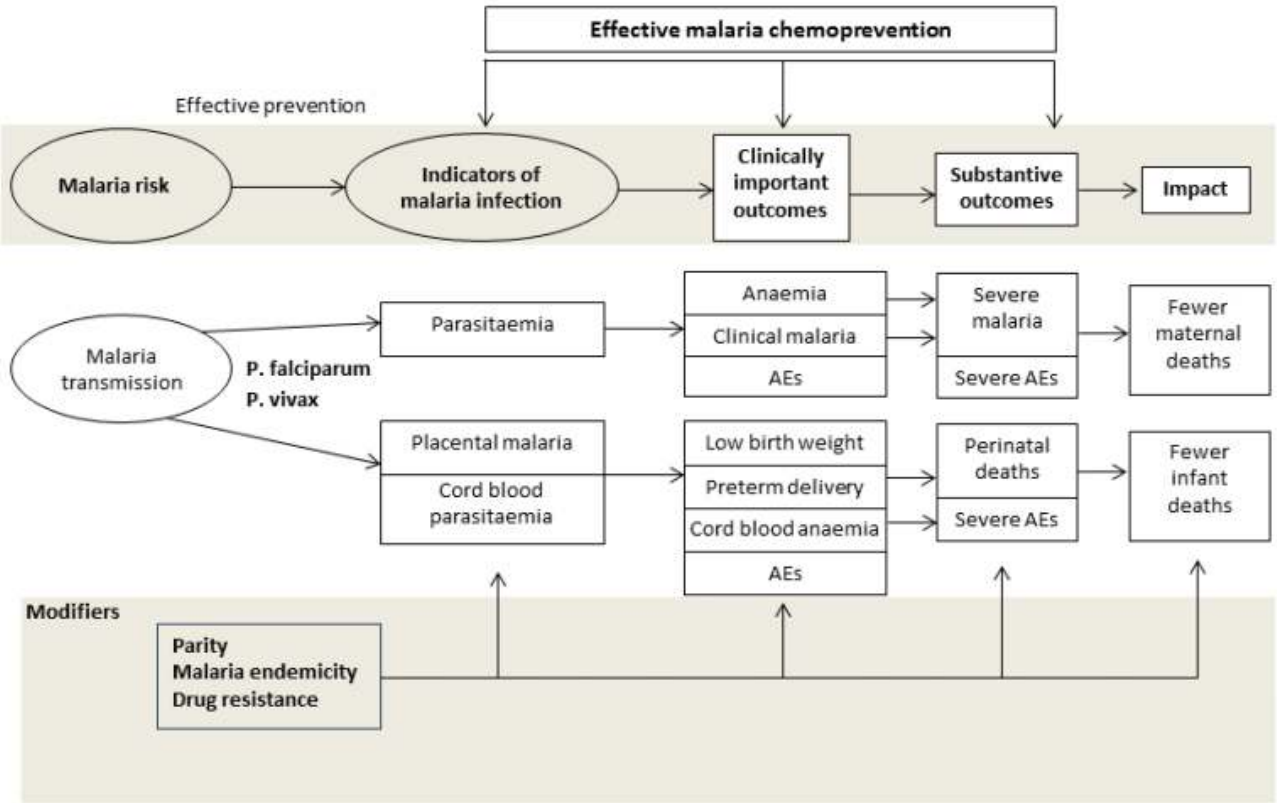
- Cord blood parasitaemia
- Cord blood haemoglobin and anaemia (as defined in the original studies)
- Mean birth weight
- Low birth weight prevalence (< 2500 g)
- Prematurity prevalence (< 37 weeks of gestation)
- Morbidity in first year of life

Adverse events

- Serious adverse events (SAEs)[2]
  - Illnesses that were life threatening or required hospitalization during pregnancy (SAEs in pregnancy)
  - Adverse pregnancy outcomes: spontaneous abortion, stillbirth, congenital malformation
  - Maternal mortality
  - Perinatal, neonatal, infant mortality
  - Mother-to-child transmission of HIV frequency (at six weeks of age)
- Non-serious adverse events
  - Frequency and severity of reported all-cause and drug-related adverse events

[1]Placental malaria diagnosed by histology, microscopy, or any method used in the included study. Figure 2 shows the relations between different outcomes.

Figure 2. Conceptual framework of malaria chemoprevention. Reproduced under the terms of a Creative Commons Licence from Radeva-Petrova 2014.



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[2]Review authors acknowledge the limitation of analyzing rare serious adverse events because randomized controlled trials usually are not powered enough to detect them.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We searched the following databases using the search terms and strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register (up to 31 January 2018); the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (January 2018); MEDLINE (PubMed; from 1966 to 31 January 2018); Embase (OVID; 1974 to 31 January 2018); and Latin American Caribbean Health Sciences Literature (LILACS) (BIREME; 1982 to 31 January 2018). We also searched the Malaria in Pregnancy (MiP) Library (www.mip-consortium.org/resources/index.htm), the WHO International Clinical Trial Registry Platform (ICTRP; www.who.int/ictrp/search/en), ClinicalTrials.gov, and the International Standard Randomized Controlled Trial Number (ISRCTN) registry (www.isrctn.com/), using 'mefloquine', 'malaria', and 'pregnan*' as search terms.

Searching other resources

We contacted researchers working in the field to ask for unpublished data, confidential reports, and raw data from published trials. We also checked the citations of all trials identified by the methods described.

Data collection and analysis

Selection of studies

Two review authors independently screened all trials identified by the search strategy by title or abstract, or both (Appendix 1). We coded studies as 'retrieve' or 'do not retrieve'. We retrieved the full-text copies of trials deemed potentially relevant. Two review authors then independently assessed study eligibility using a form based on the review inclusion criteria. We resolved disagreements through discussion or by consultation with a third review author. Any review author who participated in trials that potentially met the review inclusion criteria did not participate in the procedure to select studies for inclusion. We listed all studies excluded after full-text assessment and reasons for their exclusion in a 'Characteristics of excluded studies' table. We illustrated the study selection process in a PRISMA diagram.

Data extraction and management

Three review authors (RG, CPD, and MP) used a data extraction form to independently extract data on trial characteristics, including trial site, year, local malaria transmission estimates, antimalarial resistance pattern of mefloquine and the comparator drug (when possible), trial methods, participants, interventions, doses, and outcomes.

We extracted the number of participants randomized and the number of participants analyzed in experimental and control groups for each outcome. For dichotomous outcomes, we extracted the number of participants experiencing the event and the number assessed in each treatment group. For continuous outcomes, we extracted the arithmetic means, standard deviations for each treatment group (when provided), and the number of participants assessed in each group. We also extracted medians and ranges when provided. For outcomes reported as incidences, we extracted the number of participants experiencing the event (cases) and the person-years at risk.

Any review author who participated in any of the trials included in the review did not participate in data extraction nor 'Risk of bias' assessment of their own articles.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each included trial using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). This approach assesses the risk of bias across seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other potential sources of bias (Higgins 2011). For each domain, we assigned a judgment of low, high, or unclear risk of bias. We judged the risk of bias for blinding on the presence of blinding and whether lack of blinding could potentially influence the results.

Measures of treatment effect

We presented dichotomous outcomes using risk ratios (RRs), count outcomes as incidence rate ratios (IRRs), and continuous outcomes as mean differences (MDs). We presented all measures of effect with 95% confidence intervals (CIs).

Unit of analysis issues

When conducting a meta-analysis, we ensured that participants and cases in the placebo group were not counted more than once.

Dealing with missing data

We aimed to conduct the analysis according to the intention-to-treat principle. However, when there was loss to follow-up, we used a complete-case analysis such that participants for whom no outcome was reported were excluded from the analysis. This analysis assumes that participants for whom an outcome is available are representative of the original randomized patients. We aimed to conduct a sensitivity analysis to evaluate the robustness of this method, but this was not possible, as described below. If data from trial reports were insufficient, unclear, or missing, we contacted the study authors for additional information.

Assessment of heterogeneity

We calculated the I^2 statistic using values of 30% to 59%, 60% to 89%, and 90% to 100% to denote moderate, substantial, and considerable levels of heterogeneity, respectively.

Assessment of reporting biases

We aimed to assess the risk of publication bias by constructing funnel plots and looking for asymmetry, but the small number of trials included in each comparison of the meta-analysis made this assessment impossible.

Data synthesis

We performed data analysis using Review Manager 5 (RevMan 5) (RevMan 2014). We intended to perform subgroup analysis by gravidity and HIV status when possible. HIV status subgroup

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analysis was not possible in any case owing to different study designs for different HIV status populations. In the absence of heterogeneity, we used a fixed-effect model for the meta-analysis; when we detected moderate or considerable heterogeneity, we used a random-effects model. Additionally, we assessed the certainty of evidence using the GRADE approach (GRADEpro GDT 2015) for the following main outcomes of analysis: maternal peripheral parasitaemia at delivery, clinical malaria episodes during pregnancy, placental malaria, maternal anaemia at delivery, low birth weight, spontaneous abortion and stillbirth, dizziness, and vomiting.

Subgroup analysis and investigation of heterogeneity

We aimed to investigate heterogeneity by conducting prespecified subgroup analysis to evaluate the contributions of differences in trial characteristics such as risk of bias, geographical region, malaria transmission pattern, antimalarial resistance, drug regimen, use of ITNs, gravidity (primigravidae versus multigravidae), HIV status (uninfected, infected, unknown), and trial methods. Only the gravidity subgroup analysis was possible for one outcome of the main comparison. The other subgroup analyses were not possible because of the small number of trials included in each comparison.

Sensitivity analysis

We planned to conduct a sensitivity analysis to restore the integrity of the randomization process and to test the robustness of our results; however, the small number of trials included in each comparison – two at most – made this impossible. Additionally, missing outcome data were balanced in numbers across intervention groups, and reasons for missing data were similar across groups.

RESULTS

Description of studies

Results of the search

The literature search, conducted up to 31 January 2018, identified 254 references, of which two were duplicate trial reports. Of the 252 remaining articles, we excluded 231 articles and one ongoing trial after title/abstract screening. We assessed 20 full-text articles for eligibility, of which we excluded 14 articles. Six trials (in six publications) met the inclusion criteria of the review (Figure 3).

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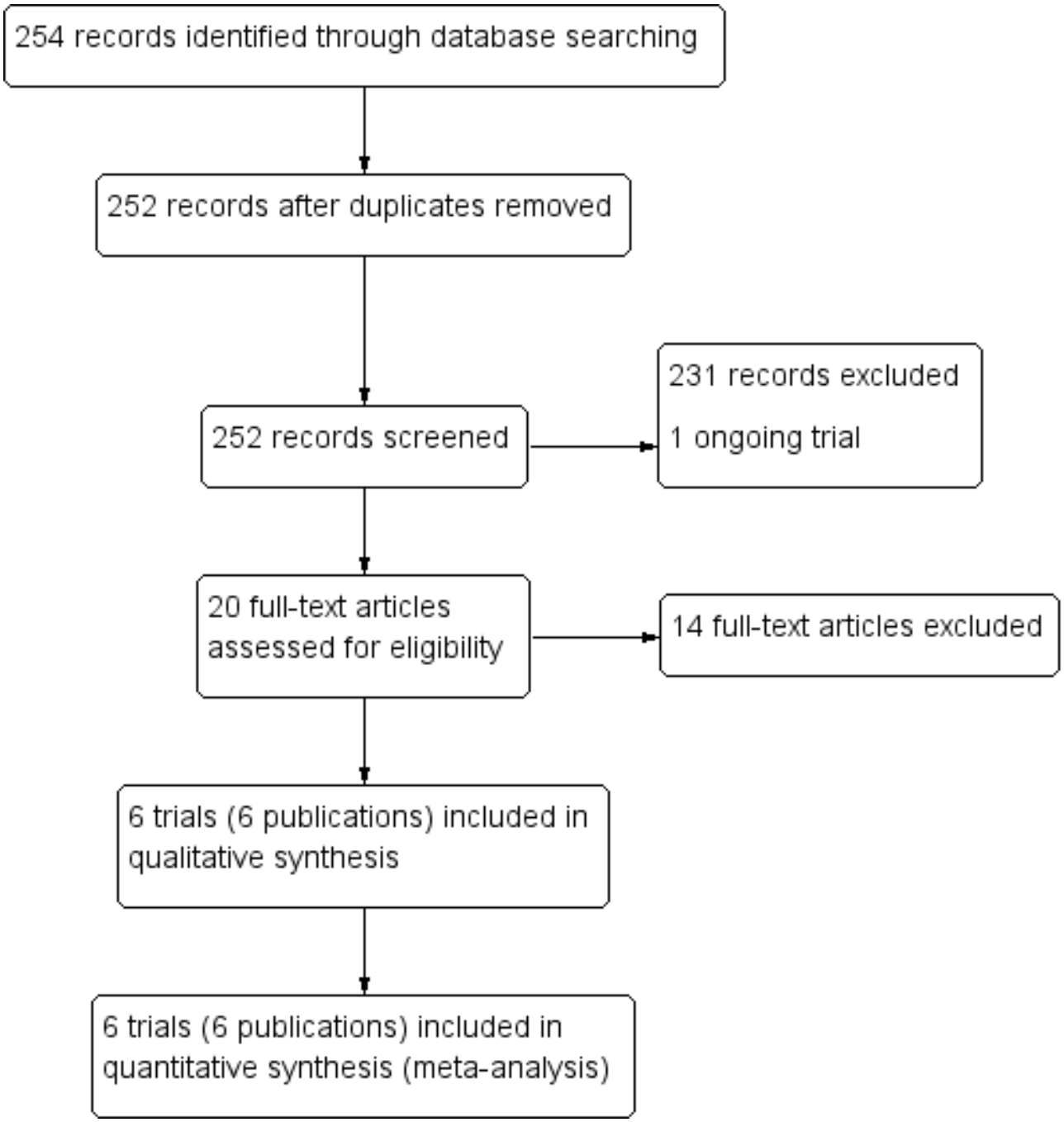
Figure 3. Study flow diagram.



Included studies

Six chemoprevention trials that included 8192 pregnant women met our inclusion criteria (see the Characteristics of included studies section). These trials were conducted between 1987 and 2013 in Thailand (one trial), Benin (three trials), Gabon (one trial), Kenya (one trial), Mozambique (two trials), and Tanzania (two trials).

The included trials recruited women of all gravidities of all ages (four trials) or over 18 years of age (two trials). Gestational age at recruitment was greater than 20 weeks (one trial), between 16 and 28 weeks (three trials), or ≤ 28 weeks (two trials).

Two trials evaluated mefloquine against sulfadoxine-pyrimethamine as IPTp in HIV-uninfected pregnant women. Three trials evaluated mefloquine IPTp alone (or in combination with daily cotrimoxazole) against cotrimoxazole in HIV-infected pregnant women. Finally, one trial in Thailand compared weekly mefloquine prophylaxis against placebo in women of unknown HIV status. All included trials reported that drug administration was supervised.

All included trials recruited women in all gravidity groups; five reported aggregate results and one disaggregated by gravidity for the primary outcome. In five trials, all women in both intervention

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and control groups received a long-lasting ITN at recruitment and iron, and investigators routinely administered folic acid.

Excluded studies

We excluded one trial for the reasons given in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

See Figure 4 and Figure 5 for a summary of the 'Risk of bias' assessments. We have presented further details in the 'Characteristics of included studies' table.

Figure 4. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

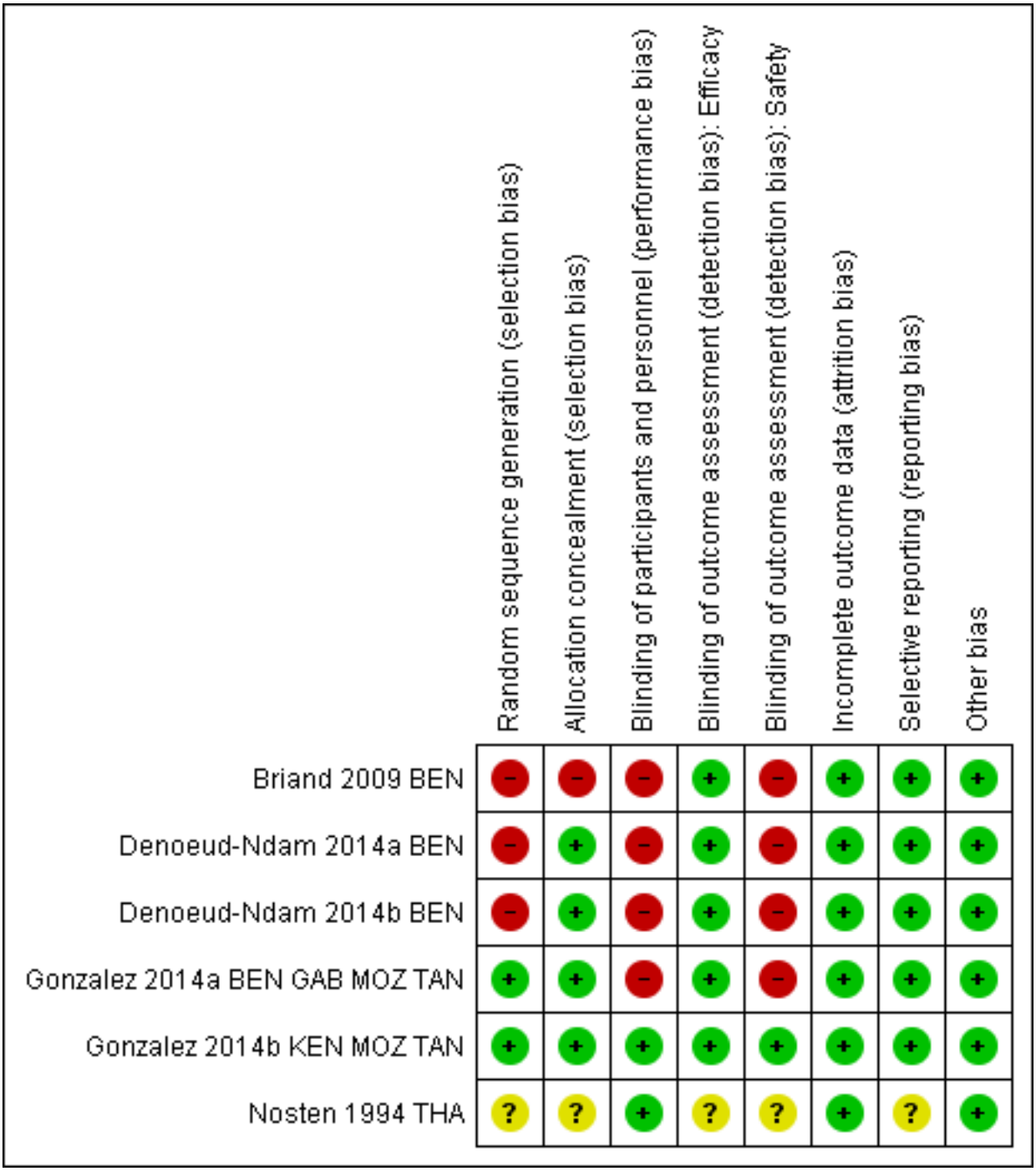

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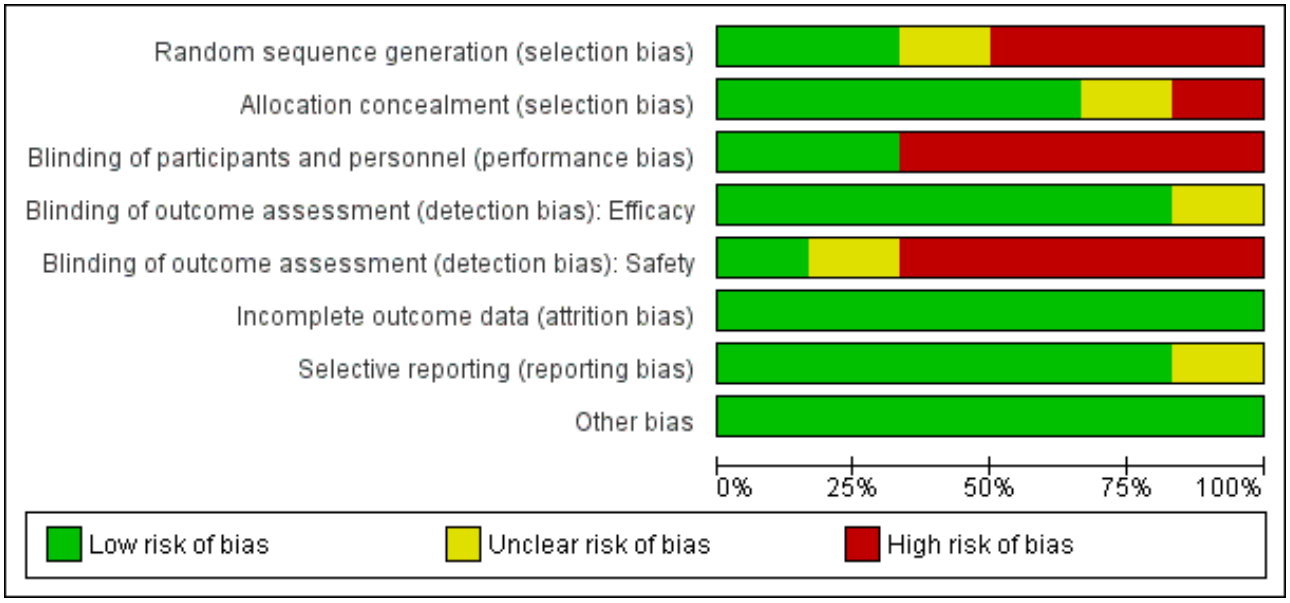
Figure 5. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation (selection bias)

Two trials adequately described methods of sequence generation (Gonzalez 2014a BEN GAB MOZ TAN; Gonzalez 2014b KEN MOZ TAN), three described a non-random component in the sequence generation process (Briand 2009 BEN; Denoeud-Ndam 2014a BEN; Denoeud-Ndam 2014b BEN), and in the remaining trial, the risk was unclear (Nosten 1994 THA).

Allocation concealment (selection bias)

Four trials described adequate methods of allocation concealment (Denoeud-Ndam 2014a BEN; Denoeud-Ndam 2014b BEN; Gonzalez 2014a BEN GAB MOZ TAN; Gonzalez 2014b KEN MOZ TAN), one trial reported no concealment of allocation (Briand 2009 BEN), and in the remaining trial, the risk was unclear (Nosten 1994 THA).

Blinding

Blinding of participants and personnel (performance bias)

Four trials were open (Briand 2009 BEN; Denoeud-Ndam 2014a BEN; Denoeud-Ndam 2014b BEN; Gonzalez 2014a BEN GAB MOZ TAN), and we assessed these as having high risk of performance risk. Two trials were double-blind and placebo-controlled (Gonzalez 2014b KEN MOZ TAN; Nosten 1994 THA), and we assessed these as having low risk of performance bias.

Blinding of efficacy outcome assessment (detection bias)

For five trials, we judged the efficacy outcome as not influenced by blinding or lack of blinding. In the remaining trial, the risk of detection bias for efficacy outcomes was unclear (Nosten 1994 THA).

Blinding of safety outcome assessment (detection bias)

For the four open trials, we judged the risk of detection bias as high for assessment of safety outcomes (Briand 2009 BEN; Denoeud-Ndam 2014a BEN; Denoeud-Ndam 2014b BEN; Gonzalez 2014a BEN GAB MOZ TAN). In one trial, the risk of detection bias was unclear (Nosten 1994 THA). For the remaining trial, which was double-blinded, we judged the risk of detection bias as low (Gonzalez 2014b KEN MOZ TAN).

Incomplete outcome data

In all included trials, missing outcome data were balanced in numbers across groups, and we judged the risk of attrition bias to be low.

Selective reporting

We considered the risk of reporting bias as low in five trials and unclear in one (Nosten 1994 THA).

Other potential sources of bias

All included trials appeared to be free of other sources of bias, and we judged this risk as low.

Effects of interventions

See: **Summary of findings for the main comparison** Mefloquine compared with sulfadoxine-pyrimethamine for preventing malaria in pregnant women; **Summary of findings 2** Mefloquine plus cotrimoxazole compared with cotrimoxazole for preventing malaria in pregnant women

Comparison 1: Mefloquine versus sulfadoxine-pyrimethamine (HIV-uninfected pregnant women)

See Summary of findings for the main comparison.

Maternal outcomes

We included in this comparison two trials that evaluated two doses of IPTp (Briand 2009 BEN; Gonzalez 2014a BEN GAB MOZ TAN). Data show a decrease in the number of clinical malaria episodes during pregnancy among mefloquine recipients, but this does not

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clearly constitute an effect of mefloquine because the 95% CIs do not exclude the possibility of no different effects (IRR 0.83, 95% CI 0.65 to 1.05; 2 studies; high-certainty evidence; Analysis 1.1). Overall, IPTp-mefloquine was associated with a 35% reduction in the risk of maternal peripheral parasitaemia at delivery (RR 0.65, 95% CI 0.48 to 0.86; 5455 participants, 2 studies; I^2 statistic = 16%; high-certainty evidence; Analysis 1.2), but the absolute difference between treatments was small. We found no significant evidence of an effect of mefloquine or sulfadoxine-pyrimethamine on placental malaria infections (RR 1.04, 95% CI 0.58 to 1.86; 4668 participants, 2 studies; I^2 statistic = 63%; low-certainty evidence; Analysis 1.3). The mefloquine group showed a slight increase in the mean haemoglobin level at delivery (MD 0.10, 95% CI 0.01 to 0.19; 5588 participants, 2 studies; I^2 statistic = 0%; Analysis 1.4) and a decrease in maternal anaemia cases at delivery (RR 0.84, 95% CI 0.76 to 0.94; 5469 participants, 2 studies; I^2 statistic = 0%; moderate-certainty evidence; Analysis 1.5), but the data show no significant differences in severe maternal anaemia at delivery between groups (RR 0.93, 95% CI 0.58 to 1.48; 5469 participants, 2 studies; I^2 statistic = 41%; Analysis 1.6). The original definitions of maternal moderate anaemia and severe maternal anaemia were different in the two trials included in the analysis (Gonzalez 2014a BEN GAB MOZ TAN defined anaemia as haemoglobin < 11 g/dL and severe anaemia as haemoglobin < 7 g/dL), but we homogenized data for the analysis as < 9.5 g/dL and < 8 g/dL (as defined in Briand 2009 BEN), respectively.

Foetal/infant outcomes

No effect was evident for the outcomes of cord blood parasitaemia (RR 0.44, 95% CI 0.13 to 1.46; 5309 participants, 2 studies; I^2 statistic = 33%; Analysis 1.7) and cord blood anaemia (RR 1.04, 95% CI 0.87 to 1.23; 4006 participants, 1 study; Analysis 1.8).

Regarding newborn outcomes, mean birth weight did not show significant differences between groups (MD 2.52, 95% CI -25.66 to 30.69; 5241 participants, 2 studies; I^2 statistic = 0%; Analysis 1.9). Low birth weight (RR 0.95, 95% CI 0.78 to 1.17; 5641 participants, 2 studies; I^2 statistic = 33%; high-certainty evidence; Analysis 1.10) and prematurity prevalence (RR 1.03, 95% CI 0.76 to 1.40; 4640 participants, 2 studies; I^2 statistic = 0%; Analysis 1.12) also showed no differences between groups. Subgroup analysis of low birth weight by gravidity yielded results that did not vary (primigravidae: RR 1.02, 95% CI 0.80 to 1.30; 1576 participants, 2 studies; I^2 statistic = 3%; Analysis 1.11; multigravidae: RR 0.94, 95% CI 0.78 to 1.14; 4065 participants, 2 studies; I^2 statistic = 0%; Analysis 1.11).

Only one trial reported data on infant morbidity, and results followed the same trend; the IRR was near 1, and the CIs did not discard the possibility of no difference between mefloquine and sulfadoxine-pyrimethamine. Chosen proxies for infant morbidity were malaria in the first year of life (IRR 0.97, 95% CI 0.82 to 1.15; 1 study; Analysis 1.13) and hospital admissions in the first year of life (IRR 0.93, 95% CI 0.75 to 1.17; 1 study; Analysis 1.14).

Safety outcomes

No difference was evident between mefloquine and sulfadoxine-pyrimethamine in overall serious adverse events reporting (RR 0.98, 95% CI 0.81 to 1.20; 4674 participants, 1 study; Analysis 1.15). Definitions of stillbirth and abortion were different for the two trials included in this comparison; therefore we aggregated both outcomes into a single outcome (RR 1.20, 95% CI 0.91 to 1.58; 6219 participants, 2 studies; I^2 statistic = 0%; moderate-certainty evidence; Analysis 1.16). Congenital malformation cases were also similar in both intervention groups (RR 1.10, 95% CI 0.51 to 2.37; 5931 participants, 2 studies; I^2 statistic = 33%; Analysis 1.17).

Regarding maternal mortality, one of the trials reported maternal deaths only in the mefloquine group, and the other trial showed a similar proportion of maternal deaths in both IPTp groups; the CI of the meta-analysis was wide, and heterogeneity was moderate (RR 2.41, 95% CI 0.27 to 21.23; 6219 participants, 2 studies; I^2 statistic = 54%; Analysis 1.18). Only one of the trials reported neonatal and infant mortality (Gonzalez 2014a BEN GAB MOZ TAN), but we obtained neonatal mortality rates for the other trial by contacting the study authors (Briand 2009 BEN). Neither of the two outcomes showed a significant effect of mefloquine or sulfadoxine-pyrimethamine (neonatal deaths: RR 0.98, 95% CI 0.67 to 1.43; 6134 participants, 2 studies; I^2 statistic = 0%; Analysis 1.19; incidence of infant deaths: IRR 1.00, 95% CI 0.66 to 1.52; 1 study; Analysis 1.20).

Overall, IPTp-mefloquine increased the risk of adverse events; results of individual trials and of meta-analyses were significant for vomiting (RR 4.76, 95% CI 4.13 to 5.49; 6272 participants, 2 studies; I^2 statistic = 0%; high-certainty evidence; Analysis 1.21), fatigue/weakness (RR 4.62, 95% CI 1.80 to 11.85; 6272 participants, 2 studies; I^2 statistic = 91%; high-certainty evidence; Analysis 1.22), and dizziness (RR 4.21, 95% CI 3.36 to 5.27; 6272 participants, 2 studies; I^2 statistic = 66%; moderate-certainty evidence; Analysis 1.23), with the exception of headache (RR 0.70, 95% CI 0.25 to 1.94; 6272 participants, 2 studies; I^2 statistic = 85%; Analysis 1.24).

Comparison 2: Mefloquine plus cotrimoxazole versus cotrimoxazole (HIV-infected pregnant women)

See Summary of findings 2.

Maternal outcomes

This comparison included two trials evaluating three IPTp doses of mefloquine (Denoeud-Ndam 2014a BEN; Gonzalez 2014b KEN MOZ TAN). Only one of the trials reported clinical malaria episodes during pregnancy, noting no significant differences in malaria episodes between groups (IRR 0.76, 95% CI 0.33 to 1.76; 1 study; high-certainty evidence; Analysis 2.1). IPTp-mefloquine plus cotrimoxazole prophylaxis was associated with a 48% reduction in the risk of maternal peripheral parasitaemia at delivery measured by polymerase chain reaction (PCR) (RR 0.52, 95% CI 0.30 to 0.93; 989 participants, 2 studies; I^2 statistic = 0%; moderate-certainty evidence; Analysis 2.2), a 49% reduction in the risk of placental malaria measured by blood smear (RR 0.51, 95% CI 0.29 to 0.89; 1144 participants, 2 studies; I^2 statistic = 0%; Analysis 2.3), and a 72% reduction in the risk of placental malaria measured by PCR (RR 0.28, 95% CI 0.14 to 0.57; 977 participants, 2 studies; I^2 statistic = 0%; moderate-certainty evidence; Analysis 2.4). The other maternal-related outcomes at delivery included in this comparison did not show evidence that they were effects of mefloquine owing to the wideness of the CIs (mean haemoglobin: MD 0.07, 95% CI -0.32 to 0.46; 1167 participants, 2 studies; I^2 statistic = 62%; Analysis 2.5; maternal anaemia: RR 0.94, 95% CI 0.73 to 1.20; 1197 participants, 2 studies; I^2 statistic = 12%; moderate-certainty evidence; Analysis 2.6; severe maternal anaemia: RR 0.93, 95% CI 0.41 to 2.08; 1167 participants, 2 studies; I^2 statistic = 0%; Analysis 2.7). The original definitions of maternal anaemia were different

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in the two trials included in the analysis (Gonzalez 2014b KEN MOZ TAN defined anaemia as haemoglobin < 11 g/dL), but we homogenized definitions for the analysis as < 9.5 g/dL (as defined in Denoeud-Ndam 2014a BEN). The two trials defined severe maternal anaemia as haemoglobin < 7 g/dL.

Foetal/infant outcomes

Meta-analyses of foetal and neonatal outcomes were underpowered to detect significant effects of mefloquine on cord blood parasitaemia (RR 0.33, 95% CI 0.03 to 3.13; 1166 participants, 2 studies; I^2 statistic = 0%; Analysis 2.8), mean birth weight (MD -25.75, 95% CI -86.99 to 35.49; 1220 participants, 2 studies; I^2 statistic = 0%; Analysis 2.9), low birth weight rates (RR 1.20, 95% CI 0.89 to 1.60; 1220 participants, 2 studies; I^2 statistic = 0%; moderate-certainty evidence; Analysis 2.10), and prematurity rates (RR 1.07, 95% CI 0.58 to 1.72; 824 participants, 2 studies; I^2 statistic = 32%; Analysis 2.11). These CIs did not exclude the possibility of no different effects between groups.

Safety outcomes

Overall, serious adverse events during pregnancy were significantly less frequent in the group of IPTp-mefloquine plus cotrimoxazole prophylaxis than in the cotrimoxazole alone group (RR 0.69, 95% CI 0.50 to 0.95; 1347 participants, 2 studies; I^2 statistic = 0%; Analysis 2.12). However, analysis of individual adverse events did not show differences between groups, for example, spontaneous abortions and stillbirths (RR 1.12, 95% CI 0.42 to 2.98; 1347 participants, 2 studies; I^2 statistic = 69%; very low-certainty evidence; Analysis 2.13) and congenital malformations (RR 0.61, 95% CI 0.22 to 1.67; 1312 participants, 2 studies; I^2 statistic = 0%; Analysis 2.14). Definitions of spontaneous abortion and stillbirth were different in the two included trials (that is, difference in the gestational age cutoff for classifying miscarriage or stillbirth); therefore, we combined both indicators and analyzed them as one. Only one trial included information on maternal deaths (Gonzalez 2014b KEN MOZ TAN), and we obtained this information by contacting the authors in the other trial (Denoeud-Ndam 2014a BEN). Analyses of maternal deaths revealed no significant differences between groups (RR 0.51, 95% CI 0.13 to 2.01; 1347 participants, 2 studies; I^2 statistic = 0%; Analysis 2.15). Also, we found that neonatal mortality rates were not significantly different among groups, as revealed by the CI (RR 1.32, 95% CI 0.65 to 2.69; 1239 participants, 2 studies; I^2 statistic = 0%; Analysis 2.16). It is important to note that mefloquine plus cotrimoxazole recipients were at 1.92 times greater risk of mother-to-child transmission of HIV than the group that took only cotrimoxazole (RR 1.92, 95% CI 1.13 to 3.25; 1019 participants, 2 studies; I^2 statistic = 0%; Analysis 2.17).

Vomiting, fatigue/weakness, and dizziness displayed substantial and considerable levels of heterogeneity in the meta-analysis. Individual trials showed significant increases in three drug-related adverse events in the groups given IPTp-mefloquine plus cotrimoxazole prophylaxis, but random-effects analyses show a significant effect of IPTp-mefloquine only in the case of vomiting (RR 20.88, 95% CI 1.40 to 311.66; 1347 participants, 2 studies; I^2 statistic = 74%; Analysis 2.18), while fatigue (RR 2.95, 95% CI 0.26 to 32.93; 1347 participants, 2 studies; I^2 statistic = 91%; Analysis 2.19) and dizziness (RR 16.34, 95% CI 0.39 to 684.99; 1347 participants, 2 studies; I^2 statistic = 86%; Analysis 2.20) show no significant evidence. In the three cases, CIs are considerably wide. Headache cases were not significantly different across groups (RR 0.76, 95% CI 0.28 to 2.10; 1347 participants, 2 studies; I^2 statistic = 30%; Analysis 2.21).

Comparison 3: Mefloquine versus cotrimoxazole (HIV-infected pregnant women)

Maternal outcomes

Only one trial conducted in Benin provided data on this comparison of three IPTp-mefloquine doses versus cotrimoxazole prophylaxis (Denoeud-Ndam 2014b BEN). The few observations reported in the trial made the analyses, in general, underpowered to detect differences between groups. Efficacy outcomes directly related to malaria yielded RR indicating beneficial effects of IPTp-mefloquine in reducing infection, but CIs did not exclude the possibility of no difference between groups (maternal peripheral parasitaemia during pregnancy measured by PCR: RR 0.21, 95% CI 0.03 to 1.72; 98 participants, 1 study; Analysis 3.1; placental malaria measured by PCR: RR 0.73, 95% CI 0.13 to 4.15; 94 participants, 1 study; Analysis 3.2; placental malaria measured by blood smear: RR 0.35, 95% CI 0.01 to 8.30; 108 participants, 1 study; Analysis 3.3). Data show no differences across groups for mean haemoglobin (MD -0.10, 95% CI -0.67 to 0.47; 100 participants, 1 study; Analysis 3.4) or maternal anaemia at delivery (RR 0.90, 95% CI 0.26 to 3.16; 100 participants, 1 study; Analysis 3.5).

Foetal/infant outcomes

All newborn outcomes included in the trial displayed wide CIs, providing no evidence of differences between groups (mean birth weight: MD -102.00, 95% CI -255.52 to 51.52; 120 participants, 1 study; Analysis 3.6; low birth weight rate: RR 1.52, 95% CI 0.56 to 4.13; 120 participants, 1 study; Analysis 3.7; prematurity rate: RR 1.08, 95% CI 0.33 to 3.56; 125 participants, 1 study; Analysis 3.8).

Safety outcomes

Serious adverse events reported in the trial were balanced across groups and were infrequent. The CIs reveal the possibility of no different effects between interventions in overall serious adverse events (RR 1.06, 95% CI 0.28 to 4.07; 140 participants, 1 study; Analysis 3.9), stillbirths (RR 4.30, 95% CI 0.49 to 37.49; 139 participants, 1 study; Analysis 3.10), spontaneous abortions (RR 1.07, 95% CI 0.07 to 16.84; 139 participants, 1 study; Analysis 3.11), and congenital malformations (RR 1.07, 95% CI 0.16 to 7.41; 139 participants, 1 study; Analysis 3.12). No maternal deaths occurred during the trial (139 participants, 1 study; Analysis 3.13), and only one neonate in each intervention group died (RR 1.05, 95% CI 0.07 to 16.39; 129 participants, 1 study; Analysis 3.14). The trial did not record infant mortality and regarded infant deaths after seven days of birth until six weeks of age as a proxy; small numbers of observations and infant deaths made demonstration of differences between groups impossible (RR 2.10, 95% CI 0.19 to 22.54; 129 participants, 1 study; Analysis 3.15).

Drug-related adverse events were significantly more frequent in the mefloquine group. Despite wide CIs, results show an effect of mefloquine in increasing the frequency of vomiting (RR 13.43, 95% CI 3.31 to 54.54; 139 participants, 1 study; Analysis 3.16), fatigue/weakness (RR 6.99, 95% CI 1.64 to 29.81; 139 participants, 1 study; Analysis 3.17), and dizziness (RR 52.60, 95% CI 3.26 to 848.24; 139 participants, 1 study; Analysis 3.18). Data show no differences

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between groups in drug-related headache (RR 0.21, 95% CI 0.01 to 4.39; 139 participants, 1 study; Analysis 3.19).

Comparison 4: Mefloquine versus placebo (pregnant women of unknown HIV status)

Maternal and foetal/infant outcomes

Only one trial provided data on this comparison, which comprised two phases of mefloquine prophylaxis with different doses of the drug (Nosten 1994 THA); the results belong to the pooled samples of both trial phases. This trial did not report clinical malaria episodes during pregnancy, maternal anaemia at delivery, cord blood parasitaemia and anaemia, serious adverse events, neonatal mortality, and adverse events, or data reporting was incomplete.

The only observed significant effect that could be attributed to mefloquine was the decrease in maternal peripheral parasitaemia at delivery (RR 0.13, 95% CI 0.05 to 0.33; 339 participants, 1 study; Analysis 4.1). The other efficacy outcomes evaluated in this trial - both maternal and newborn-related outcomes - showed wide CIs and did not demonstrate different effects between placebo and mefloquine prophylaxis (placental malaria: RR 0.14, 95% CI 0.01 to 2.68; 220 participants, 1 study; Analysis 4.2; mean birth weight: MD -80.00, 95% CI -184.65 to 24.65; 290 participants, 1 study; Analysis 4.3; low birth weight: RR 1.39, 95% CI 0.78 to 2.48; 290 participants, 1 study; Analysis 4.4; prematurity: RR 0.48, 95% CI 0.15 to 1.53; 199 participants, 1 study; Analysis 4.5).

Safety outcomes

This trial reported only serious adverse events, and adverse events data were not complete in the published article. Stillbirths were more prevalent in the group given mefloquine prophylaxis, but the small number of observed events made the analysis unpowered to detect differences between groups (RR 2.63, 95% CI 0.86 to 8.08; 311 participants, 1 study; Analysis 4.6). Investigators reported only three spontaneous abortions and five congenital malformations, thus the CIs of analyses were very wide to detect differences in effects (spontaneous abortion: RR 0.48, 95% CI 0.04 to 5.22; 311 participants, 1 study; Analysis 4.7; congenital malformation: RR 3.82, 95% CI 0.43 to 33.83; 311 participants, 1 study; Analysis 4.8). During the trial, only one maternal death occurred in the mefloquine group, but the power of the analysis was too low to attribute the effects to an intervention (RR 2.95, 95% CI 0.12 to 71.85; 339 participants, 1 study; Analysis 4.9). Infant deaths were equally frequent in both trial groups (RR 1.04, 95% CI 0.63 to 1.74; 288 participants, 1 study; Analysis 4.10).

DISCUSSION

Summary of main results

We included in this Cochrane Review six trials, enrolling 8192 pregnant women.

For HIV-uninfected women, two doses of intermittent preventive mefloquine treatment in pregnancy (IPTp-mefloquine) reduced the risk of maternal peripheral parasitaemia at delivery by 35% (high-certainty evidence) and the risk of anaemia by 16% (moderate-certainty evidence) compared with two doses of intermittent preventive sulfadoxine-pyrimethamine treatment in pregnancy (IPTp-sulfadoxine-pyrimethamine). Investigators have reported no significant evidence of an effect of mefloquine on placental malaria, cord blood parasitaemia and anaemia, mean birth weight, prevalence of low birth weight, prematurity, stillbirths and abortions, and congenital malformations. Overall, IPTp-mefloquine increases by approximately four-fold the risk of drug-related adverse events including vomiting, fatigue/weakness, and dizziness (high- or moderate-certainty evidence), when compared with sulfadoxine-pyrimethamine.

For HIV-infected women, three doses of IPTp-mefloquine plus cotrimoxazole prophylaxis compared with cotrimoxazole alone reduced the risk of maternal peripheral parasitaemia at delivery (measured by polymerase chain reaction (PCR)) by 48% (moderate-certainty evidence) and the risk of placental malaria (measured by PCR) by 72% (high-certainty evidence). Meta-analyses were underpowered to detect differences between effects of mefloquine plus cotrimoxazole and cotrimoxazole on other maternal, foetal, and neonatal outcomes. Regarding drug-related adverse events, random-effects analyses showed a significant effect of IPTp-mefloquine plus cotrimoxazole prophylaxis compared with cotrimoxazole alone only in the case of vomiting (RR 7.95, 95% CI 4.79 to 13.18; 1055 participants; high-certainty evidence). It is important to note that mefloquine plus cotrimoxazole recipients were at 1.92 times greater risk of mother-to-child transmission of HIV than the group that received cotrimoxazole alone (RR 1.92, 95% CI 1.13 to 3.25; 1019 participants). A secondary analysis of one of the included trials revealed this finding (Gonzalez 2014b KEN MOZ TAN).

One trial among HIV-infected women comparing three doses of IPTp-mefloquine and cotrimoxazole was underpowered to detect an effect of mefloquine on maternal, foetal, infant, and safety outcomes, except for drug-related adverse events, which were more frequent in the mefloquine group.

Finally, the single trial conducted in Thailand (where *Plasmodium vivax* coexists) found a significant effect attributable to mefloquine weekly prophylaxis (compared with placebo) only in reducing the risk of maternal peripheral parasitaemia at delivery (RR 0.13, 95% CI 0.05 to 0.33; 339 participants).

Overall completeness and applicability of evidence

Trials were carried out in sub-Saharan Africa, except for one conducted in Thailand, and were published between 1994 and 2014. Findings evidenced that mefloquine chemoprevention reduces the risk of maternal parasitaemia at delivery in both HIV-uninfected and HIV-infected women compared with other antimalarials or placebo. Additionally, in HIV-infected women, Mefloquine was found to reduce the risk of placental malaria. Results from these trials show fairly consistent clinically important benefits for women and their infants. However, the risk of drug-related adverse events was increased among mefloquine recipients, and it is notable that mefloquine increased the risk of mother-to-child transmission in one trial.

Included trials evaluated two or three IPTp doses of sulfadoxine-pyrimethamine as per World Health Organization (WHO) recommendations, whereas current evidence suggests that monthly doses may provide a better prophylactic effect (Kayentao 2013). Additionally, the WHO currently recommends IPTp administration at each scheduled antenatal contact (WHO 2012b).

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The findings of this review, derived from a variety of sub-Saharan African settings and comparing mefloquine chemoprevention in pregnancy with varied antimalarial drugs and placebo, may be applied worldwide. Mefloquine is currently recommended as malaria chemoprevention for pregnant women of all gestational ages travelling to malaria-endemic areas (CDC 2016). This drug is also recommended for treatment of uncomplicated malaria episodes in combination with artesunate (WHO 2015), and a fixed-dose formulation is available in some malaria-endemic countries. In 2013, the WHO Evidence Review Group (ERG) on IPTp met to assess evidence obtained from IPTp-mefloquine trials, and the WHO Malaria Policy Advisory Committee (MPAC) reviewed ERG recommendations and agreed that mefloquine at the 15-mg/kg dose regimen should not be recommended for IPTp, given its adverse events and poor tolerability (WHO MPAC 2013).

Certainty of the evidence

We assessed the certainty of evidence in this review by using the GRADE approach and presented the evidence in two 'Summary of findings' tables for efficacy and safety outcomes (Summary of findings for the main comparison; Summary of findings 2).

For HIV-uninfected pregnant women, evidence that IPTp-mefloquine was superior to IPTp-sulfadoxine-pyrimethamine in reducing the risk of maternal peripheral parasitaemia and anaemia at delivery was of moderate certainty, and evidence that IPTp-mefloquine increased drug-related adverse effects (namely, vomiting and dizziness) compared with IPTp-sulfadoxine-pyrimethamine was of high and moderate certainty (respectively). We considered the effects of IPTp-mefloquine in decreasing placental malaria risk compared with IPTp-sulfadoxine-pyrimethamine to be of low certainty because of substantial heterogeneity among trials. Finally, we considered evidence of no effects of mefloquine compared with sulfadoxine-pyrimethamine on low birth weight and stillbirths and abortions to be of moderate certainty.

For HIV-infected women, evidence that cotrimoxazole plus IPTp-mefloquine was superior to cotrimoxazole in reducing the risk of maternal peripheral parasitaemia and anaemia at delivery was of moderate certainty, whereas evidence regarding lack of effect on risk of placental malaria was of high certainty. Evidence of no effects of cotrimoxazole plus IPTp-mefloquine compared with cotrimoxazole on low birth weight and stillbirths and abortions was of moderate and very low certainty, respectively, because of serious risk of bias of one of the included trials and substantial heterogeneity. Finally, we considered evidence of mefloquine increasing risks of vomiting and dizziness to be of low certainty because heterogeneity among trials was substantial and the 95% CI was wide.

Potential biases in the review process

It seems unlikely that we have missed any trials examining mefloquine for prevention of malaria in pregnant women.

Agreements and disagreements with other studies or reviews

A previous Cochrane Review on drugs for preventing malaria in pregnant women in endemic areas analyzed the effects of mefloquine for prevention of malaria (Radeva-Petrova 2014). Our results are consistent with those previously reported but include more trials and thus may be more robust.

The findings of this Cochrane Review are also consistent with those of a previous systematic review assessing the safety and tolerability of mefloquine in pregnancy (González 2013).

AUTHORS' CONCLUSIONS

Implications for practice

In past decades, many clinical trials have tested mefloquine chemoprevention to prevent malaria and its consequences in pregnant women.

For HIV-uninfected pregnant women, IPTp-mefloquine better reduces malaria effects compared with IPTp-sulfadoxine-pyrimethamine, but the drug is worse tolerated than sulfadoxine-pyrimethamine. For HIV-infected pregnant women, IPTp-mefloquine added to cotrimoxazole prophylaxis reduces the risk of important malaria consequences better than cotrimoxazole alone, but drug tolerability constitutes a health issue.

The data show that mefloquine is an efficacious and safe antimalarial drug in terms of pregnancy outcomes for prevention of malaria in pregnancy. However, the high proportion of mefloquine-related adverse events constitutes an important barrier to its effectiveness for malaria preventive treatment in pregnant women.

Implications for research

Mefloquine efficacy to prevent malaria effects in pregnancy is well established. Future research should concentrate on finding a dose that would provide the same antimalarial beneficial effects while reducing its drug-related adverse events, especially as weekly prophylaxis (for example, at a dose of 5 mg/kg) for HIV-uninfected women living in areas of high sulfadoxine-pyrimethamine resistance. Researchers also should further examine findings on the two-fold increased risk of mother-to-child transmission of HIV among mefloquine recipients.

ACKNOWLEDGEMENTS

We thank David Sinclair and Ragna Boerma for their contributions to protocol development and analysis inputs for this review. We thank Valérie Briand, Michel Cot, and Lise Denoeud-Ndam for contributing unpublished data. Finally, we thank Vittoria Lutje, Anne-Marie Stephani, and Paul Garner from the Cochrane Infectious Diseases Group, and Marta Roqué from the Iberoamerican Cochrane Centre. for support and help provided throughout all phases of development of this Cochrane Review.

The editorial base of the Cochrane Infectious Diseases Group is funded by UK aid from the UK Government for the benefit of low- and middle-income countries (Grant: 5242). The views expressed in this review do not necessarily reflect UK government policy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Briand 2009 BEN

Methods	Trial design: open-label, randomized, 2-arm trial of 2 doses of IPTp Follow-up: the second IPTp dose was administered from 30 weeks of gestation and at least 1 month after administration of the first dose. Women were visited at home, at delivery, and until 6 weeks after the end of pregnancy. Adverse event (AE) monitoring: AEs were recorded via an open-labelled questionnaire during visits at home occurring within 1 week after each IPTp intake.
Participants	Numbers of participants randomized: 802 (IPTp-mefloquine), 799 (IPTp-sulfadoxine-pyrimethamine) Inclusion criteria: HIV-uninfected women of all gravidities at 16 to 28 weeks of gestation who had no history of a neurological or psychiatric disorder and who had not previously used sulfadoxine-pyrimethamine or mefloquine nor reported having adverse reactions to medications containing sulfa. Exclusion criteria: pregnant women not meeting inclusion criteria.
Interventions	• Two doses of IPTp with sulfadoxine-pyrimethamine (1500 mg of sulfadoxine and 75 mg of pyrimethamine per dose) • Two doses of IPTp with mefloquine (15 mg/kg per dose; Mepha)
Outcomes	• Maternal peripheral parasitaemia at delivery • Placental malaria (presence of asexual stage parasites in blood smear) • Maternal anaemia at delivery (defined by haemoglobin < 10 g/dL) • Mean haemoglobin at delivery • Clinical malaria episodes during pregnancy • Cord blood parasitaemia • Mean birth weight • Low birth weight rates • Prematurity rates • Spontaneous abortion (expulsion of a foetus at < 28 weeks of gestation) rates • Stillbirth rates (delivery of a dead child at < 28 weeks of gestation) • Congenital malformation rates • Maternal mortality • Neonatal mortality • Frequency of adverse events: vomiting, headache, weakness, and dizziness

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Briand 2009 BEN *(Continued)*

Notes	Country: Benin Setting: antenatal care clinics from Ouidah,a semi-rural town Transmission: perennial with seasonal peaks Resistance: in 2005, rates of sulfadoxine-pyrimethamine and mefloquine resistance in vivo in children < 5 years of age were estimated to be 50% and 2.5% by day 28 of treatment, respectively. Dates: 2005 to 2008 Funding: Fonds de Solidarité Prioritaire (French Ministry of Foreign Affairs; project no. 2006–22); Institut de Recherche pour le Développement; Fondation pour la Recherche Médicale (grant FDM20060907976 to V.B.); Fondation de France; and Fondation Mérieux

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Randomization of subjects was stratified according to maternity clinic and gravidity".
Allocation concealment (selection bias)	High risk	Allocation was not concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was reported, and safety outcomes are likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Efficacy	Low risk	No blinding of outcome assessment was reported, but the review authors judge that the efficacy outcome measurement is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Safety	High risk	No blinding of outcome assessment was reported; thus the review authors judge that the safety outcome measurement is likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced in numbers across intervention groups, and similar reasons for missing data were reported across groups.
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were prespecified.
Other bias	Low risk	The study appears to be free of other sources of bias.

Denoeud-Ndam 2014a BEN

Methods	Trial design: randomized, open-label trial of 3 doses of IPTp Follow-up: 3 scheduled IPTp administrations with at least a 1-month interval between them. IPTp-mefloquine administration and provision of cotrimoxazole. Clinical and adherence information, complete blood count, CD4 count, malaria screening, and treatment of malaria. At delivery: blood smears from placenta and umbilical cords and evaluation of newborns. Infant evaluation at 6 weeks, 4 months, and 2 months after weaning

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Denoeud-Ndam 2014a BEN *(Continued)*

	Adverse event (AE) monitoring: self-reporting of all AEs. All adverse events were recorded at each visit. In addition, direct observation of early adverse reactions to mefloquine within 30 minutes after supervised intake was noted and later reactions were collected by phone the same day/evening or on the next day. Medical examination was performed 2 weeks after cotrimoxazole initiation to search for cutaneous reactions. An independent data and safety monitoring board reviewed all SAEs.
Participants	Numbers of participants randomized: 146 (cotrimoxazole), 146 (cotrimoxazole+mefloquine) Inclusion criteria: HIV-infected pregnant women of all gravidities aged > 18 years, living permanently in the study area, between 16 and 28 weeks of gestation; last dosage of IPTp taken 1 month before enrolment; women requiring antimalarial treatment enrolled at least 2 weeks after completion of treatment Exclusion criteria: history of neuropsychiatric disorder; severe kidney or liver disease; serious adverse reaction to mefloquine, sulfa drugs, or quinine
Interventions	IPTp with mefloquine plus cotrimoxazole • 15 mg/kg single dose (250 mg tablet, Lariam, Roche), 3 doses 1 month apart • Daily dose of 800 mg sulfamethoxazole and 160 mg trimethoprim Cotrimoxazole • Daily dose of 800 mg sulfamethoxazole and 160 mg trimethoprim All study participants were given LLITNs and daily supplementation with 100 mg ferrous sulphate and 5 mg folic acid. The first dose was given at ≥ 16 weeks of gestation. All women were observed for 30 minutes following IPTp administration. Women vomiting within the first 30 minutes were given a second full IPTp dose. Asymptomatic women and women with low parasitaemia (< 1000 parasites/µL) were treated by the IPTp-mefloquine dose in the mefloquine groups. Otherwise, women received artemether-lumefantrine or oral quinine. Those with severe malaria were treated with intravenous quinine.
Outcomes	• Maternal peripheral parasitaemia at delivery (PCR) • Placental parasitaemia at delivery (blood smear and PCR) • Mean maternal haemoglobin at delivery • Maternal anaemia (< 9.5 g/dL) at delivery • Cord blood parasitaemia at delivery • Mean birth weight • Low birth weight (< 2500 g) • Prematurity • Serious adverse events (SAEs) during pregnancy • Spontaneous abortions (< 28 weeks) • Stillbirths (≥ 28 weeks of gestation) • Congenital malformations (< 28 weeks of gestation) • Early neonatal mortality (< 7 days) • Neonatal mortality • Infant deaths after 7 days • Vomiting • Dizziness • Headache • Fatigue/weakness
Notes	Country: Benin Setting: 5 urban hospitals with PMTCT programmes

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Denoeud-Ndam 2014a BEN *(Continued)*

Malaria transmission: intense and perennial transmission, with peaks during rainy seasons

Resistance: increasing risk of resistance to sulfa drugs. Parasite resistance to cotrimoxazole

Dates: 2009 to 2012

Funding: Sidaction Grant AI19-3-01528

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Randomization was stratified according to the study site and the number of previous pregnancies".
Allocation concealment (selection bias)	Low risk	Quote: "The study coordination center retained the master list and assigned treatment by phone".
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial blinded only the microscopist who evaluated blood smears.
Blinding of outcome assessment (detection bias) Efficacy	Low risk	No blinding of outcome assessment was reported, but the review authors judge that the efficacy outcome measurement is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Safety	High risk	No blinding of outcome assessment was reported; thus the review authors judge that the safety outcome measurement is likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced in numbers across groups.
Selective reporting (reporting bias)	Low risk	Protocol was not available, but published report describes all expected outcomes including those prespecified.
Other bias	Low risk	The study appears to be free of other sources of bias.

Denoeud-Ndam 2014b BEN

Methods	Trial design: randomized, open-label trial of 3 doses of IPTp Follow-up: 3 scheduled IPTp administrations with at least a 1-month interval between them. IPTp-mefloquine administration and provision of cotrimoxazole. Clinical and adherence information, complete blood count, CD4 count, malaria screening, and treatment of malaria. At delivery: blood smears from placenta and umbilical cords and evaluation of newborns. Infant evaluation at 6 weeks, 4 months, and 2 months after weaning Adverse event (AE) monitoring: self-reporting of all AEs. All adverse events were recorded at each visit. In addition, direct observation of early adverse reactions to mefloquine within 30 minutes after supervised intake was noted and later reactions were collected by phone the same day/evening or on the next day. Medical examination was performed 2 weeks after cotrimoxazole initiation to search for cutaneous reactions. An independent data and safety monitoring board reviewed all SAEs.
Participants	Numbers of participants randomized: 72 (cotrimoxazole), 68 (mefloquine)

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Denoeud-Ndam 2014b BEN *(Continued)*

	Inclusion criteria: HIV-infected pregnant women of all gravidities aged > 18 years, living permanently in the study area, between 16 and 28 weeks of gestation, last dosage of IPTp taken 1 month before enrolment, women requiring antimalarial treatment enrolled at least 2 weeks after completion of treatment Exclusion criteria: history of neuropsychiatric disorder; severe kidney or liver disease; serious adverse reaction to mefloquine, sulfa drugs, or quinine
Interventions	IPTp with mefloquine • 15 mg/kg single dose (250 mg tablet, Lariam, Roche) • Three doses 1 month apart Cotrimoxazole • Daily dose of 800 mg sulfamethoxazole and 160 mg trimethoprim All study participants were given LLITNs and daily supplementation with 100 mg ferrous sulphate and 5 mg folic acid. The first dose was given at ≥ 16 weeks of gestation. All women were observed for 30 minutes following IPTp administration. Women vomiting within the first 30 minutes were given a second full IPTp dose. Asymptomatic women and women with low parasitaemia (< 1000 parasites/µL) in the mefloquine groups were treated by the IPTp-mefloquine dose. Otherwise, women received artemether-lumefantrine or oral quinine. Thos with severe malaria were treated with intravenous quinine.
Outcomes	• Maternal peripheral parasitaemia at delivery (PCR) • Placental parasitaemia at delivery (blood smear and PCR) • Mean maternal haemoglobin at delivery • Maternal anaemia (< 9.5 g/dL) at delivery • Cord blood parasitaemia at delivery • Mean birth weight • Low birth weight (< 2500 g) • Prematurity • Serious adverse events (SAEs) during pregnancy • Spontaneous abortions (< 28 weeks) • Stillbirths (≥ 28 weeks of gestation) • Congenital malformations (< 28 weeks of gestation) • Early neonatal mortality (< 7 days) • Neonatal mortality • Infant deaths after 7 days • Vomiting • Dizziness • Headache • Fatigue/weakness
Notes	Country: Benin Setting: 5 urban hospitals with PMTCT programmes Malaria transmission: intense and perennial transmission, with peaks during rainy seasons Resistance: increasing risk of resistance to sulfa drugs. Parasite resistance to cotrimoxazole Dates: 2009 to 2012 Funding: Sidaction Grant AI19-3-01528

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Denoeud-Ndam 2014b BEN *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Randomization was stratified according to the study site and the number of previous pregnancies".
Allocation concealment (selection bias)	Low risk	Quote: "The study coordination center retained the master list and assigned treatment by phone".
Blinding of participants and personnel (performance bias) All outcomes	High risk	The trial blinded only the microscopist who evaluated blood smears.
Blinding of outcome assessment (detection bias) Efficacy	Low risk	No blinding of outcome assessment was reported, but the review authors judge that the efficacy outcome measurement is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Safety	High risk	No blinding of outcome assessment was reported; thus the review authors judge that the safety outcome measurement is likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced in numbers across groups.
Selective reporting (reporting bias)	Low risk	Protocol was not available, but published report describes all expected outcomes including those prespecified.
Other bias	Low risk	The study appears to be free of other sources of bias.

Gonzalez 2014a BEN GAB MOZ TAN

Methods	Trial design: open-label, randomized, 3-arm trial of 2 doses of IPTp Follow-up: at each scheduled and unscheduled visit, a standardized symptom questionnaire was completed, as were blood smears for malaria parasites, and haemoglobin if symptoms and/or signs were suggestive of malaria. At delivery, blood samples were collected for haematological and parasitological evaluation. Weighting of newborns and gestational age at birth were recorded. Malaria parasite was determined 6 weeks after the end of pregnancy. Adverse event monitoring: home visits by field workers were done 2 days after IPTp administration to assess drug tolerability. Solicited and unsolicited adverse events (AEs) were assessed. The former were assessed by directed questioning regarding malaria-related signs and symptoms during unscheduled visits, whereas the latter were assessed through open questioning during scheduled visits.
Participants	Numbers of participants randomized: 1578 (sulfadoxine-pyrimethamine), 1580 (mefloquine full dose), 1591 (mefloquine split) Inclusion criteria: HIV-uninfected women of all gravidities attending the antenatal care clinic for the first time, did not receive IPTp during current pregnancy, permanent residence in the study area, gestational age of ≤ 28 weeks

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Gonzalez 2014a BEN GAB MOZ TAN *(Continued)*

	Exclusion criteria: HIV-positive; history of allergy to sulfa drugs or mefloquine; history of severe renal, hepatic, psychiatric, or neurological disease; mefloquine or halofantrine treatment in the preceding 4 weeks; participating in other intervention studies
Interventions	IPTp with sulfadoxine-pyrimethamine, 3 tablets • 500 mg/25 mg • Two doses 1 month apart IPTp with mefloquine • 15 mg/kg given once as a full dose (250-mg tablets) • Two doses 1 month apart IPTp with mefloquine (split dose) • 15 mg/kg given as a split dose over 2 days (250-mg tablets) • Two doses 1 month apart All study participants were given LLITNs. The first dose was given at > 13 weeks of gestation. All women were observed for 60 minutes following IPT administration. Women vomiting within the first 30 minutes were given a second full IPT dose, and those vomiting 30 to 60 minutes after drug intake were given a half replacement dose. Uncomplicated malaria episodes were treated with oral quinine (first trimester) or artemether-lumefantrine (second and third trimesters); severe malaria episodes were treated with parenteral quinine.
Outcomes	• Maternal peripheral parasitaemia at delivery • Placental parasitaemia at delivery • Mean maternal haemoglobin at delivery • Maternal anaemia (< 10 g/dL) at delivery • Clinical malaria episodes during pregnancy • Cord blood parasitaemia at delivery • Cord blood anaemia • Mean birth weight • Low birth weight (< 2500 g) • Low birth weight by gravidity • Prematurity • Malaria in first year of life • Hospital admissions in first year of life • Malaria in first year of life (infant morbidity) • Hospital admissions in first year of life (infant morbidity) • Serious adverse events (SAEs) during pregnancy • Spontaneous abortions (< 20 complete weeks of gestation) • Stillbirths (> 20 complete weeks of gestation) • Congenital malformations • Maternal mortality • Neonatal mortality • Infant mortality • Vomiting • Headache • Fatigue/weakness • Dizziness

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Gonzalez 2014a BEN GAB MOZ TAN *(Continued)*

Notes	Country: Tanzania, Mozambique, Benin, and Gabon Setting: antenatal care clinics Transmission: mesoendemic in Tanzania and Mozambique, hyperendemic in Benin and Gabon Resistance: resistance to sulfadoxine-pyrimethamine due to long-term sulfadoxine-pyrimethamine for IPTp Dates: 2009 to 2013 Funding: this study was funded by the European Developing Countries Clinical Trials Partnership (EDCTP; IP.2007.31080.002), the Malaria in Pregnancy Consortium, and the Instituto de Salud Carlos III (PI08/0564), in Spain. RG and MR were partially supported by grants from the Spanish Ministry of Health (ref. CM07/0015 and CM11/00278, respectively). The CISM receives core funding from the Spanish Agency for International Cooperation (AECID). LLITNs (Permanet) were donated by Vestergaard Frandsen.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation of the participants to the study arms was done centrally by randomization stratified by country according to a 1:1:1 scheme. The sponsor's institution biostatistician produced the computer-generated randomization list for each recruiting site".
Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation for each participant was concealed in opaque sealed envelopes that were opened only after recruitment. Study participants were assigned a unique study number linked to the allocated treatment group".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "The study was designed as an open-label, randomized, three-arm trial to compare two-dose mefloquine with two-dose SP for IPTp".
Blinding of outcome assessment (detection bias) Efficacy	Low risk	No blinding of outcome assessment was reported, but the review authors judge that the efficacy outcome measurement is not likely to be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) Safety	High risk	No blinding of outcome assessment was reported; thus the review authors judge that the safety outcome measurement is likely to be influenced by lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All excluded participants, at any stage of the trial, are counted in the flow chart (both ITT and ATP cohorts). Missing outcome data were balanced in numbers across groups.
Selective reporting (reporting bias)	Low risk	Not observed. Protocol available
Other bias	Low risk	The study appears to be free of other sources of bias.

Gonzalez 2014b KEN MOZ TAN

Methods	Trial design: individually randomized, double-blind, placebo-controlled trial of 3 doses of IPTp

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Gonzalez 2014b KEN MOZ TAN *(Continued)*

	Follow-up: at each scheduled and unscheduled visit, a standardized symptom questionnaire was completed, as were blood smears for malaria parasites, and haemoglobin if symptoms and/or signs were suggestive of malaria. On a monthly basis, adherence to cotrimoxazole and LLITN was assessed. At delivery, blood samples were collected for haematological and parasitological evaluation with CD4 cell count and HIV viral load. Weighting of newborns and gestational age at birth were recorded. Malaria parasite was determined 6 weeks after the end of pregnancy. Adverse event monitoring: home visits by field workers were done 2 days after IPTp administration to assess drug tolerability. Solicited and unsolicited adverse events (AEs) were assessed. The former were assessed by directed questioning of malaria-related signs and symptoms during unscheduled visits, whereas the latter were assessed through open questioning during scheduled visits.
Participants	Numbers of participants randomized: 537 (placebo+cotrimoxazole), 534 (mefloquine+cotrimoxazole) Inclusion criteria: HIV-infected women of all gravidities attending the antenatal care clinic for the first time, did not receive IPTp during current pregnancy, permanent residence in the study area, gestational age of ≤ 28 weeks, HIV positive Exclusion criteria: history of allergy to sulfa drugs or mefloquine; history of severe renal, hepatic, psychiatric, or neurological disease; mefloquine or halofantrine treatment in the preceding 4 weeks; participating in other intervention studies
Interventions	IPTp with mefloquine • 15 mg/kg single dose (maximum dosage would not exceed 1500 mg of mefloquine) • Three doses 1 month apart IPTp with placebo • Identical to mefloquine tablets in shape and colour • Three doses 1 month apart All study participants had monthly cotrimoxazole prophylaxis (fixed combination 800 mg of trimethroprim and 160 mg of sulfamethoxazole/tablet). All study participants were given LLITNs. The first dose was given at > 13 weeks of gestation. All women were observed for 60 minutes following IPT administration. Women vomiting within the first 30 minutes were given a second full IPTp dose, and those vomiting 30 to 60 minutes after drug intake were given a half replacement dose. Uncomplicated malaria episodes were treated with oral quinine (first trimester) or artemether-lumefantrine (second and third trimesters); severe malaria episodes were treated with parenteral quinine.
Outcomes	• Maternal peripheral parasitaemia at delivery (PCR) • Placental parasitaemia at delivery (blood smear and PCR) • Mean maternal haemoglobin at delivery • Maternal anaemia (< 9.5 g/dL) at delivery • Clinical malaria episodes during pregnancy • Cord blood parasitaemia at delivery • Mean birth weight • Low birth weight (< 2500 g) • Prematurity • Serious adverse events (SAEs) during pregnancy • Spontaneous abortions (< 20 complete weeks of gestation) • Stillbirths (> 20 weeks of gestation)

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Gonzalez 2014b KEN MOZ TAN *(Continued)*

- Congenital malformations
- Maternal mortality
- Perinatal mortality
- Early neonatal mortality (< 7 days)
- Neonatal mortality
- Vomiting
- Headache
- Fatigue/weakness
- Dizziness

Notes	Countries: Tanzania, Mozambique, and Kenya Setting: antenatal care clinics Transmission: mesoendemic in Tanzania and Mozambique, holoendemic in Kenya Resistance: resistance to sulfadoxine-pyrimethamine due to long-term sulfadoxine-pyrimethamine for IPTp Dates: 2010 to 2013 Funding: this study was funded by the European Developing Countries Clinical Trials Partnership (EDCTP; IP.2007.31080.002), the Malaria in Pregnancy Consortium, and the Instituto de Salud Carlos III (PI08/0564), in Spain. RG and MR were partially supported by grants from the Spanish Ministry of Health (ref. CM07/0015 and CM11/00278, respectively). The CISM receives core funding from the Spanish Agency for international Cooperation (AECID). LLITNs (Permanet) were donated by Vestergaard Frandsen, and cotrimoxazole tablets (Septrin) by UCB Pharma, in Spain.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation of the participants to the study arms was done centrally by block randomization (block size of 6) stratified by country".
Allocation concealment (selection bias)	Low risk	Quote: "The Pharmacy Department of the Hospital Clinic in Barcelona produced and safeguarded the computer-generated randomization list for each recruiting site until unblinding, and carried out the masking, labelling, and packaging of all study interventional drugs. Study number allocation for each participant was concealed in opaque sealed envelopes that were sequentially numbered and opened only after recruitment by study health personnel".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study participants were assigned a unique study number linked to the allocated treatment group. Investigators, laboratory staff, care providers, and study participants were blinded to intervention throughout the study". Placebo tablets were identical to mefloquine tables in shape and colour.
Blinding of outcome assessment (detection bias) Efficacy	Low risk	Quote: "Investigators, laboratory staff, care providers, and study participants were blinded to intervention throughout the study".
Blinding of outcome assessment (detection bias) Safety	Low risk	Quote: "Investigators, laboratory staff, care providers, and study participants were blinded to intervention throughout the study".

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Gonzalez 2014b KEN MOZ TAN *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All excluded participants, at any stage of the trial, are counted in the flow chart (both ITT and ATP cohorts). Missing outcome data were balanced in numbers across groups.
Selective reporting (reporting bias)	Low risk	Not observed. Protocol available
Other bias	Low risk	The study appears to be free of other sources of bias.

Nosten 1994 THA

Methods	Trial design: double-blind, placebo-controlled trial. Phase 1 and phase 2 Follow-up: in both phases, weekly visits included assessment of weight, temperature, pulse, blood pressure, fundal height, presence of oedema and anaemia, a symptom questionnaire on gastrointestinal and central nervous system side effects, malaria blood smear, electrocardiogram, and haematology and biochemistry every 2 weeks. Treatment of malaria and anaemia and food supply were provided when needed. At phase 2, expanded questionnaires and Romberg test were used. At delivery, measurement of newborn weight, details of labour, cord and maternal blood samples (malaria and anaemia), and placental biopsy were included. At phase 2, autopsy of death was performed in newborns. Follow-up consisted of different measurements in children until 2 years of age (weight, height, head and arm circumferences) and determination of age when baby could first crawl, sit, walk, and talk. At phase 2, age at first symptomatic malaria, malaria blood smear, haematocrit, and full clinical examination were performed. Adverse event monitoring: weekly symptom questionnaire focusing on gastrointestinal, neurological, dermatological, and systemic symptoms
Participants	Numbers of participants randomized: 170 (mefloquine - 60 phase 1, 110 phase 2), 169 (placebo - 59 phase 1, 110 phase 2) Inclusion criteria: women of all gravidities and unknown HIV status (not tested) who attended the ANC clinic and were at > 20 weeks of estimated gestation. Exclusion criteria: women not meeting inclusion criteria.
Interventions	IPTp with mefloquine • Phase 1: 500 mg of base loading dose followed by 250 mg weekly for 4 weeks and thereafter 125 mg weekly until delivery • Phase 2: 250 mg of base weekly given for 4 weeks followed by 125 mg weekly until delivery IPTp with placebo • Identical to mefloquine tablets (weekly dosage) The first dose was given at > 20 weeks of gestation. Anaemia was treated with ferrous sulphate and folic acid. Uncomplicated *Plasmodium falciparum* malaria was treated with quinine sulphate, *P vivax* with chloroquine sulphate, and severe malaria with intravenous quinine dihydrochloride.
Outcomes	• Maternal peripheral parasitaemia during pregnancy • Placental malaria • Mean birth weight • Low birth weight • Prematurity • Stillbirths

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Nosten 1994 THA *(Continued)*

- Spontaneous abortions
- Congenital malformations
- Maternal mortality
- Infant mortality

Notes	Country: Thailand Setting: 3 camps for displaced people: phase 1 antenatal clinics, phase 2 hospital Dates: 1987 to 1990 Transmission: seasonal malaria transmission (mesoendemic) Resistance: resistances to mefloquine, quinine, chloroquine, and antifolates Funding: United Nations Development Programme/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases; Wellcome Trust of Great Britain; Prevention Fundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Women were randomized to receive mefloquine or placebo. Not well explained how women were randomized
Allocation concealment (selection bias)	Unclear risk	Not explained
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial Quote: "The investigators were unaware of the randomization". Placebo tablets were identical to mefloquine tablets.
Blinding of outcome assessment (detection bias) Efficacy	Unclear risk	Not explained
Blinding of outcome assessment (detection bias) Safety	Unclear risk	Not explained
Incomplete outcome data (attrition bias) All outcomes	Low risk	All excluded participants and those who decided to drop out are correctly reported along with reasons. Missing outcome data were balanced in numbers across groups.
Selective reporting (reporting bias)	Unclear risk	Results of cord and maternal blood smears are not shown (published elsewhere?). No protocol is available. Nothing else was observed.
Other bias	Low risk	The study appears to be free of other sources of bias.

Abbreviations: AE: adverse event; AECID: Spanish Agency for International Cooperation; ANC: antenatal care; ATP: adenosine triphosphate; CISM: Centro de Investigação em Saúde da Manhiça; IPTp: intermittent preventive treatment for malaria in pregnancy; IPTp-mefloquine: intermittent preventive mefloquine treatment in pregnancy; IPTp-sulfadoxine-pyrimethamine: intermittent preventive sulfadoxine-pyrimethamine treatment in pregnancy; ITT: intention-to-treat; LLITN: long-lasting insecticide-treated net; PCR: polymerase chain reaction; PMTCT: prevention of mother-to-child transmission; SAE: serious adverse event.

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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Balocco 1992	Letter to editor reporting on the results of pregnancy of 24 women exposed to mefloquine in early pregnancy. The report was excluded because it did not meet the inclusion criteria.
Briand 2015	This publication reports the findings of a re-analysis of previous published data comparing mefloquine with sulphadoxine-pyrimethamine for IPTp in Benin using a multiple outcome approach, which allowed the joint assessment of efficacy and tolerability. This analysis was not included in the review because the original study (Briand 2009 BEN) was already included and it did not add additional data.
Denoeud-Ndam 2012	Study comparing mefloquine tolerability as IPTp between HIV-infected and uninfected women participating in three included trials from Benin (Briand 2009 BEN and Denoeud-Ndam 2014a and b). This analysis was excluded from the review because it did not provide additional data from already included trials.
Nosten 1990 THA	The study was designed as a dose-finding pharmacokinetic study in 20 pregnant women in the third trimester of pregnancy who received mefloquine as prophylaxis. The trial did not compare the safety and efficacy of mefloquine with another antimalarial drug and thus, it did not meet inclusion criteria.
Phillips-Howard 1998	Publication reporting on a data analysis of reported use of mefloquine during the 1st trimester of pregnancy in European travellers. This analysis was excluded from the review because it did not meet inclusion criteria.
Schlagenhauf 2012	This publication presents the analysis of the reports of exposure to mefloquine in pregnancy received by the Roche post-marketing surveillance system. This analysis was excluded from the review because it did not meet inclusion criteria.
Smoak 1997	This publication reports a case series of 72 US soldiers who inadvertently took mefloquine during pregnancy for prophylaxis. This publication was excluded from the review because it did not meet inclusion criteria.
Steketee 1996 MAL	We were not convinced that allocation was unbiased. Quote: "The assignment of regimens was based on the clinic day of enrolment. All women making their first antenatal clinic visit on a given day were assigned to the same regimen; the following clinic day, enrolled women were assigned a different regimen". We noted bias in allocation supported by statistically and clinically significant differences between intervention groups (3 groups under different chloroquine regimens versus 1 group under mefloquine regimen).
Vanhauwere 1998	Study evaluating 1627 reports of mefloquine exposure pregnancy, mainly for chemoprophylaxis received by the Roche Post-marketing surveillance system between 1986 and 1996.This analysis was excluded from the review because it did not meet inclusion criteria.

Characteristics of ongoing studies *[ordered by study ID]*

Akinyotu 2015 NIG

Trial name or title	A comparative study of mefloquine and SP as prophylaxis against malaria in pregnant HIV-infected patients
Methods	Allocation: randomized

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Akinyotu 2015 NIG *(Continued)*	Intervention model: parallel assignment Masking: single-blind (outcomes assessor) Primary purpose: prevention
Participants	Inclusion criteria: • Pregnant HIV-infected patients • Gestational age ≥ 16 weeks • No history of use of mefloquine or sulphadoxine • Pyrimethamine 4 weeks before recruitment Exclusion criteria: • Anaemia packed cell volume < 30% • Pre-existing medical conditions - diabetes mellitus, hypertension • Allergy to sulphadoxine-pyrimethamine or mefloquine • Non-consenting patients • Multiple gestation • Known psychiatric illness • Known seizure disorder • History of severe renal or hepatic disease
Interventions	• Mefloquine: 250 mg 3 doses 4 weeks apart • Sulfadoxine-pyrimethamine: 500 mg sulphadoxine and 25 mg pyrimethamine, 3 tablets 4 weeks apart for 3 doses
Outcomes	No information available
Starting date	September 2015
Contact information	Oriyomi O Akinyotu, MBBS; Ibadan: +2348035044590; oriyomiddoc@yahoo.com
Notes	We contacted the study authors, but they could not provide the data to us because the study was part of a thesis not yet defended.

DATA AND ANALYSES

Comparison 1. Mefloquine versus sulfadoxine-pyrimethamine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical malaria episodes during pregnancy	2		Rate Ratio (Fixed, 95% CI)	0.83 [0.65, 1.05]
2 Maternal peripheral parasitaemia at delivery	2	5455	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.48, 0.86]
3 Placental malaria	2	4668	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.58, 1.86]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Mean haemoglobin at delivery	2	5588	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.01, 0.19]
5 Maternal anaemia at delivery	2	5469	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.76, 0.94]
6 Severe maternal anaemia at delivery	2	5469	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.58, 1.48]
7 Cord blood parasitaemia	2	5309	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.13, 1.46]
8 Cord blood anaemia	1	4006	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.87, 1.23]
9 Mean birth weight	2	5241	Mean Difference (IV, Fixed, 95% CI)	2.52 [-25.66, 30.69]
10 Low birth weight	2	5641	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.17]
11 Low birth weight by gravidity	2	5641	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.84, 1.13]
11.1 Primigravidae	2	1576	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.80, 1.30]
11.2 Multigravidae	2	4065	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.14]
12 Prematurity	2	4640	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.76, 1.40]
13 Malaria in first year of life	1		Rate Ratio (Fixed, 95% CI)	0.97 [0.82, 1.15]
14 Hospital admissions in first year of life	1		Rate Ratio (Fixed, 95% CI)	0.93 [0.75, 1.17]
15 SAEs during pregnancy	1	4674	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.81, 1.20]
16 Stillbirths and abortions	2	6219	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.91, 1.58]
17 Congenital malformations	2	5931	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.51, 2.37]
18 Maternal mortality	2	6219	Risk Ratio (M-H, Random, 95% CI)	2.41 [0.27, 21.23]
19 Neonatal mortality	2	6134	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.67, 1.43]
20 Infant mortality	1		Rate Ratio (Fixed, 95% CI)	1.00 [0.66, 1.52]
21 AEs: vomiting	2	6272	Risk Ratio (M-H, Fixed, 95% CI)	4.76 [4.13, 5.49]
22 AEs: fatigue/weakness	2	6272	Risk Ratio (M-H, Random, 95% CI)	4.62 [1.80, 11.85]
23 AEs: dizziness	2	6272	Risk Ratio (M-H, Random, 95% CI)	4.21 [3.36, 5.27]

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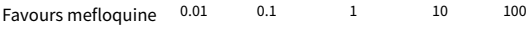
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24 AEs: headache	2	6272	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.25, 1.94]

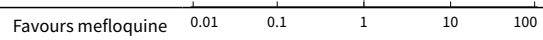
Analysis 1.1. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 1 Clinical malaria episodes during pregnancy.

Study or subgroup	Mefloquine N	Sulfadoxine-pyrimethamine N	log[Rate Ratio] (SE)	Rate Ratio IV, Fixed, 95% CI	Weight	Rate Ratio IV, Fixed, 95% CI
Briand 2009 BEN	0	0	-0.4 (0.42)		8.74%	0.66[0.29,1.5]
Gonzalez 2014a BEN GAB MOZ TAN	0	0	-0.2 (0.13)		91.26%	0.84[0.65,1.09]
Total (95% CI)					**100%**	**0.83[0.65,1.05]**
Heterogeneity: Tau²=0; Chi²=0.32, df=1(P=0.57); I²=0%						
Test for overall effect: Z=1.54(P=0.12)						



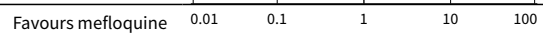
Analysis 1.2. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 2 Maternal peripheral parasitaemia at delivery.

Study or subgroup	Mefloquine n/N	Sulfadoxine-pyrimethamine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Briand 2009 BEN	11/675	24/671		22.29%	0.46[0.22,0.92]
Gonzalez 2014a BEN GAB MOZ TAN	88/2737	63/1372		77.71%	0.7[0.51,0.96]
Total (95% CI)	**3412**	**2043**		**100%**	**0.65[0.48,0.86]**
Total events: 99 (Mefloquine), 87 (Sulfadoxine-pyrimethamine)					
Heterogeneity: Tau²=0; Chi²=1.19, df=1(P=0.28); I²=15.91%					
Test for overall effect: Z=2.97(P=0)					



Analysis 1.3. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 3 Placental malaria.

Study or subgroup	Mefloquine n/N	Sulfadoxine-pyrimethamine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Briand 2009 BEN	11/163	29/656		37.28%	1.53[0.78,2.99]
Gonzalez 2014a BEN GAB MOZ TAN	119/2568	72/1281		62.72%	0.82[0.62,1.1]
Total (95% CI)	**2731**	**1937**		**100%**	**1.04[0.58,1.86]**



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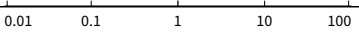
Study or subgroup	Mefloquine	Sulfadoxine-pyrimethamine	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Total events: 130 (Mefloquine), 101 (Sulfadoxine-pyrimethamine)					
Heterogeneity: Tau²=0.12; Chi²=2.74, df=1(P=0.1); I²=63.44%					
Test for overall effect: Z=0.12(P=0.9)					



Favours mefloquine — Favours sulfadoxine-pyrimethamine

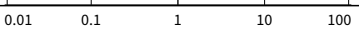
Analysis 1.4. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 4 Mean haemoglobin at delivery.

Study or subgroup	Mefloquine		Sulfadoxine-pyrimethamine		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Briand 2009 BEN	735	11.4 (1.6)	730	11.3 (1.6)		27.06%	0.1[-0.07,0.27]
Gonzalez 2014a BEN GAB MOZ TAN	2743	11.1 (1.5)	1380	11 (1.6)		72.94%	0.1[-0,0.2]
Total ***	**3478**		**2110**			**100%**	**0.1[0.01,0.19]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%							
Test for overall effect: Z=2.26(P=0.02)							

Favours mefloquine — Favours sulfadoxine-pyrimethamine

Analysis 1.5. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 5 Maternal anaemia at delivery.

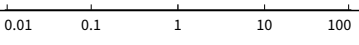
Study or subgroup	Mefloquine	Sulfadoxine-pyrimethamine	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Briand 2009 BEN	103/626	129/640		23.17%	0.82[0.65,1.03]
Gonzalez 2014a BEN GAB MOZ TAN	541/2804	317/1399		76.83%	0.85[0.75,0.96]
Total (95% CI)	**3430**	**2039**		**100%**	**0.84[0.76,0.94]**
Total events: 644 (Mefloquine), 446 (Sulfadoxine-pyrimethamine)					
Heterogeneity: Tau²=0; Chi²=0.1, df=1(P=0.75); I²=0%					
Test for overall effect: Z=3.07(P=0)					



Favours mefloquine — Favours sulfadoxine-pyrimethamine

Analysis 1.6. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 6 Severe maternal anaemia at delivery.

Study or subgroup	Mefloquine	Sulfadoxine-pyrimethamine	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Briand 2009 BEN	19/626	15/640		34.06%	1.29[0.66,2.53]
Gonzalez 2014a BEN GAB MOZ TAN	72/2804	46/1399		65.94%	0.78[0.54,1.12]



Favours mefloquine — Favours sulfadoxine-pyrimethamine

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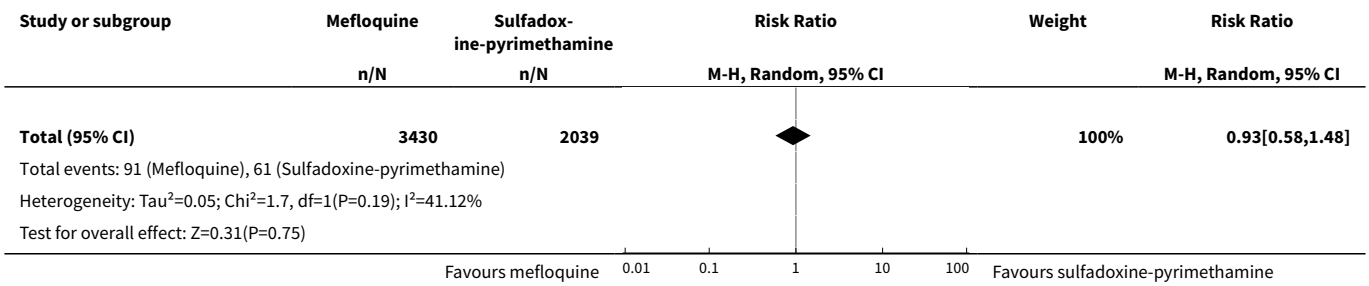
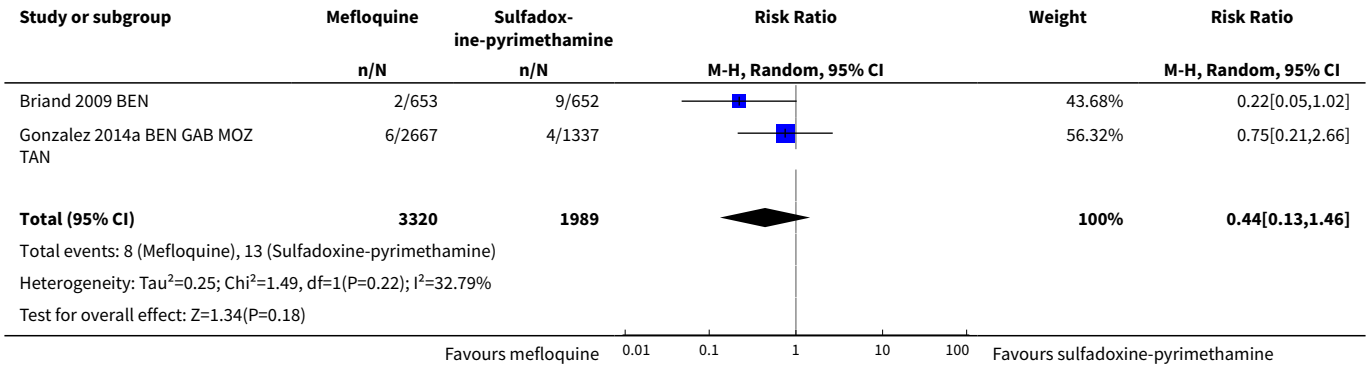
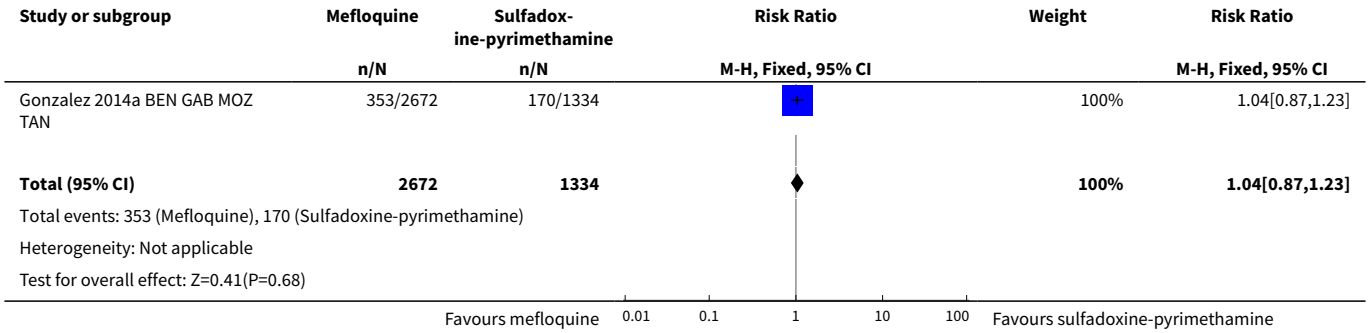


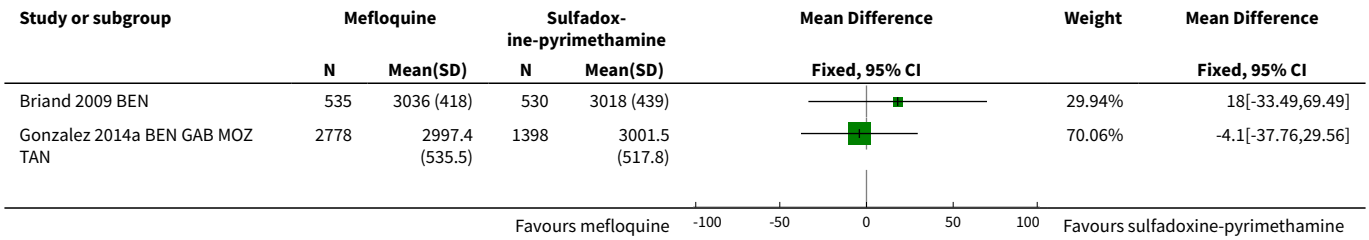
Analysis 1.7. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 7 Cord blood parasitaemia.



Analysis 1.8. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 8 Cord blood anaemia.



Analysis 1.9. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 9 Mean birth weight.



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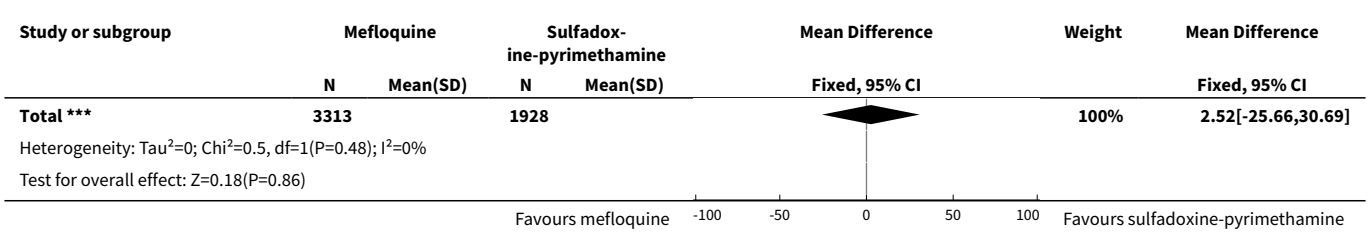
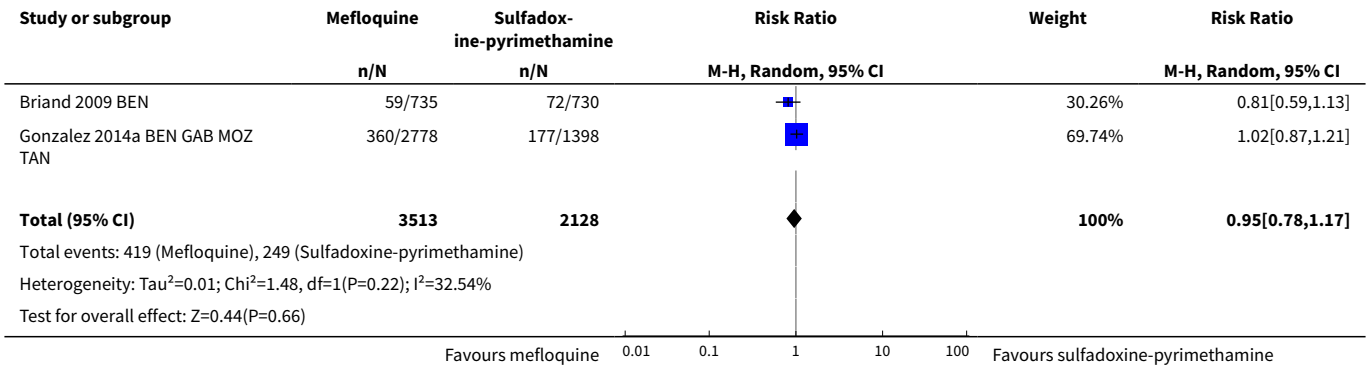
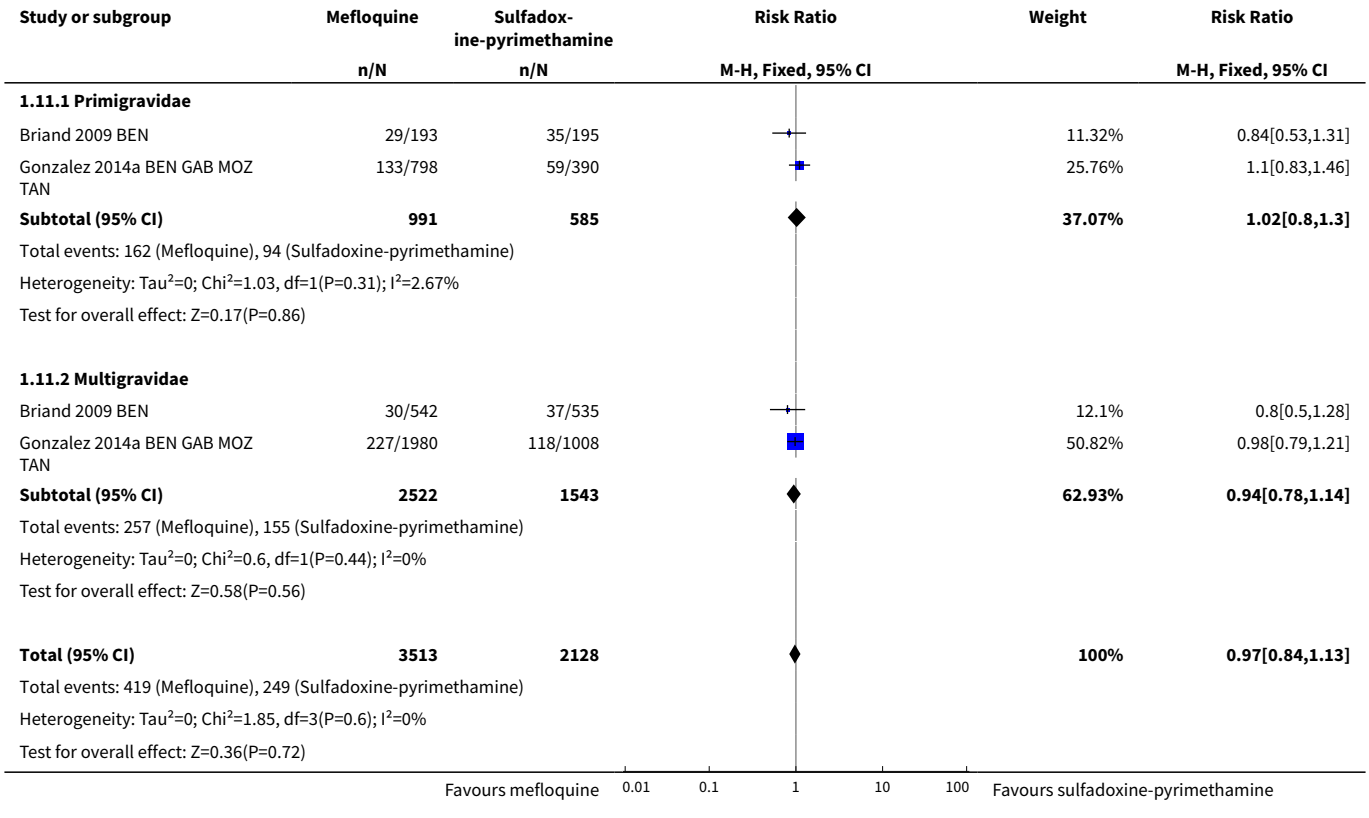


Analysis 1.10. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 10 Low birth weight.



Analysis 1.11. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 11 Low birth weight by gravidity.



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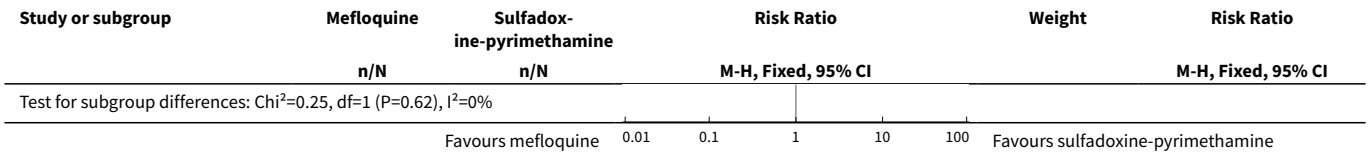
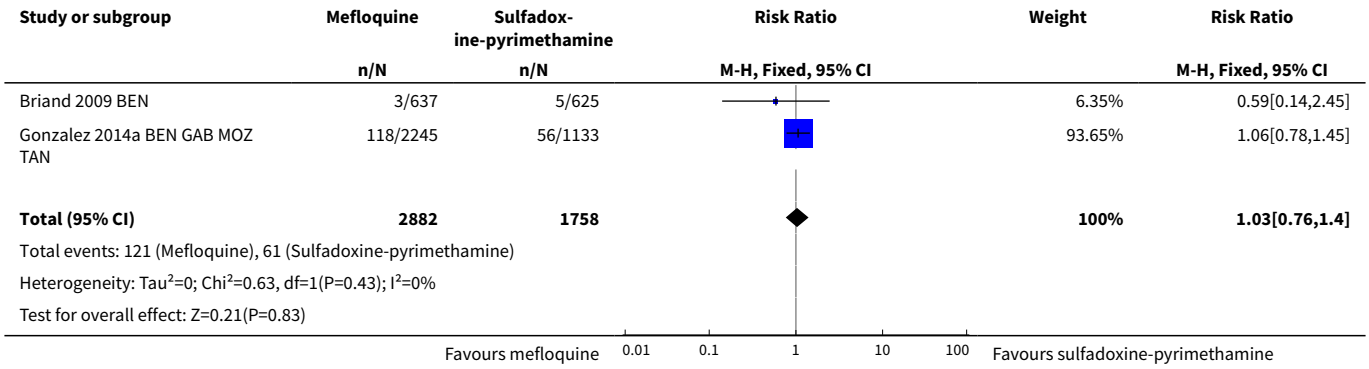
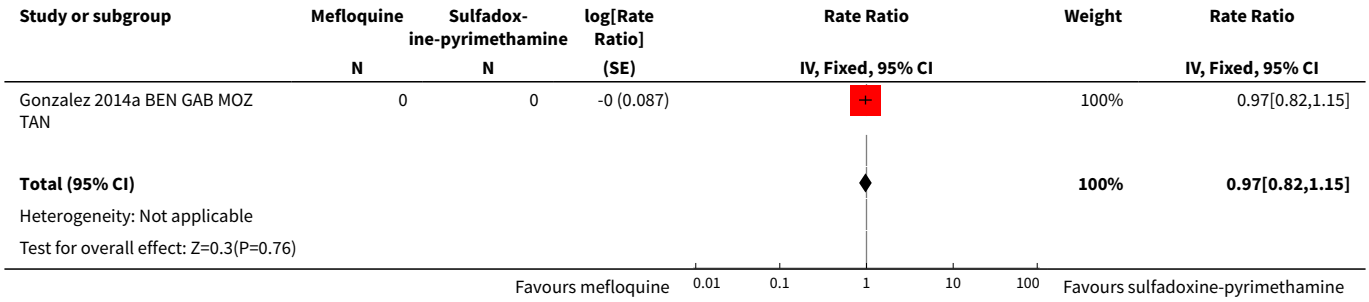


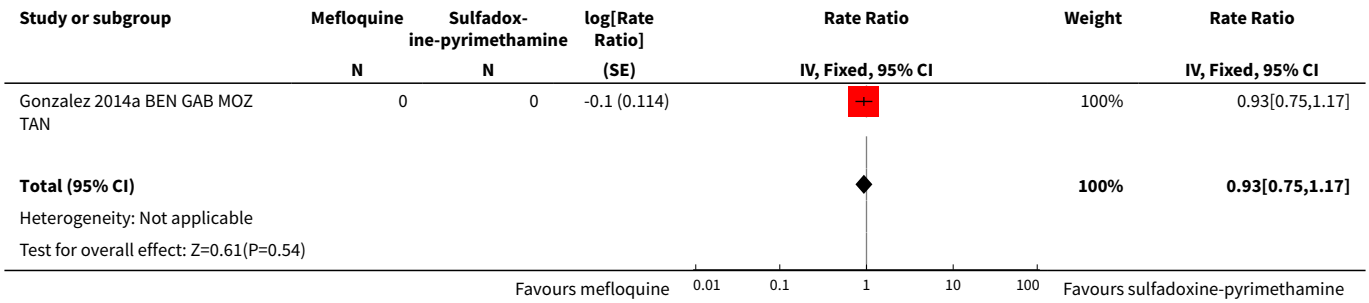
Analysis 1.12. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 12 Prematurity.



Analysis 1.13. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 13 Malaria in first year of life.



Analysis 1.14. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 14 Hospital admissions in first year of life.



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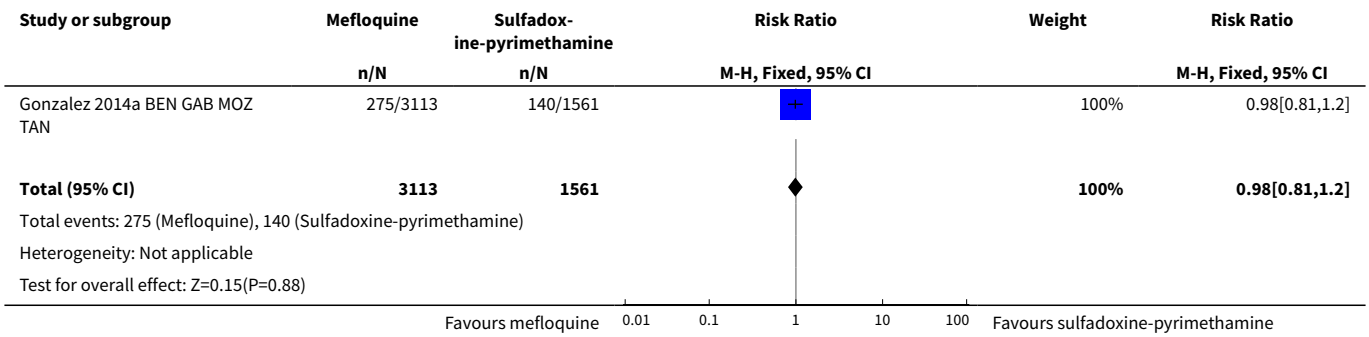
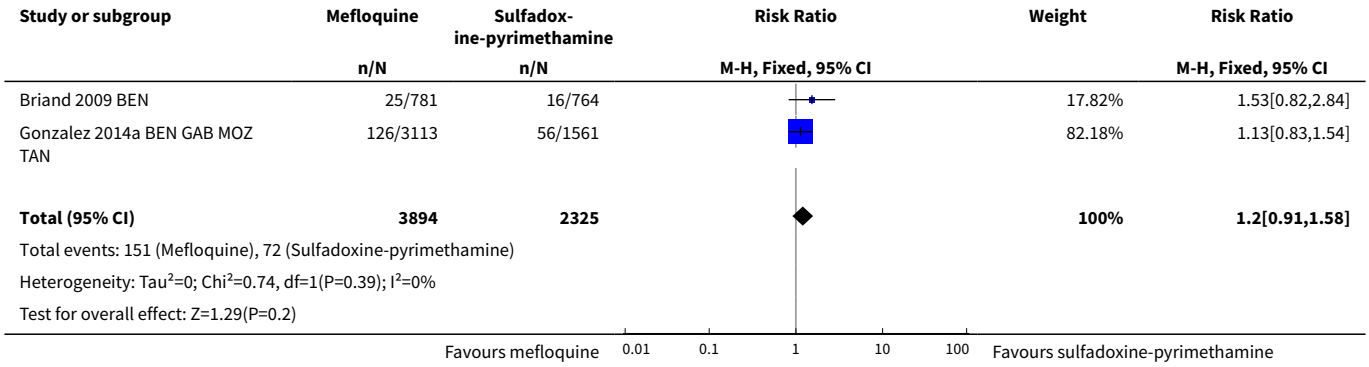
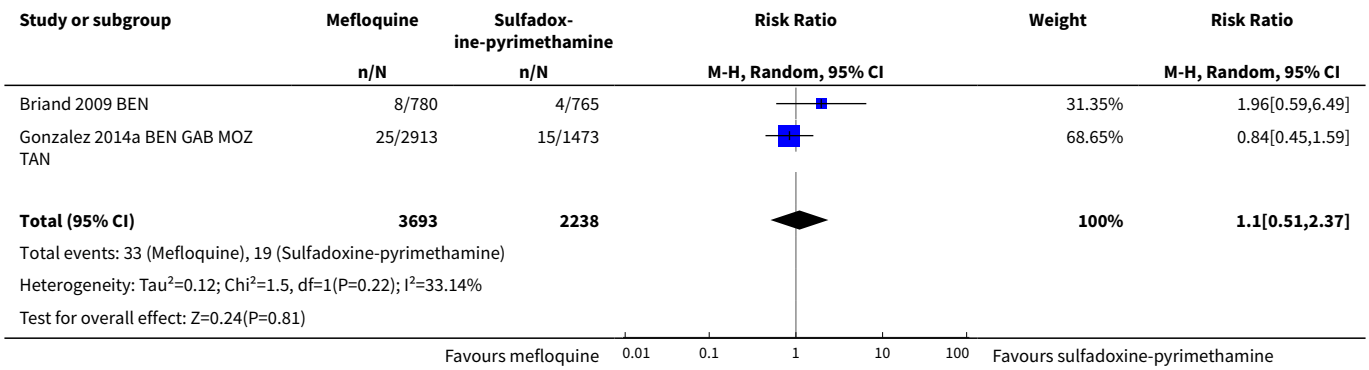
Analysis 1.15. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 15 SAEs during pregnancy.



Analysis 1.16. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 16 Stillbirths and abortions.



Analysis 1.17. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 17 Congenital malformations.



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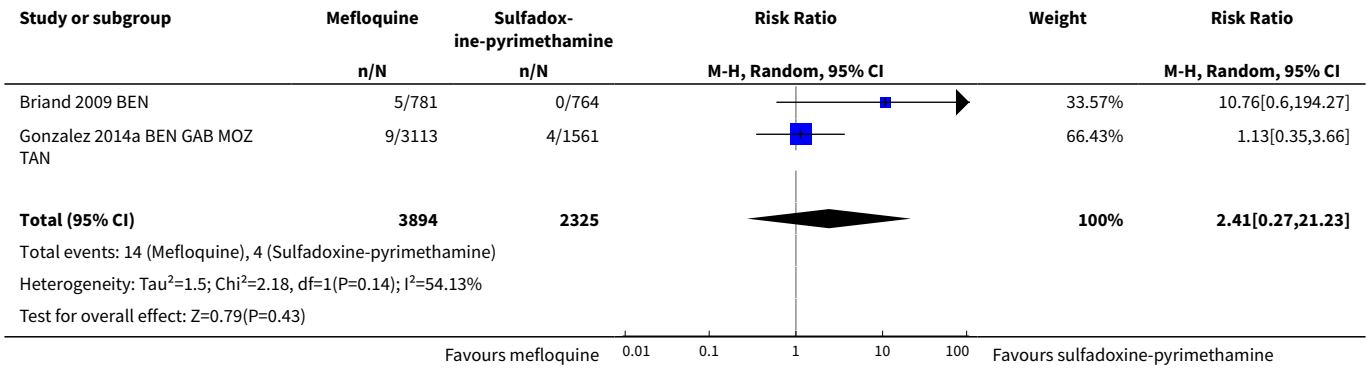
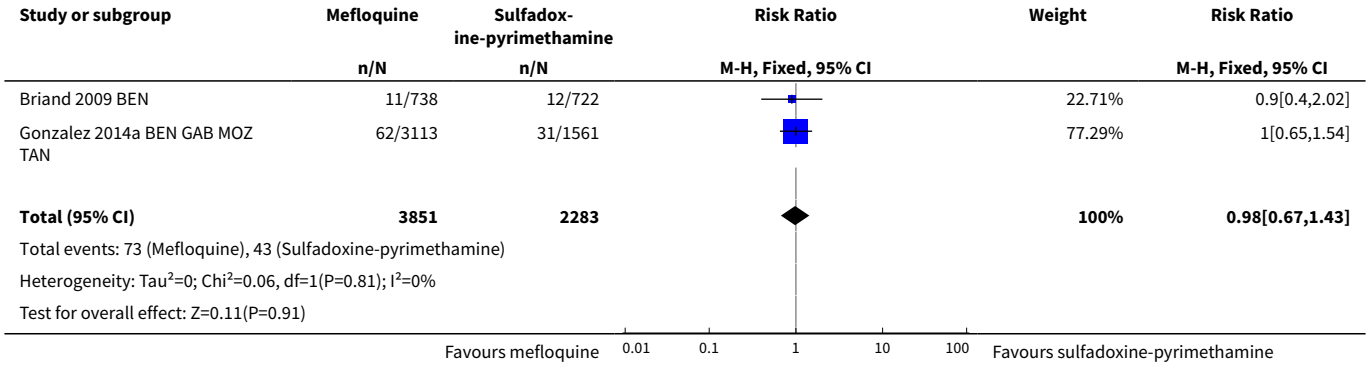
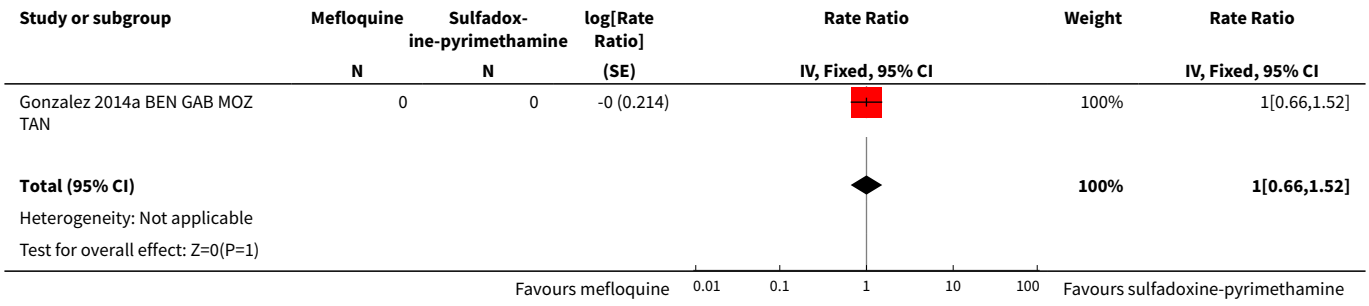
Analysis 1.18. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 18 Maternal mortality.



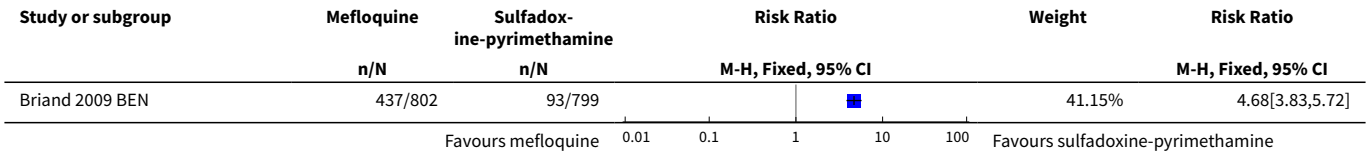
Analysis 1.19. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 19 Neonatal mortality.



Analysis 1.20. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 20 Infant mortality.



Analysis 1.21. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 21 AEs: vomiting.



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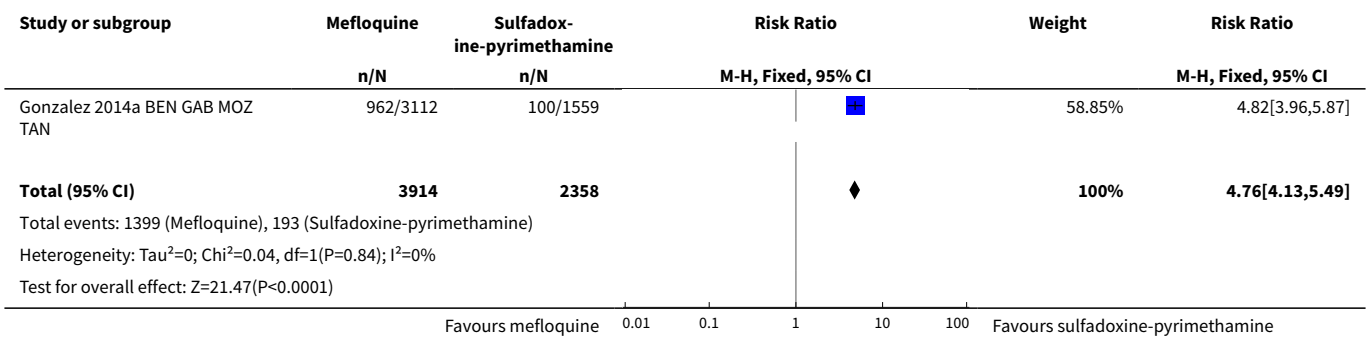
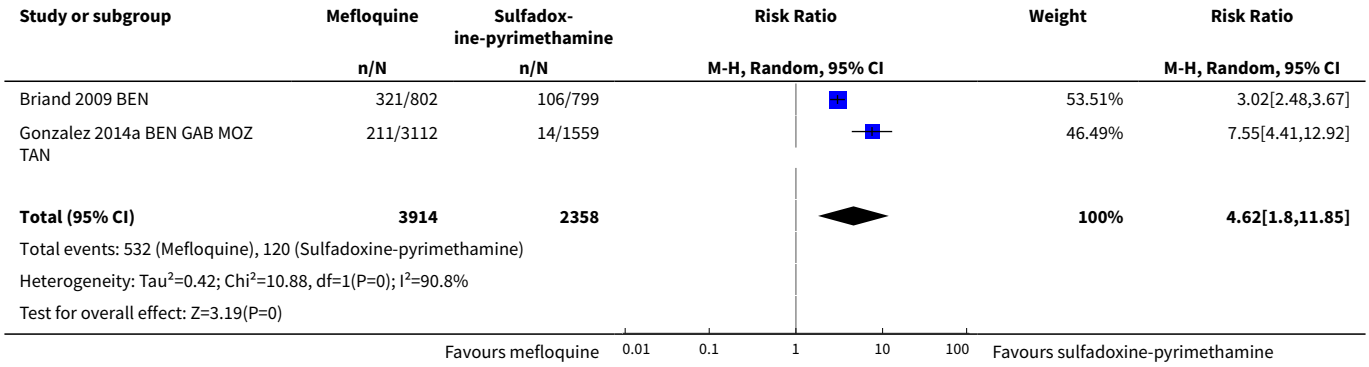
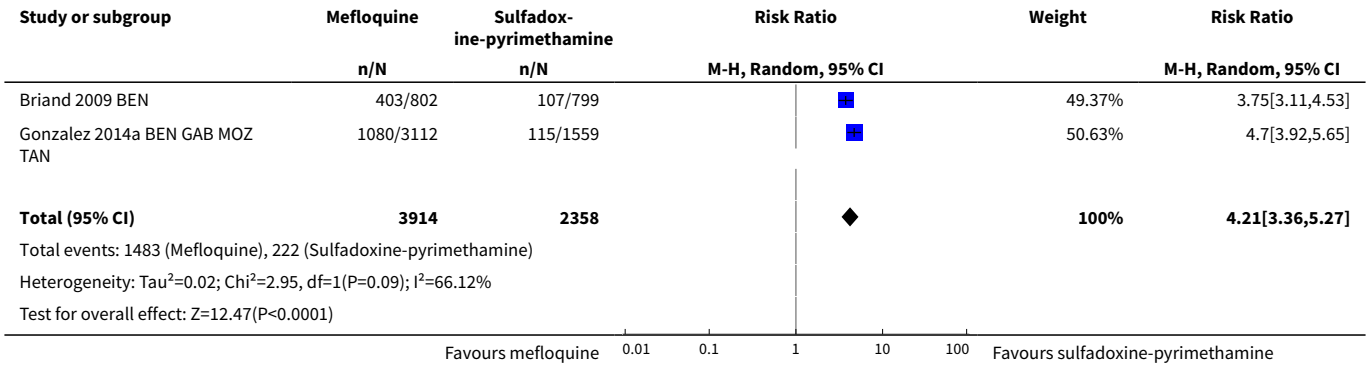


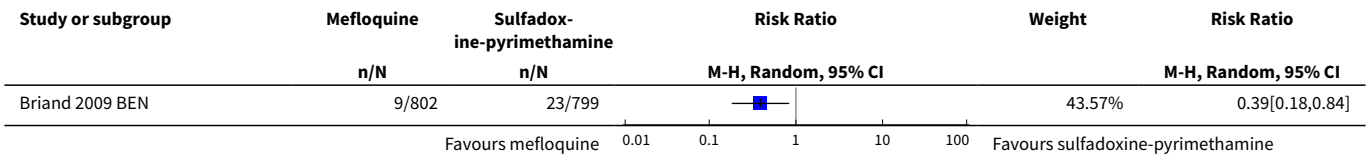
Analysis 1.22. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 22 AEs: fatigue/weakness.



Analysis 1.23. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 23 AEs: dizziness.



Analysis 1.24. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 24 AEs: headache.



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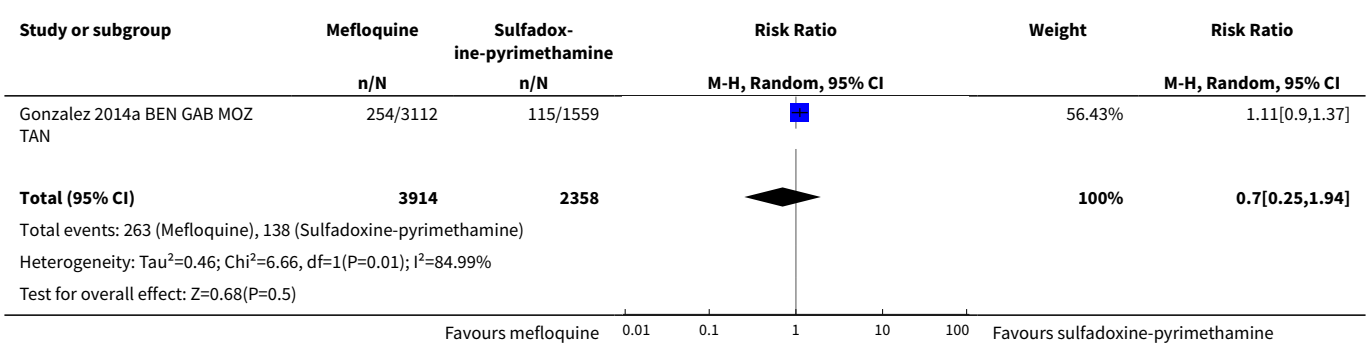

Comparison 2. Mefloquine plus cotrimoxazole versus cotrimoxazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical malaria episodes during pregnancy	1		Rate Ratio (Fixed, 95% CI)	0.76 [0.33, 1.76]
2 Maternal peripheral parasitaemia at delivery (PCR)	2	989	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.30, 0.93]
3 Placental malaria (blood smear)	2	1144	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.29, 0.89]
4 Placental malaria (PCR)	2	977	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.14, 0.57]
5 Mean haemoglobin at delivery	2	1167	Mean Difference (IV, Random, 95% CI)	0.07 [-0.32, 0.46]
6 Maternal anaemia at delivery (< 9.5 g/dL)	2	1197	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.73, 1.20]
7 Maternal severe anaemia at delivery	2	1167	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.41, 2.08]
8 Cord blood parasitaemia	2	1166	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.13]
9 Mean birth weight	2	1220	Mean Difference (IV, Random, 95% CI)	-25.75 [-86.99, 35.49]
10 Low birth weight	2	1220	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.60]
11 Prematurity	2	824	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.58, 1.96]
12 SAEs during pregnancy	2	1347	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.50, 0.95]
13 Spontaneous abortions and stillbirths	2	1347	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.42, 2.98]
14 Congenital malformations	2	1312	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.22, 1.67]
15 Maternal mortality	2	1347	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.13, 2.01]
16 Neonatal mortality	2	1239	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.65, 2.69]

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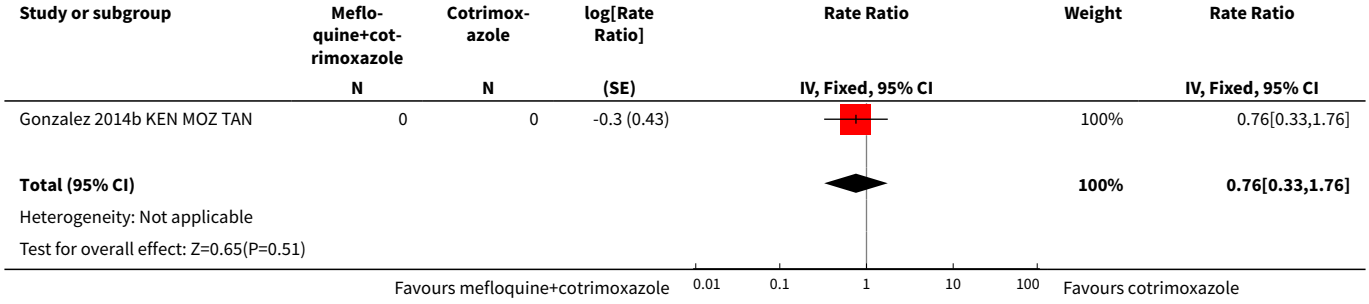
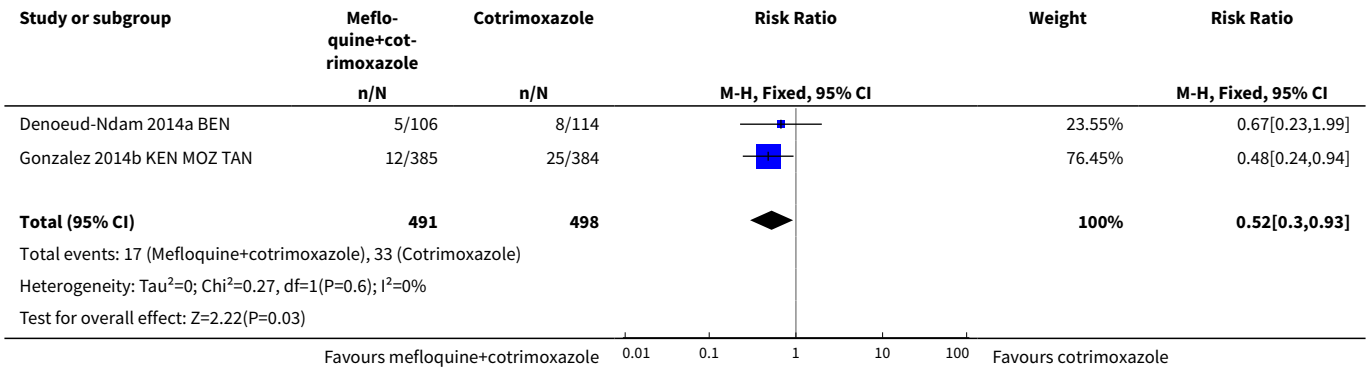
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
17 Mother-to-child transmission HIV	2	1019	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.13, 3.25]
18 AEs: vomiting	2	1347	Risk Ratio (M-H, Random, 95% CI)	20.88 [1.40, 311.66]
19 AEs: fatigue/weakness	2	1347	Risk Ratio (M-H, Random, 95% CI)	2.95 [0.26, 32.93]
20 AEs: dizziness	2	1347	Risk Ratio (M-H, Random, 95% CI)	16.34 [0.39, 684.99]
21 AEs: headache	2	1347	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.28, 2.10]

Analysis 2.1. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 1 Clinical malaria episodes during pregnancy.



Analysis 2.2. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 2 Maternal peripheral parasitaemia at delivery (PCR).



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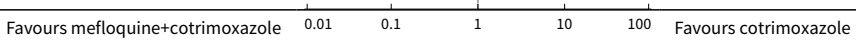
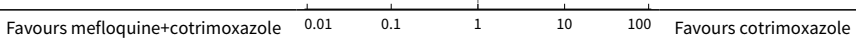
Analysis 2.3. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 3 Placental malaria (blood smear).

Study or subgroup	Mefloquine+cotrimoxazole n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a BEN	0/117	1/116		4.3%	0.33[0.01,8.03]
Gonzalez 2014b KEN MOZ TAN	17/449	34/462		95.7%	0.51[0.29,0.91]
Total (95% CI)	**566**	**578**		**100%**	**0.51[0.29,0.89]**
Total events: 17 (Mefloquine+cotrimoxazole), 35 (Cotrimoxazole)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%					
Test for overall effect: Z=2.39(P=0.02)					



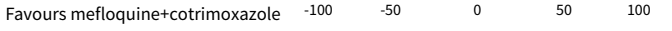
Analysis 2.4. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 4 Placental malaria (PCR).

Study or subgroup	Mefloquine+cotrimoxazole n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a BEN	0/105	5/103		16.42%	0.09[0,1.59]
Gonzalez 2014b KEN MOZ TAN	9/388	28/381		83.58%	0.32[0.15,0.66]
Total (95% CI)	**493**	**484**		**100%**	**0.28[0.14,0.57]**
Total events: 9 (Mefloquine+cotrimoxazole), 33 (Cotrimoxazole)					
Heterogeneity: Tau^2=0; Chi^2=0.71, df=1(P=0.4); I^2=0%					
Test for overall effect: Z=3.53(P=0)					



Analysis 2.5. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 5 Mean haemoglobin at delivery.

Study or subgroup	Mefloquine+cotrimoxazole N	Mean(SD)	Cotrimoxazole N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Denoeud-Ndam 2014a BEN	96	11.1 (1.4)	108	10.8 (1.5)		43.11%	0.3[-0.1,0.7]
Gonzalez 2014b KEN MOZ TAN	479	11.2 (2.1)	484	11.3 (2.2)		56.89%	-0.1[-0.37,0.17]
Total ***	**575**		**592**			**100%**	**0.07[-0.32,0.46]**
Heterogeneity: Tau^2=0.05; Chi^2=2.65, df=1(P=0.1); I^2=62.21%							
Test for overall effect: Z=0.37(P=0.71)							



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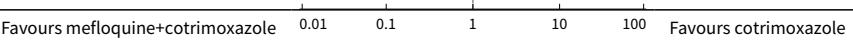
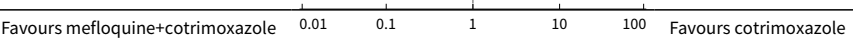
Analysis 2.6. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 6 Maternal anaemia at delivery (< 9.5 g/dL).

Study or subgroup	Mefloquine+cotrimoxazole n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a BEN	12/96	20/108		17.67%	0.68[0.35,1.31]
Gonzalez 2014b KEN MOZ TAN	87/495	88/498		82.33%	0.99[0.76,1.3]
Total (95% CI)	**591**	**606**		**100%**	**0.94[0.73,1.2]**
Total events: 99 (Mefloquine+cotrimoxazole), 108 (Cotrimoxazole)					
Heterogeneity: Tau^2=0; Chi^2=1.13, df=1(P=0.29); I^2=11.89%					
Test for overall effect: Z=0.5(P=0.61)					



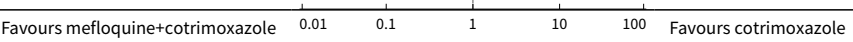
Analysis 2.7. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 7 Maternal severe anaemia at delivery.

Study or subgroup	Mefloquine+cotrimoxazole n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a BEN	0/96	0/108			Not estimable
Gonzalez 2014b KEN MOZ TAN	11/479	12/484		100%	0.93[0.41,2.08]
Total (95% CI)	**575**	**592**		**100%**	**0.93[0.41,2.08]**
Total events: 11 (Mefloquine+cotrimoxazole), 12 (Cotrimoxazole)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.19(P=0.85)					



Analysis 2.8. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 8 Cord blood parasitaemia.

Study or subgroup	Mefloquine+cotrimoxazole n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a BEN	0/117	0/116			Not estimable
Gonzalez 2014b KEN MOZ TAN	1/471	3/462		100%	0.33[0.03,3.13]
Total (95% CI)	**588**	**578**		**100%**	**0.33[0.03,3.13]**
Total events: 1 (Mefloquine+cotrimoxazole), 3 (Cotrimoxazole)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.97(P=0.33)					



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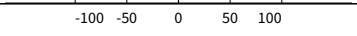
Analysis 2.9. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 9 Mean birth weight.

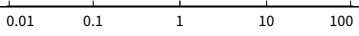
Study or subgroup	Mefloquine+cotrimoxazole N	Mefloquine+cotrimoxazole Mean(SD)	Cotrimoxazole N	Cotrimoxazole Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Denoeud-Ndam 2014a BEN	119	2856 (454)	126	2889 (478)		27.54%	-33[-149.7,83.7]
Gonzalez 2014b KEN MOZ TAN	489	3036.3 (570.6)	486	3059.3 (575.5)		72.46%	-23[-94.94,48.94]
Total ***	**608**		**612**			**100%**	**-25.75[-86.99,35.49]**
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.89); I²=0%							
Test for overall effect: Z=0.82(P=0.41)							



Favours mefloquine+cotrimoxazole — Favours cotrimoxazole

Analysis 2.10. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 10 Low birth weight.

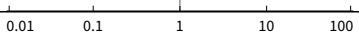
Study or subgroup	Mefloquine+cotrimoxazole n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a BEN	24/119	26/126		35.37%	0.98[0.6,1.6]
Gonzalez 2014b KEN MOZ TAN	61/489	46/486		64.63%	1.32[0.92,1.89]
Total (95% CI)	**608**	**612**		**100%**	**1.2[0.89,1.6]**
Total events: 85 (Mefloquine+cotrimoxazole), 72 (Cotrimoxazole)					
Heterogeneity: Tau²=0; Chi²=0.92, df=1(P=0.34); I²=0%					
Test for overall effect: Z=1.21(P=0.23)					



Favours mefloquine+cotrimoxazole — Favours cotrimoxazole

Analysis 2.11. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 11 Prematurity.

Study or subgroup	Mefloquine+cotrimoxazole n/N	Cotrimoxazole n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Denoeud-Ndam 2014a BEN	16/125	20/130		59.9%	0.83[0.45,1.53]
Gonzalez 2014b KEN MOZ TAN	14/284	9/285		40.1%	1.56[0.69,3.55]
Total (95% CI)	**409**	**415**		**100%**	**1.07[0.58,1.96]**
Total events: 30 (Mefloquine+cotrimoxazole), 29 (Cotrimoxazole)					
Heterogeneity: Tau²=0.06; Chi²=1.46, df=1(P=0.23); I²=31.52%					
Test for overall effect: Z=0.22(P=0.82)					



Favours mefloquine+cotrimoxazole — Favours cotrimoxazole

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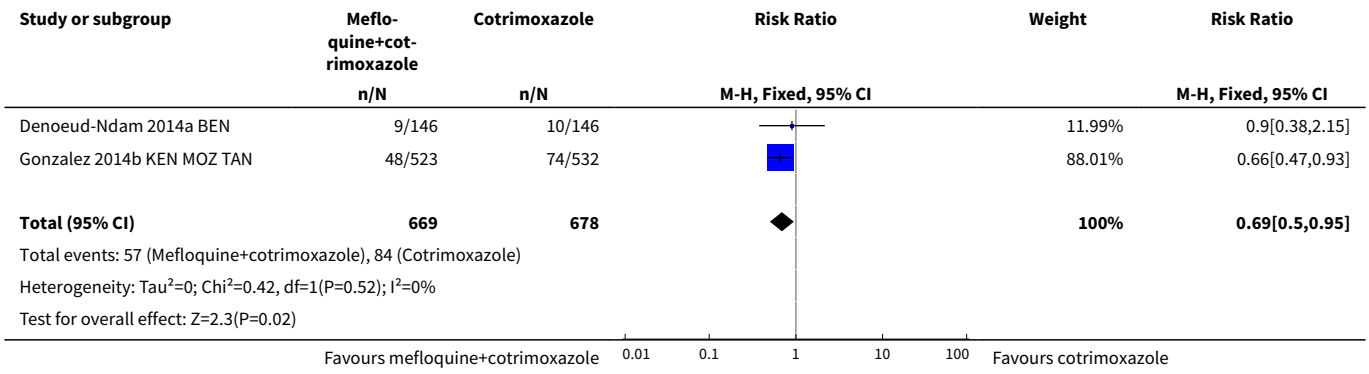
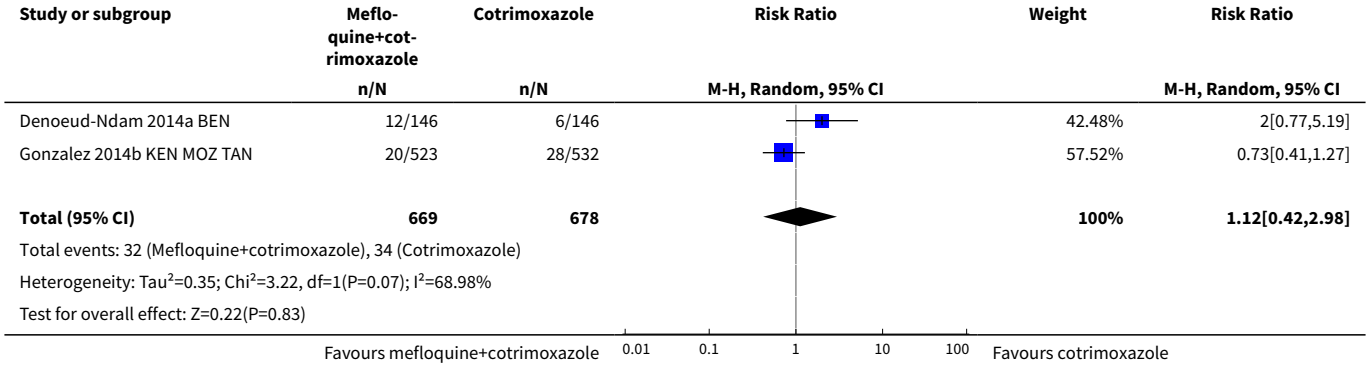
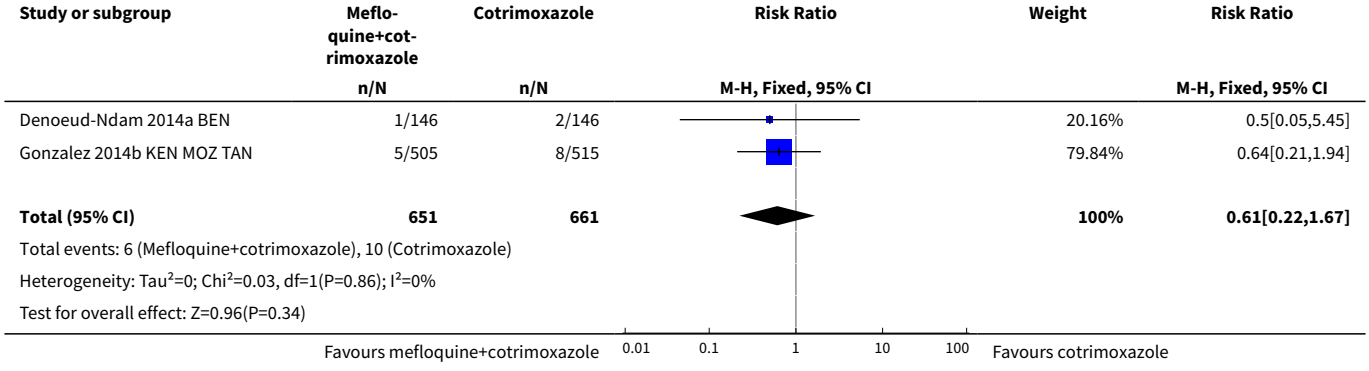
Analysis 2.12. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 12 SAEs during pregnancy.



Analysis 2.13. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 13 Spontaneous abortions and stillbirths.



Analysis 2.14. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 14 Congenital malformations.



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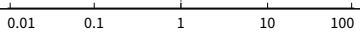
Analysis 2.15. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 15 Maternal mortality.

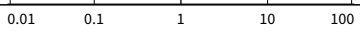
Study or subgroup	Mefloquine+cotrimoxazole n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a BEN	1/146	2/146		33.52%	0.5[0.05,5.45]
Gonzalez 2014b KEN MOZ TAN	2/523	4/532		66.48%	0.51[0.09,2.76]
Total (95% CI)	**669**	**678**		**100%**	**0.51[0.13,2.01]**
Total events: 3 (Mefloquine+cotrimoxazole), 6 (Cotrimoxazole)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					



Favours mefloquine+cotrimoxazole — Favours cotrimoxazole

Analysis 2.16. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 16 Neonatal mortality.

Study or subgroup	Mefloquine+cotrimoxazole n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a BEN	4/129	3/130		23.08%	1.34[0.31,5.88]
Gonzalez 2014b KEN MOZ TAN	13/488	10/492		76.92%	1.31[0.58,2.96]
Total (95% CI)	**617**	**622**		**100%**	**1.32[0.65,2.69]**
Total events: 17 (Mefloquine+cotrimoxazole), 13 (Cotrimoxazole)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					
Test for overall effect: Z=0.76(P=0.45)					



Favours mefloquine+cotrimoxazole — Favours cotrimoxazole

Analysis 2.17. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 17 Mother-to-child transmission HIV.

Study or subgroup	Mefloquine+cotrimoxazole n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a BEN	1/80	1/84		4.97%	1.05[0.07,16.5]
Gonzalez 2014b KEN MOZ TAN	36/420	19/435		95.03%	1.96[1.14,3.37]
Total (95% CI)	**500**	**519**		**100%**	**1.92[1.13,3.25]**
Total events: 37 (Mefloquine+cotrimoxazole), 20 (Cotrimoxazole)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.66); I^2=0%					
Test for overall effect: Z=2.41(P=0.02)					

Favours mefloquine+cotrimoxazole — Favours cotrimoxazole

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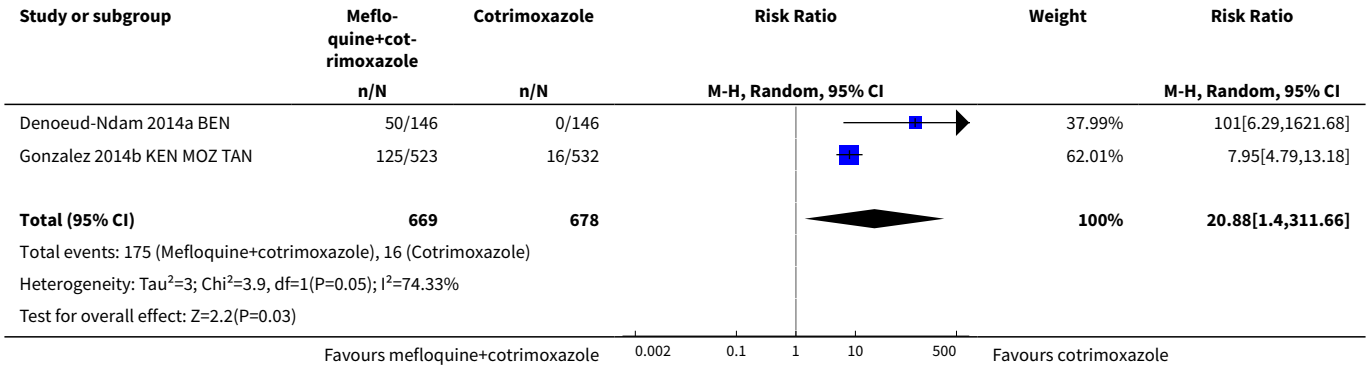
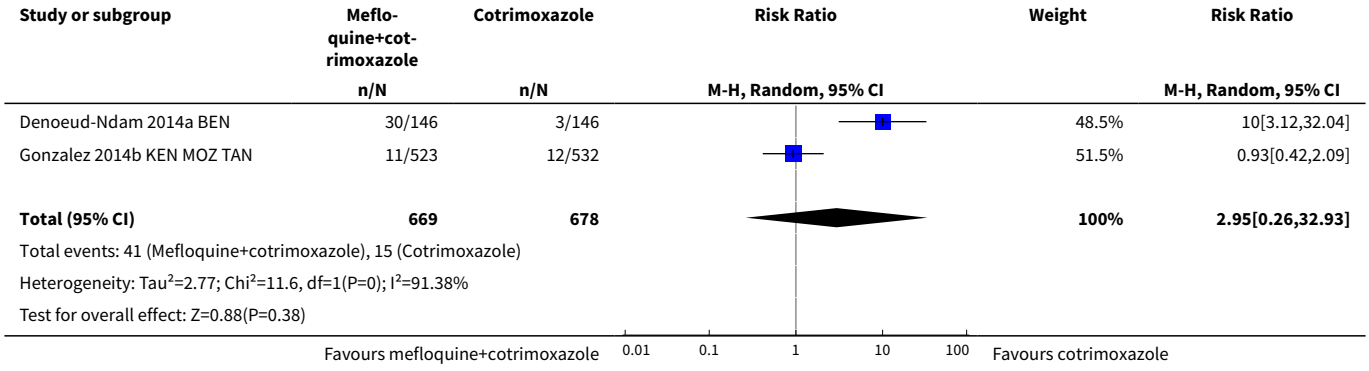
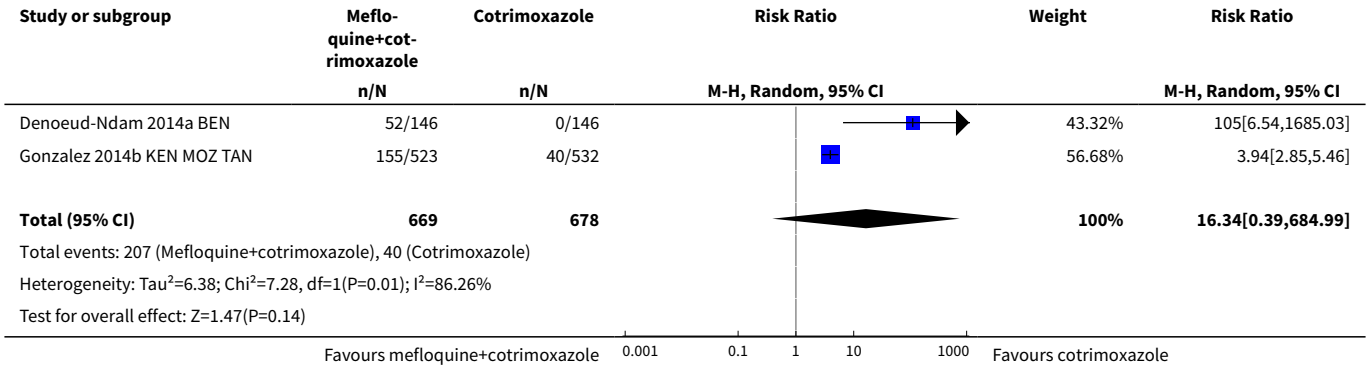
Analysis 2.18. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 18 AEs: vomiting.



Analysis 2.19. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 19 AEs: fatigue/weakness.



Analysis 2.20. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 20 AEs: dizziness.



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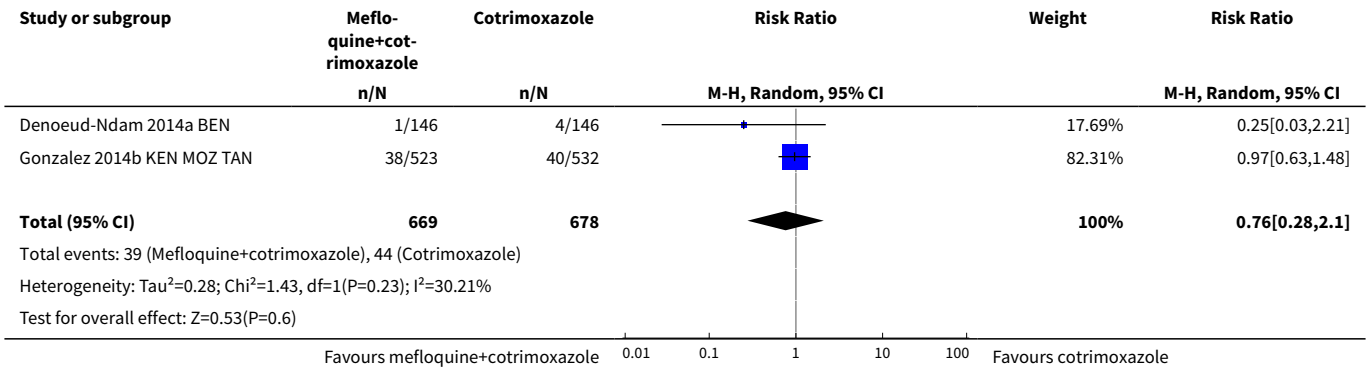
Analysis 2.21. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 21 AEs: headache.



Comparison 3. Mefloquine versus cotrimoxazole

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal peripheral parasitaemia at delivery (PCR)	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.03, 1.72]
2 Placental malaria (PCR)	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.13, 4.15]
3 Placental malaria (blood smear)	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.30]
4 Mean haemoglobin at delivery	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.67, 0.47]
5 Maternal anaemia at delivery (< 9.5 g/dL)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.26, 3.16]
6 Mean birth weight	1	120	Mean Difference (IV, Fixed, 95% CI)	-102.0 [-255.52, 51.52]
7 Low birth weight	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.56, 4.13]
8 Prematurity	1	125	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.33, 3.56]
9 SAEs during pregnancy	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.28, 4.07]
10 Stillbirths	1	139	Risk Ratio (M-H, Fixed, 95% CI)	4.30 [0.49, 37.49]
11 Spontaneous abortions	1	139	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.07, 16.84]
12 Congenital malformations	1	139	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.16, 7.41]
13 Maternal mortality	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Neonatal mortality	1	129	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.07, 16.39]
15 Infant deaths after 7 days	1	129	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [0.19, 22.54]

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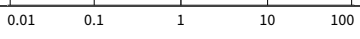
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 AEs: vomiting	1	139	Risk Ratio (M-H, Fixed, 95% CI)	13.43 [3.31, 54.54]
17 AEs: fatigue/weakness	1	139	Risk Ratio (M-H, Fixed, 95% CI)	6.99 [1.64, 29.81]
18 AEs: dizziness	1	139	Risk Ratio (M-H, Fixed, 95% CI)	52.60 [3.26, 848.24]
19 AEs: headache	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.39]

Analysis 3.1. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 1 Maternal peripheral parasitaemia at delivery (PCR).

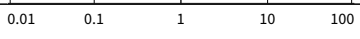
Study or subgroup	Mefloquine n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b BEN	1/48	5/50		100%	0.21[0.03,1.72]
Total (95% CI)	**48**	**50**		**100%**	**0.21[0.03,1.72]**
Total events: 1 (Mefloquine), 5 (Cotrimoxazole)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.46(P=0.15)					



Favours mefloquine — Favours cotrimoxazole

Analysis 3.2. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 2 Placental malaria (PCR).

Study or subgroup	Mefloquine n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b BEN	2/45	3/49		100%	0.73[0.13,4.15]
Total (95% CI)	**45**	**49**		**100%**	**0.73[0.13,4.15]**
Total events: 2 (Mefloquine), 3 (Cotrimoxazole)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.36(P=0.72)					



Favours mefloquine — Favours cotrimoxazole

Analysis 3.3. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 3 Placental malaria (blood smear).

Study or subgroup	Mefloquine n/N	Cotrimoxazole n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b BEN	0/53	1/55		100%	0.35[0.01,8.3]
Total (95% CI)	**53**	**55**		**100%**	**0.35[0.01,8.3]**
Total events: 0 (Mefloquine), 1 (Cotrimoxazole)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.51)					

Favours mefloquine — Favours cotrimoxazole

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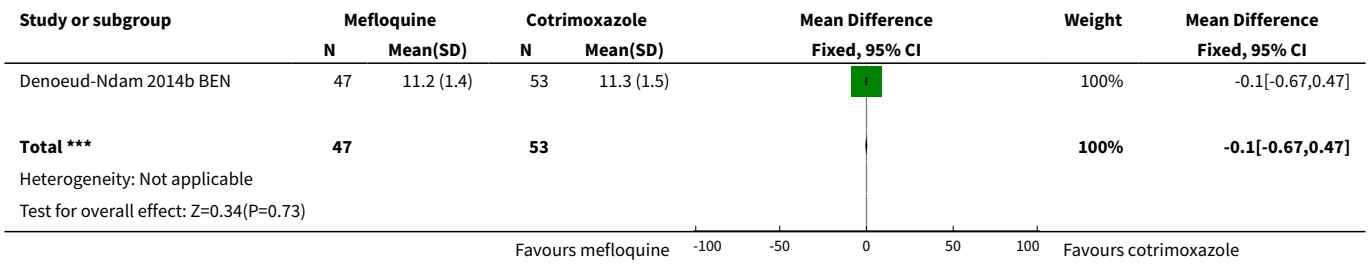
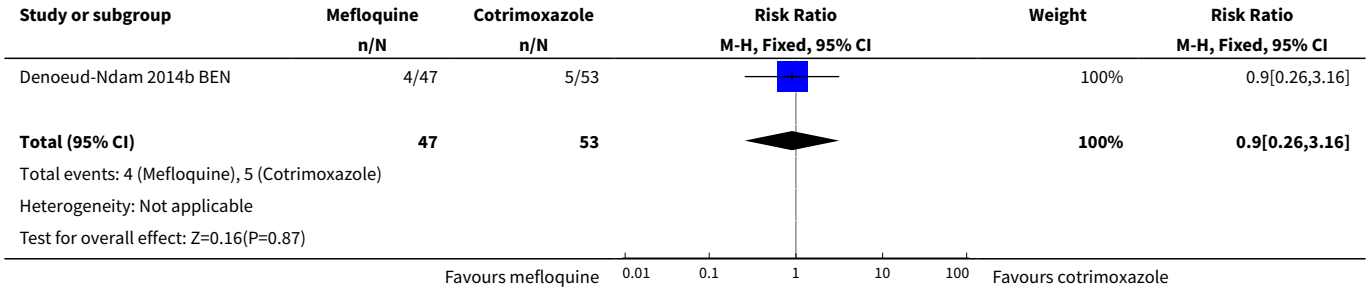
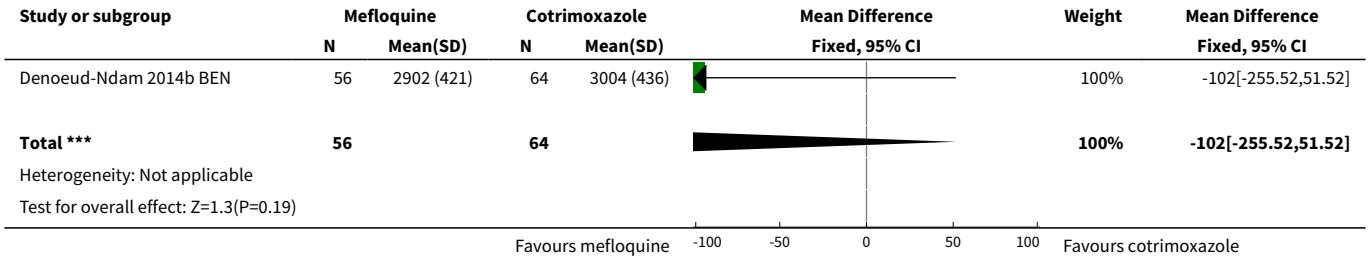
Analysis 3.4. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 4 Mean haemoglobin at delivery.



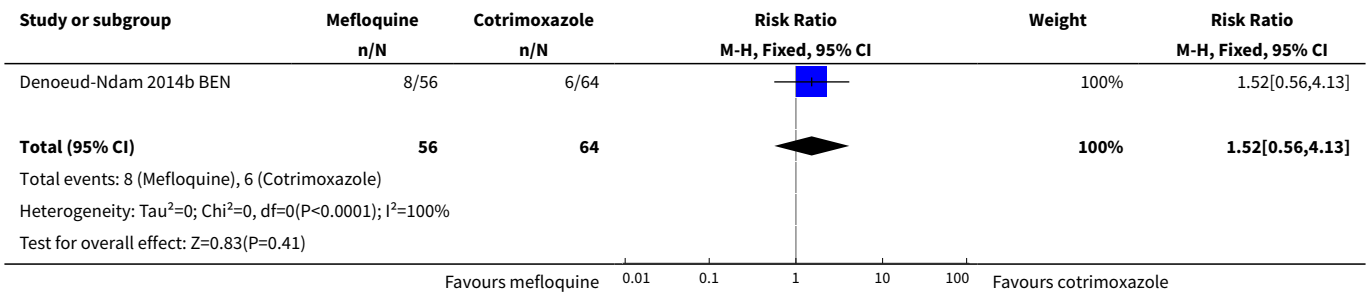
Analysis 3.5. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 5 Maternal anaemia at delivery (< 9.5 g/dL).



Analysis 3.6. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 6 Mean birth weight.



Analysis 3.7. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 7 Low birth weight.



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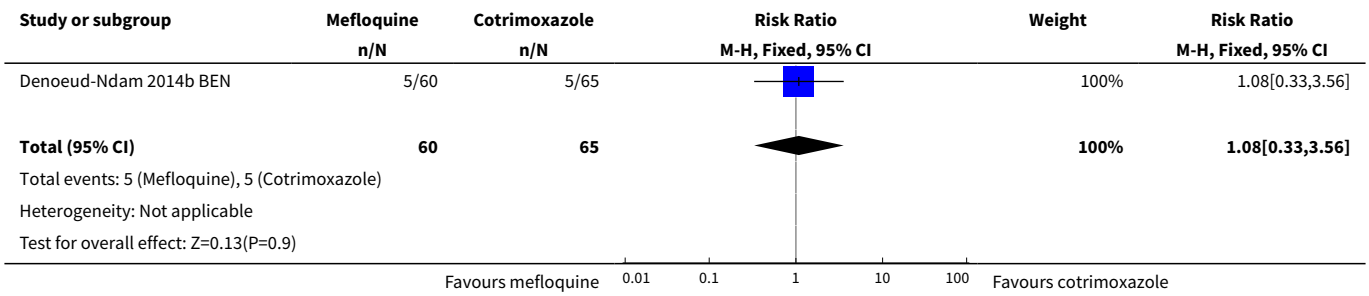
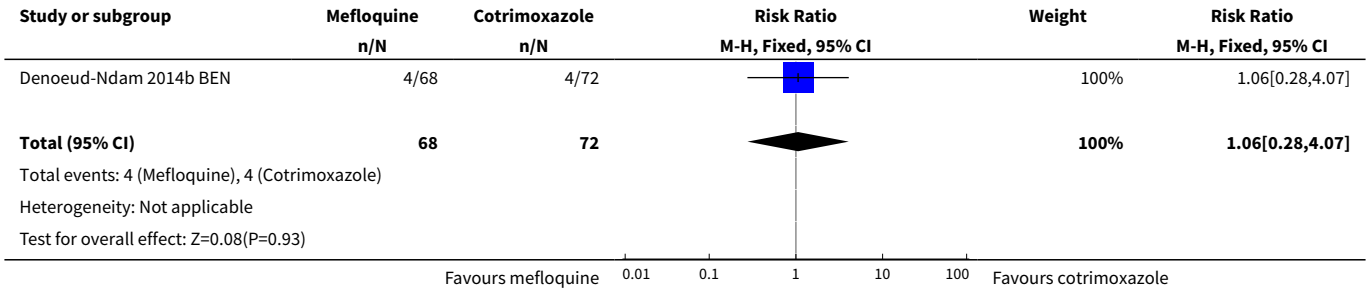
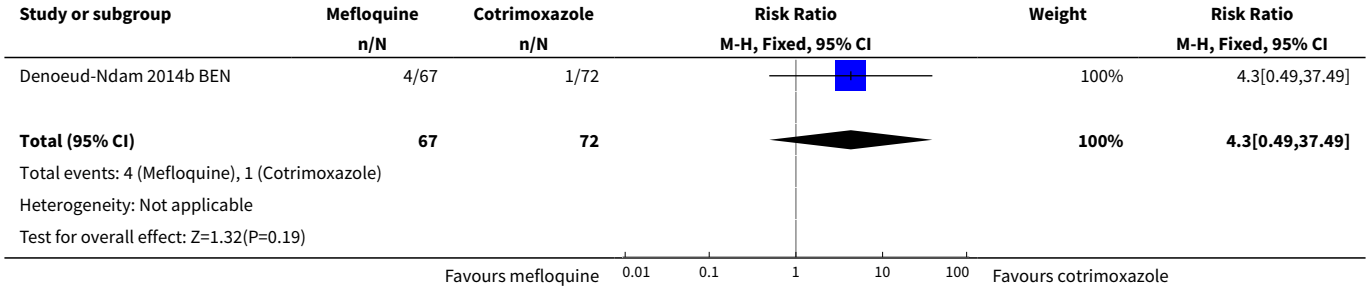
Analysis 3.8. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 8 Prematurity.



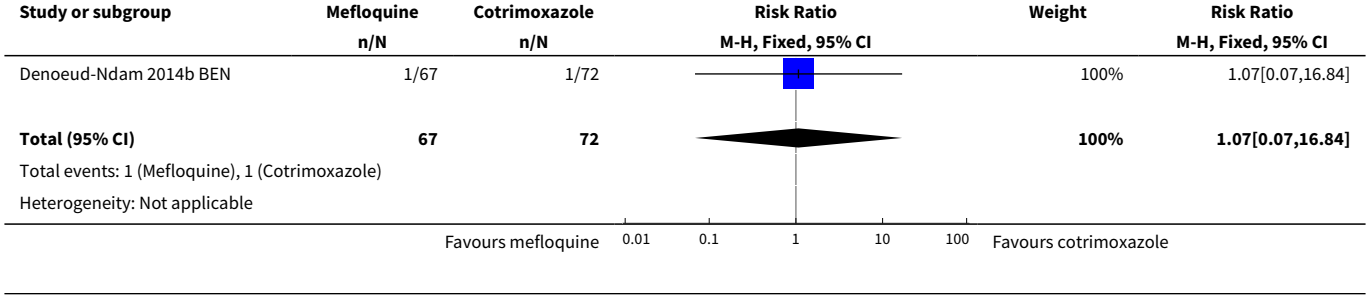
Analysis 3.9. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 9 SAEs during pregnancy.



Analysis 3.10. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 10 Stillbirths.



Analysis 3.11. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 11 Spontaneous abortions.



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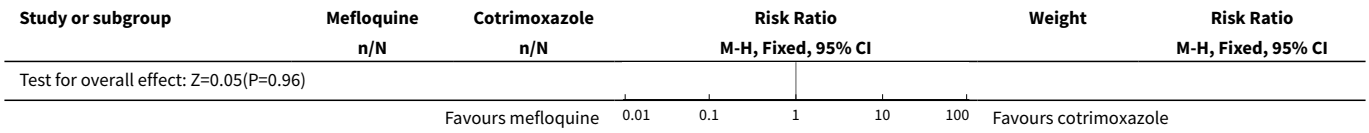
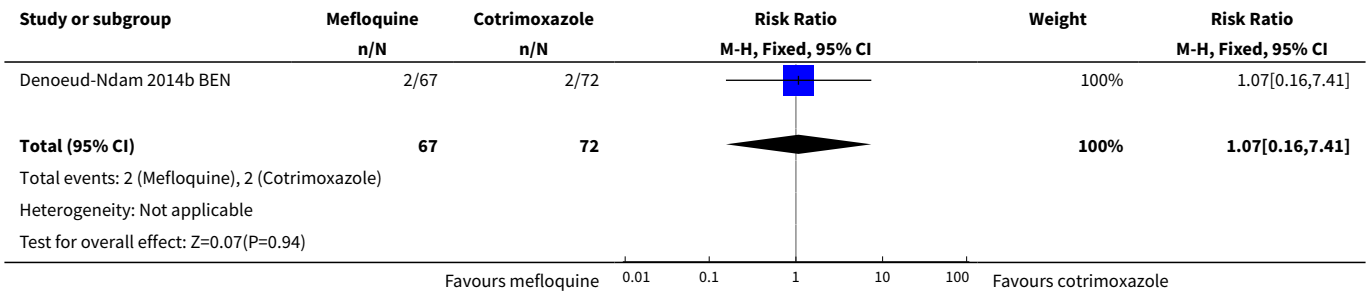
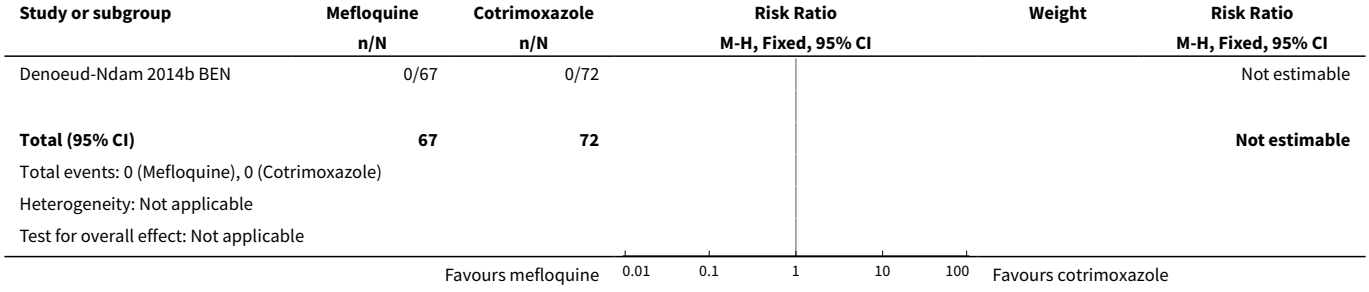


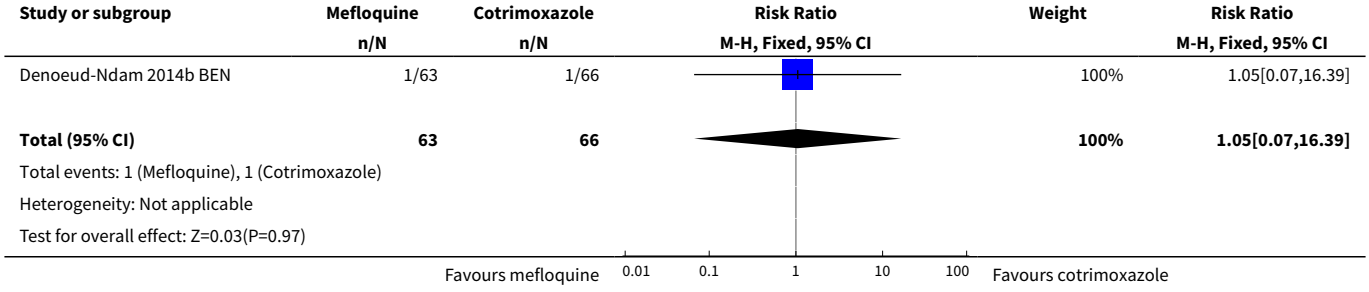
Analysis 3.12. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 12 Congenital malformations.



Analysis 3.13. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 13 Maternal mortality.



Analysis 3.14. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 14 Neonatal mortality.



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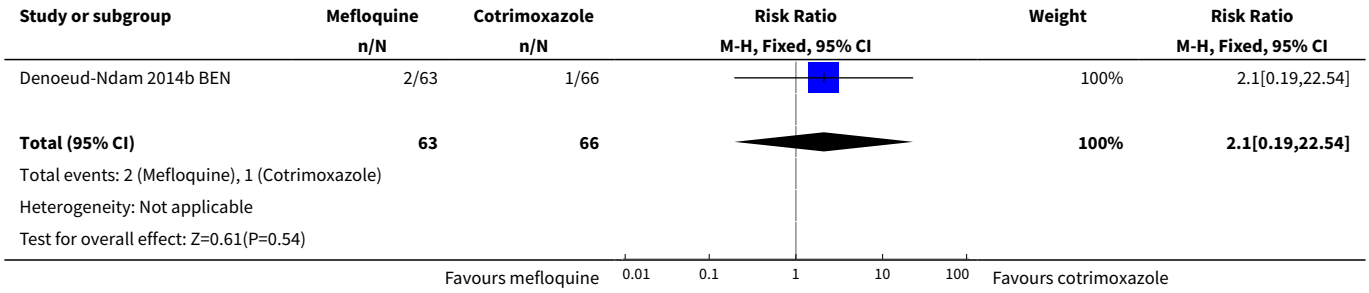
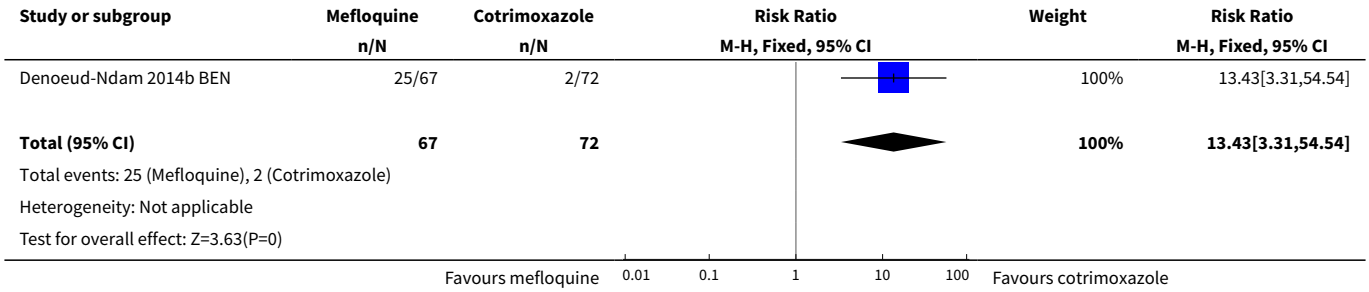
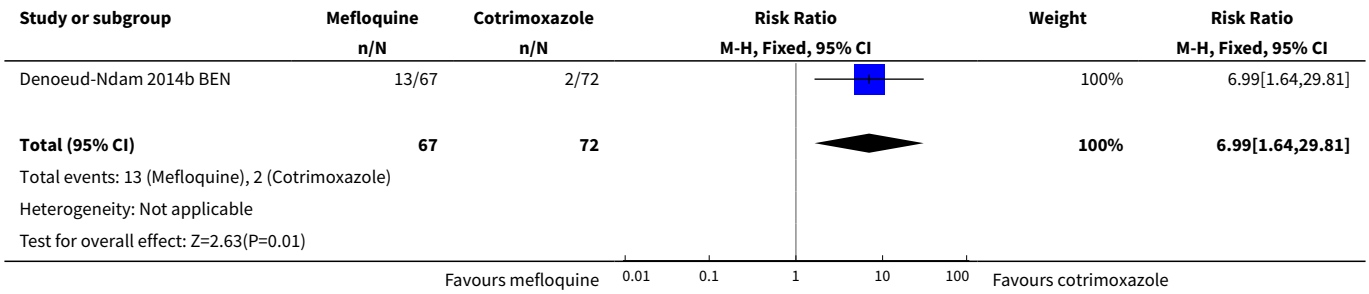
Analysis 3.15. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 15 Infant deaths after 7 days.



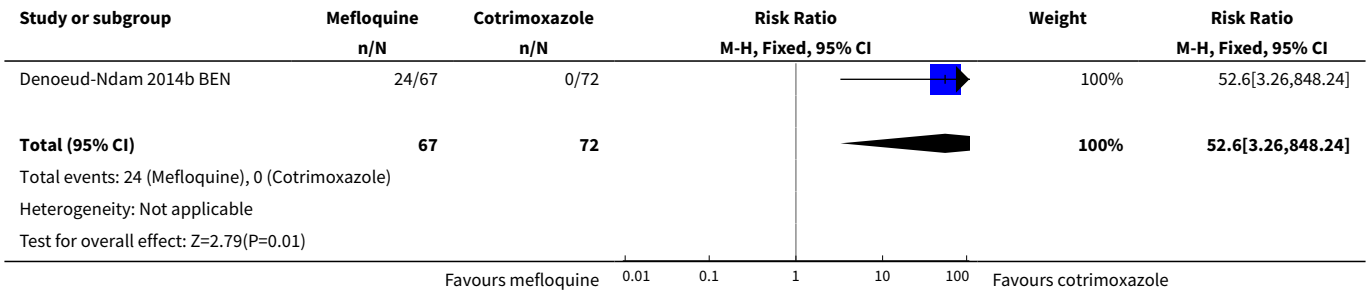
Analysis 3.16. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 16 AEs: vomiting.



Analysis 3.17. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 17 AEs: fatigue/weakness.



Analysis 3.18. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 18 AEs: dizziness.



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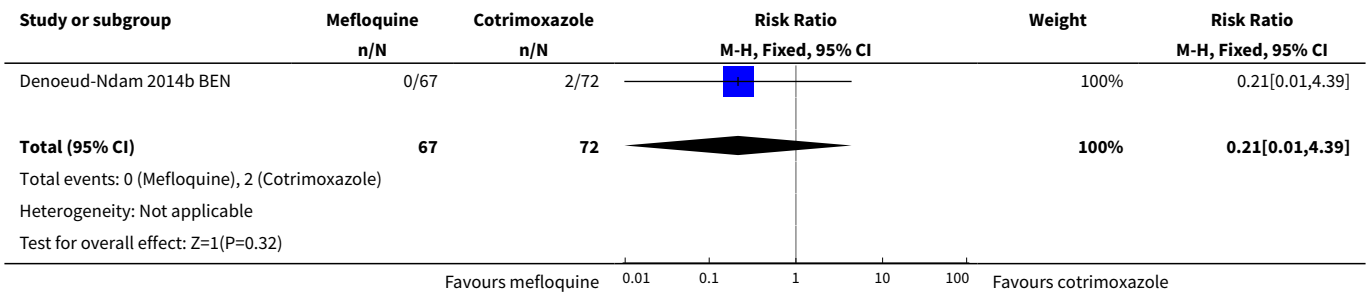
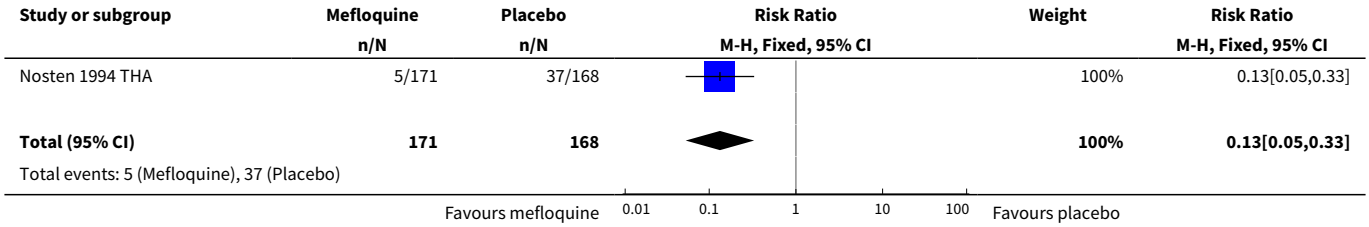
Analysis 3.19. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 19 AEs: headache.



Comparison 4. Mefloquine versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Maternal peripheral parasitaemia during pregnancy	1	339	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.05, 0.33]
2 Placental malaria	1	220	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.68]
3 Mean birth weight	1	290	Mean Difference (IV, Fixed, 95% CI)	-80.0 [-184.65, 24.65]
4 Low birth weight	1	290	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.78, 2.48]
5 Prematurity	1	199	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.15, 1.53]
6 Stillbirths	1	311	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [0.86, 8.08]
7 Spontaneous abortions	1	311	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.22]
8 Congenital malformations	1	311	Risk Ratio (M-H, Fixed, 95% CI)	3.82 [0.43, 33.83]
9 Maternal mortality	1	339	Risk Ratio (M-H, Fixed, 95% CI)	2.95 [0.12, 71.85]
10 Infant mortality	1	288	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.63, 1.74]

Analysis 4.1. Comparison 4 Mefloquine versus placebo, Outcome 1 Maternal peripheral parasitaemia during pregnancy.



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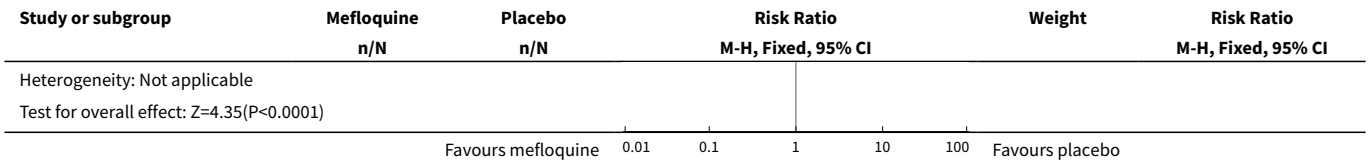
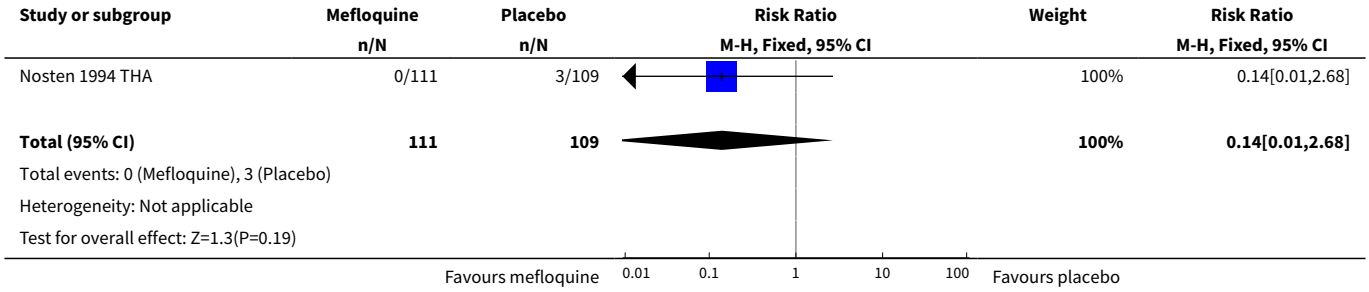
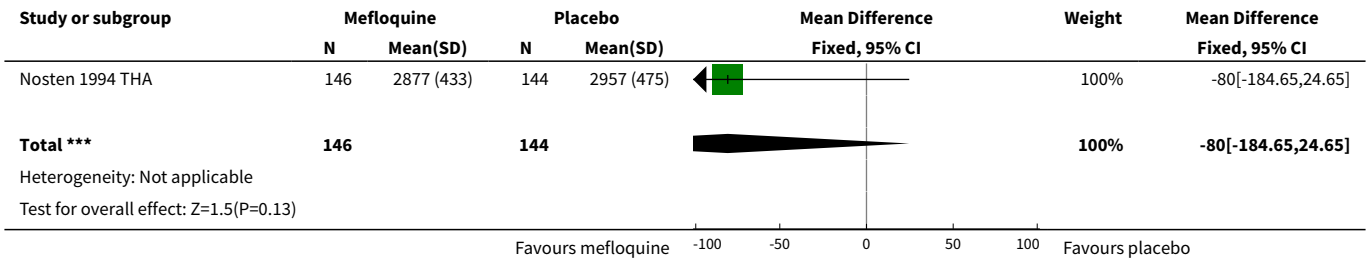


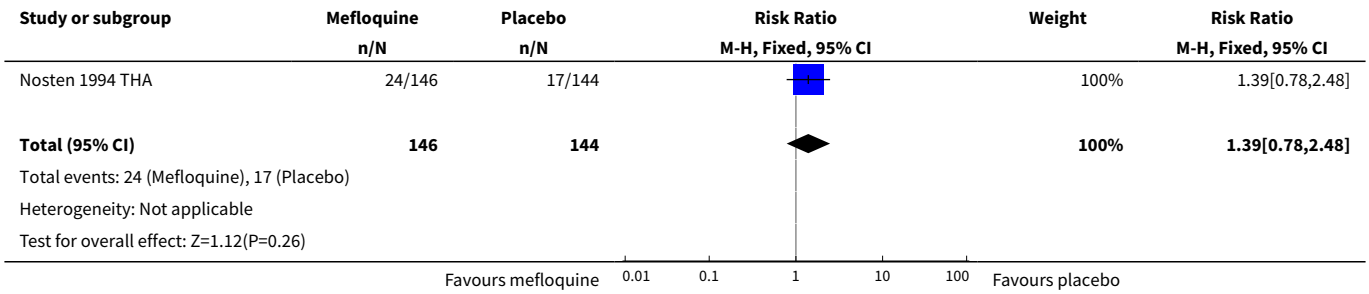
Analysis 4.2. Comparison 4 Mefloquine versus placebo, Outcome 2 Placental malaria.



Analysis 4.3. Comparison 4 Mefloquine versus placebo, Outcome 3 Mean birth weight.



Analysis 4.4. Comparison 4 Mefloquine versus placebo, Outcome 4 Low birth weight.



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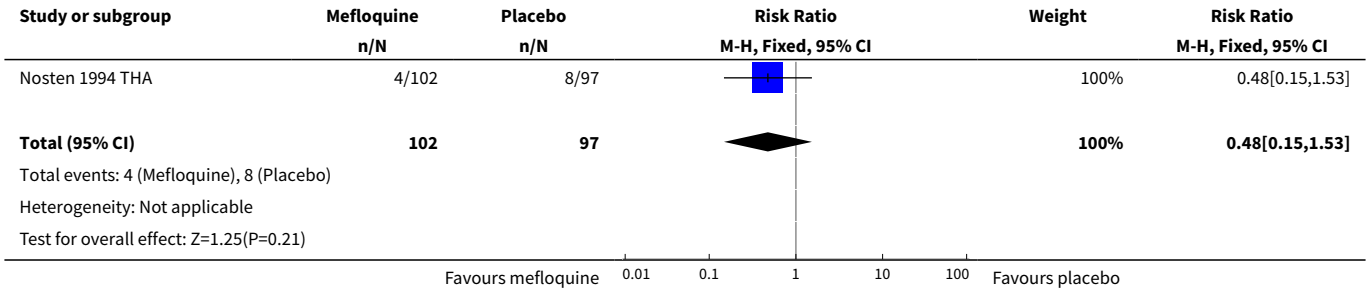
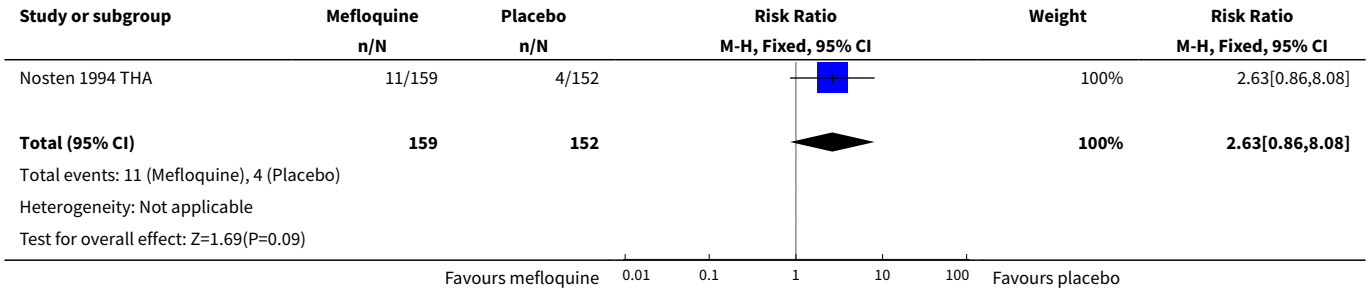
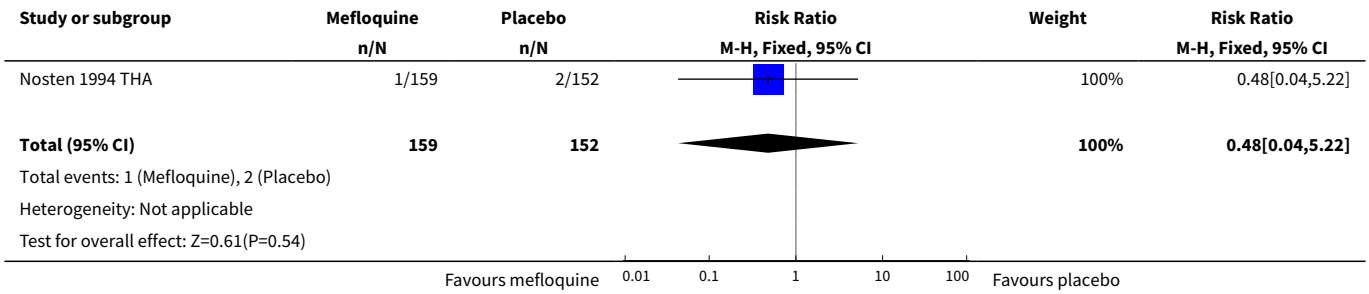
Analysis 4.5. Comparison 4 Mefloquine versus placebo, Outcome 5 Prematurity.



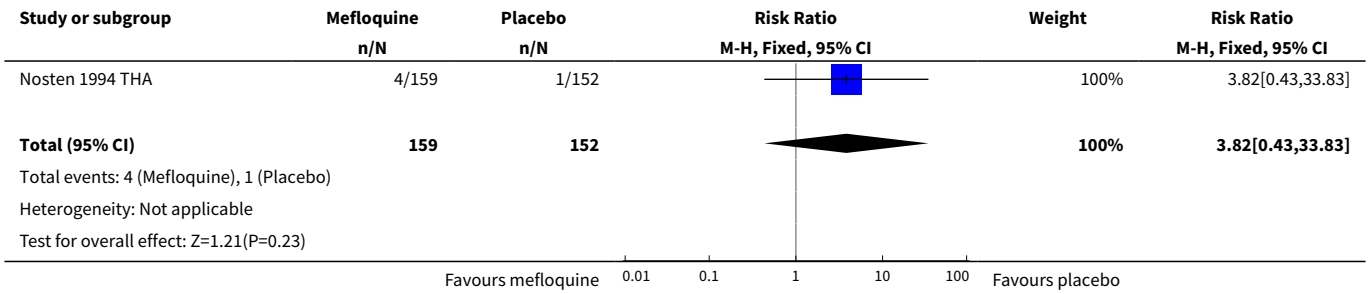
Analysis 4.6. Comparison 4 Mefloquine versus placebo, Outcome 6 Stillbirths.



Analysis 4.7. Comparison 4 Mefloquine versus placebo, Outcome 7 Spontaneous abortions.



Analysis 4.8. Comparison 4 Mefloquine versus placebo, Outcome 8 Congenital malformations.



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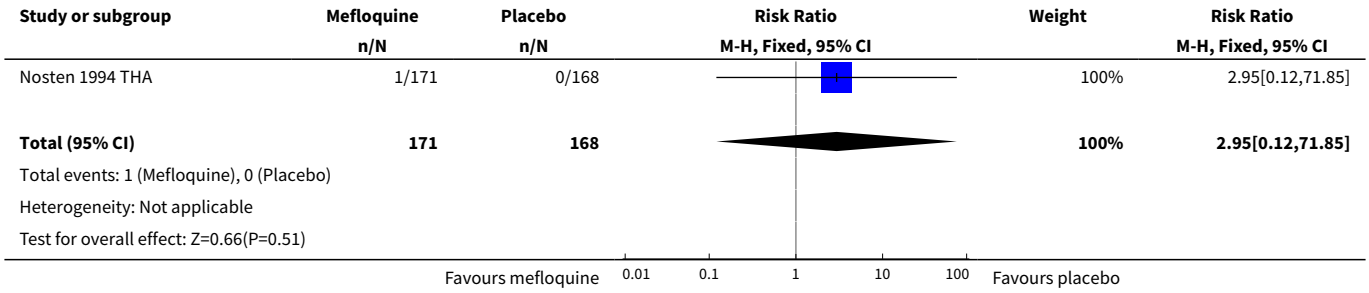
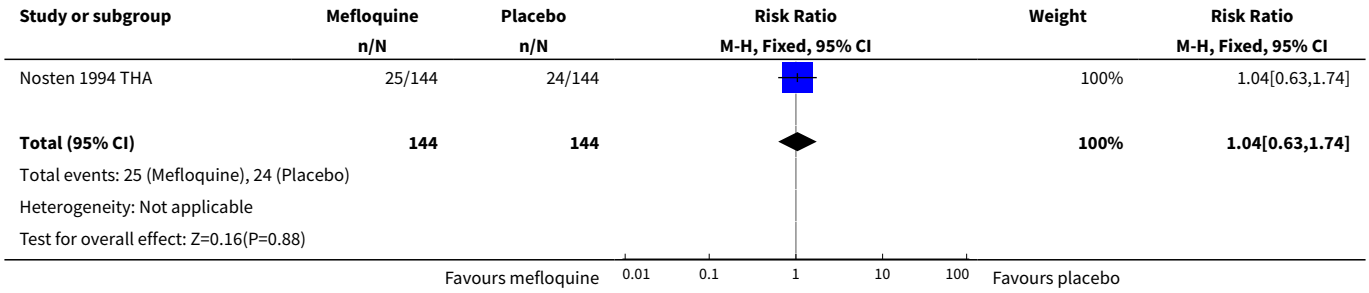
Analysis 4.9. Comparison 4 Mefloquine versus placebo, Outcome 9 Maternal mortality.



Analysis 4.10. Comparison 4 Mefloquine versus placebo, Outcome 10 Infant mortality.



APPENDICES

Appendix 1. Search strategies

Search set	CIDG Specialized Register	CENTRAL	MEDLINE	Embase	LILACS
1	malaria	Malaria ti, ab, MeSH	Malaria ti, ab, MeSH	Malaria ti, ab, Emtree	malaria
2	Mefloquine OR Lariam	Mefloquine ti, ab, MeSH	Mefloquine ti, ab, MeSH	Mefloquine ti, ab, Emtree	Mefloquine
3	Pregnan*	Lariam ti, ab	Lariam ti, ab	Lariam ti, ab	Lariam
4	1 and 2 and 3	2 or 3	2 or 3	2 or 3	2 or 3
5	-	1 and 4	1 and 4	1 and 4	1 and 4
6	-	Pregnan* ti, ab	Pregnan* ti, ab	Pregnan* ti, ab	Pregnan$
7	-	Pregnancy [Mesh]	Pregnancy [Mesh]	Pregnancy [Emtree]	5 and 6
8	-	6 or 7	6 or 7	6 or 7	-

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(Continued)

9	-	5 and 8	5 and 8	5 and 8	-

WHAT'S NEW

Date	Event	Description
12 November 2018	Amended	Following feedback from the Cochrane Editorial and Methods department, the review authors checked and corrected the GRADE assessments, 'Summary of findings' tables, and review text for consistency.
12 November 2018	New citation required and conclusions have changed	Due to inconsistencies between the review sections, we corrected the GRADE assessments and review text.

CONTRIBUTIONS OF AUTHORS

RG, JJA, FtK, and CM designed the study. RG, JJA, and FtK wrote the protocol. RG, CPD, and MP assessed trial eligibility and risk of bias. RG, CPD, and MP extracted data. RG and CPD performed analyses. RG and CPD wrote the first version of the review. All review authors interpreted trial results, contributed to writing of this review, and approved the final version of the review.

DECLARATIONS OF INTEREST

RG, JJA, and CM are authors of two trials of mefloquine to prevent malaria in pregnancy (published in 2014) that are candidates for inclusion in this review.
MP has no known conflicts of interest.
CPD has no known conflicts of interest.
FtK has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Barcelona Institute of Global Health (ISGlobal), Hospital Clínic- Universitat de Barcelona, Spain.
- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

  Grant: 5242

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we indicated that for the safety evaluation of mefloquine in pregnancy, we would include studies that used mefloquine to prevent malaria in pregnant women travelling to malaria-endemic areas. However, evaluation of mefloquine safety compared with the safety of other antimalarials was not possible because of the study design employed by retrieved studies. Consequently, no observational studies met the inclusion criteria and only randomized controlled trials met the inclusion criteria of this review.

In the protocol, we listed neonatal morbidity in the first 28 days of life as an analysis outcome. Similarly, we listed mean haemoglobin and maternal anaemia during pregnancy were as outcomes. However, the included trials did not report on these effects; consequently, we were unable to perform the analyses.

One included trial reported an unexpected increased risk of mother-to-child transmission (MTCT) of HIV associated with IPTp-mefloquine. Given the clinical relevance of this finding, we included the frequency of MTCT of HIV as an outcome of the analysis.

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INDEX TERMS

Medical Subject Headings (MeSH)

Anemia [epidemiology]; Antimalarials [adverse effects] [*therapeutic use]; Drug Combinations; Drug Therapy, Combination; HIV Seronegativity; Malaria [*prevention & control]; Mefloquine [adverse effects] [*therapeutic use]; Parasitemia [drug therapy]; Placenta Diseases [epidemiology] [parasitology]; Pregnancy Complications [chemically induced]; Pregnancy Complications, Infectious [epidemiology] [*prevention & control]; Pyrimethamine [therapeutic use]; Randomized Controlled Trials as Topic; Stillbirth; Sulfadoxine [therapeutic use]; Trimethoprim, Sulfamethoxazole Drug Combination [therapeutic use]; Vomiting [chemically induced]

MeSH check words

Female; Humans; Pregnancy

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