Mefloquine for preventing malaria in pregnant women  
(Review)

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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 In addition, we checked references and contacted study authors to identify additional studies, unpublished data, confidential reports, and raw data from published trials.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.

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 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; I² statistic = 0%; high-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; high-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; high-certainty evidence) but has little or no effect on the incidence of clinical malaria episodes during pregnancy (IRR 0.83, 95% CI 0.65 to 1.05, 2 studies; high-certainty evidence). Mefloquine decreased maternal anaemia at delivery (RR 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.

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.

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 cotrimoxazole 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.
### SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

**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-pyrimethamine** | **Risk with mefloquine** | **Number of participants** | **Certainty of the evidence** | **Comments** | |
| Clinical malaria episodes during pregnancy | - | - | IRR 0.83 (0.65 to 1.05) | (2 RCTs) | ⚫⚫⚫ HIGH | Mefloquine results in little or no difference in the incidence of clinical malaria episodes during pregnancy |
| Maternal peripheral parasitaemia at delivery | 43 per 1000 (20 to 37) | 28 per 1000 (20 to 37) | RR 0.65 (0.48 to 0.86) | 5455 (2 RCTs) | ⚫⚫⚫ HIGH | Mefloquine results in lower maternal peripheral parasitaemia at delivery |
| Placental malaria | 52 per 1000 (30 to 97) | 54 per 1000 (30 to 97) | RR 1.04 (0.58 to 1.86) | 4668 (2 RCTs) | ⚫⚫⚫ LOW | Mefloquine may result in little or no difference in placental parasitaemia |
| Maternal anaemia at delivery | 219 per 1000 (166 to 206) | 184 per 1000 (166 to 206) | RR 0.84 (0.76 to 0.94) | 5469 (2 RCTs) | ⚫⚫⚫ MODERATE | Mefloquine probably results in fewer women anaemic at delivery |
| Outcome                          | Risk Intervention Group | Risk Comparison Group | RR   | 95% CI     | GRADE | Comment                                                                 |
|---------------------------------|-------------------------|-----------------------|------|------------|-------|-------------------------------------------------------------------------|
| Low birth weight                | 117 per 1000            | 111 per 1000 (91 to 137) | RR 0.95 | (0.78 to 1.17) | ⊕⊕⊕⊕ | HIGH<sup>a</sup> 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) | ⊕⊕⊕ | HIGH<sup>a</sup> Mefloquine results in little or no difference in stillbirths or abortions |
| AEs: vomiting                   | 82 per 1000             | 390 per 1000 (338 to 449) | RR 4.76 | (4.13 to 5.49) | ⊕⊕⊕⊕ | HIGH<sup>a</sup> 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) | ⊕⊕⊕ | HIGH<sup>a,b</sup> Mefloquine 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

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**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.

<sup>a</sup>Although one trial has serious risk of bias, the other is of high certainty and exclusion of the smaller trial has little effect on the estimate of effect.

<sup>b</sup>Downgraded by 1 for imprecision: Confidence intervals range from considerable benefit to considerable harm.

<sup>c</sup>Downgraded by 1 for heterogeneity: Substantive qualitative heterogeneity is evident in the meta-analysis.

<sup>d</sup>Confidence intervals include little or no important difference to a 24% reduction in anaemic women. The estimate of 16% is judged to be clinically important.
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; Ataïde 2008). 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).

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).
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.

**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 malaria¹
- 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

¹Placental malaria diagnosed by histology, microscopy, or any method used in the included study. Figure 2 shows the relations between different outcomes.
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 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 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).
Figure 3. Study flow diagram.

254 records identified through database searching

252 records after duplicates removed

252 records screened

20 full-text articles assessed for eligibility

231 records excluded
1 ongoing trial

14 full-text articles excluded

6 trials (6 publications) included in qualitative synthesis

6 trials (6 publications) included in quantitative synthesis (meta-analysis)
**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 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.

|                       | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias): Efficacy | Blinding of outcome assessment (detection bias): Safety | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|-----------------------|--------------------------------------------|----------------------------------------|----------------------------------------------------------|---------------------------------------------------------|--------------------------------------------------------|--------------------------------------|-------------------------------------|------------|
| Briand 2009 BEN        | -                                          | -                                      | +                                                        | -                                                       | +                                                      | +                                    | +                                  | +          |
| Denoeud-Ndam 2014a BEN | -                                          | +                                      | -                                                        | +                                                       | -                                                      | +                                    | +                                  | +          |
| Denoeud-Ndam 2014b BEN | -                                          | +                                      | +                                                        | -                                                       | +                                                      | +                                    | +                                  | +          |
| Gonzalez 2014a BEN GAB MOZ TAN | +                                  | +                                      | -                                                        | +                                                       | -                                                      | +                                    | +                                  | +          |
| Gonzalez 2014b KEN MOZ TAN | +                                  | +                                      | +                                                        | +                                                       | +                                                      | +                                    | +                                  | +          |
| Nosten 1994 THA        | ?                                          | ?                                      | +                                                        | ?                                                       | ?                                                      | +                                    | ?                                  | +          |
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 Méfloquine compared with sulfadoxine-pyrimethamine for preventing malaria in pregnant women; Summary of findings 2 Méfloquine plus cotrimoxazole compared with cotrimoxazole for preventing malaria in pregnant women

**Comparison 1: Méfloquine 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 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; I² statistic = 16%; moderate-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; I² 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; I² 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; I² 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; I² 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; I² 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; I² statistic = 0%; Analysis 1.9). Low birth weight (RR 0.95, 95% CI 0.78 to 1.17; 5641 participants, 2 studies; I² statistic = 33%; moderate-certainty evidence; Analysis 1.10) and prematurity prevalence (RR 1.10, 95% CI 0.76 to 1.40; 4640 participants, 2 studies; I² 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 0.90, 95% CI 0.80 to 1.01; 1576 participants, 2 studies; I² statistic = 3%; Analysis 1.11; multigravidae: RR 0.94, 95% CI 0.78 to 1.14; 4065 participants, 2 studies; I² 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; I² 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; I² 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; I² 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; I² 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; I² statistic = 0%; high-certainty evidence; Analysis 1.21), fatigue/weakness (RR 4.62, 95% CI 1.80 to 11.85; 6272 participants, 2 studies; I² statistic = 91%; high-certainty evidence; Analysis 1.22), and dizziness (RR 4.21, 95% CI 3.36 to 5.27; 6272 participants, 2 studies; I² 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; I² 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; I² 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; I² 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; I² statistic = 0%; high 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 widthness of the CIs (mean haemoglobin: MD 0.07, 95% CI -0.32 to 0.46; 1167 participants, 2 studies; I² statistic = 62%; Analysis 2.5; maternal anaemia: RR 0.94, 95% CI 0.73 to 1.20; 1197 participants, 2 studies; I² 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; I² statistic = 0%; Analysis 2.7). The original definitions of maternal anaemia were different 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; I² statistic = 0%; Analysis 2.8), mean birth weight (MD -25.75, 95% CI -86.99 to 35.49; 1220 participants, 2 studies; I² statistic = 0%; Analysis 2.9), low birth weight rates (RR 1.20, 95% CI 0.89 to 1.60; 1220 participants, 2 studies; I² 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; I² 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; I² 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; I² 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; I² 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; I² 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; I² 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 0.69, 95% CI 0.50 to 0.95; 1347 participants, 2 studies; I² statistic = 0%; Analysis 2.12).
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; I² statistic = 74%; Analysis 2.18), while fatigue (RR 2.95, 95% CI 0.26 to 32.93; 1347 participants, 2 studies; I² statistic = 91%; Analysis 2.19) and dizziness (RR 16.34, 95% CI 0.39 to 684.99; 1347 participants, 2 studies; I² 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; I² 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 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 - 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).
### Additional Summary of Findings [Explanation]

#### 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 |                                   |                                 |                                       |
| 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 (20 to 62) | 34 per 1000 (20 to 62) | RR 0.52 (0.30 to 0.93) | 989 (2 RCTs) | ♦♦♦♦ MODERATE | Mefloquine probably results in lower maternal peripheral parasitaemia at delivery |
| Placental malaria (PCR) | 68 per 1000 (10 to 39) | 19 per 1000 (10 to 39) | RR 0.28 (0.14 to 0.57) | 977 (2 RCTs) | ♦♦♦♦♦ HIGH | Mefloquine plus cotrimoxazole results in fewer women with placental malaria at delivery |
| Maternal anaemia at delivery | 178 per 1000 (130 to 214) | 168 per 1000 (130 to 214) | RR 0.94 (0.73 to 1.20) | 1197 (2 RCTs) | ♦♦♦♦ ♦♦♦♦ ♦♦♦♦ ♦♦♦♦ MODERATE | Mefloquine plus cotrimoxazole probably results in little or no difference in maternal anaemia cases at delivery |
| Outcome                      | Actual Incidence | Expected Incidence | RR     | CI          | GRADE | Evidence |
|------------------------------|------------------|--------------------|--------|-------------|-------|----------|
| Low birth weight             | 118 per 1000     | 141 per 1000       | 1.20   | 0.89 to 1.60| MODERATE<sup>a</sup> | Mefloquine plus cotrimoxazole probably results in little or no difference in low birth weight |
| Spontaneous abortions and stillbirths | 50 per 1000     | 56 per 1000        | 1.12   | 0.42 to 2.98| VERY LOW<sup>a,b,c</sup> | Mefloquine plus cotrimoxazole may result in little or no difference in spontaneous abortions and stillbirths |
| AEs: vomiting                | 30 per 1000      | 239 per 1000       | 7.95   | 4.79 to 13.18| HIGH  | Mefloquine plus cotrimoxazole results in an eight-fold increase in vomiting |
| AEs: dizziness               | 75 per 1000      | 296 per 1000       | 3.94   | 2.85 to 5.46| HIGH  | Mefloquine plus cotrimoxazole results in a four-fold increase in dizziness |

<sup>a</sup>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).

<sup>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.

<sup>a</sup>Although one trial has serious risk of bias, the other is of high certainty and exclusion of the smaller trial has little effect on the estimate of effect.

<sup>b</sup>Downgraded by 1 for inconsistency: Trials showed substantial heterogeneity.

<sup>c</sup>Downgraded by 1 for imprecision: Confidence intervals range from considerable benefit to considerable harm.

<sup>d</sup>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.

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.
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% (moderate-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 (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 20.88, 95% CI 1.40 to 311.66; 1347 participants; low-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).

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).

Quality 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 cer-
tainty 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.

A greements 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).

A U T H O R S’ C O N C L U S I O N S

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.

A C K N O W L E D G E M E N T S

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References to studies included in this review

Briand 2009 BEN  {published and unpublished data}
Briand V, Bottero J, Noel H, Masse V, Cordel H, Guerra J, et al. Intermittent treatment for the prevention of malaria during pregnancy in Benin: a randomized, open-label equivalence trial comparing sulfadoxine-pyrimethamine with mefloquine. *Journal of Infectious Diseases* 2009;200(6):991–1001. DOI: 10.1086/605474

Denoeud-Ndam 2014a BEN  {published and unpublished data}
Denoeud-Ndam L, Zannou DM, Fourcade C, Taron-Brocard C, Porcher R, Atadokpédé F, et al. Cotrimoxazole prophylaxis versus mefloquine intermittent preventive treatment to prevent malaria in HIV-infected pregnant women: two randomized controlled trials. *Journal of Acquired Immune Deficiency Syndromes* 2014;65(2):198–206. DOI: 10.1097/QAI.0000000000000558

Denoeud-Ndam 2014b BEN  {published and unpublished data}
Denoeud-Ndam L, Zannou DM, Fourcade C, Taron-Brocard C, Porcher R, Atadokpédé F, et al. Cotrimoxazole prophylaxis versus mefloquine intermittent preventive treatment to prevent malaria in HIV-infected pregnant women: two randomized controlled trials. *Journal of Acquired Immune Deficiency Syndromes* 2014;65(2):198–206. DOI: 10.1097/QAI.0000000000000558

Gonzalez 2014a BEN GAB MOZ TAN  {published and unpublished data}
* González R, Mombo-Ngoma G, Ouédraogo S, Kakolwa MA, Abdulla S, Accrombessi M, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-negative women: a multicentre randomized controlled trial. *PLoS Medicine* 2014;11(9):e1001735. DOI: 10.1371/journal.pmed.1001735

Rupérez M, González R, Mombo-Ngoma G, Kabanywanyi AM, Sevane E, Ouédraogo S, et al. Mortality, morbidity, and developmental outcomes in infants born to women who received either mefloquine or sulfadoxine-pyrimethamine as intermittent preventive treatment of malaria in pregnancy: a cohort study. *PLoS Medicine* 2016;13(2):e1001964. DOI: 10.1371/journal.pmed.1001964

Gonzalez 2014b KEN MOZ TAN  {published and unpublished data}
González R, Mombo-Ngoma G, Ouédraogo S, Kakolwa MA, Abdulla S, Accrombessi M, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized placebo-controlled trial. *PLoS Medicine* 2014;11(9):e1001735. DOI: 10.1371/journal.pmed.1001735

Nosten 1994 THA  {published data only}
Nosten F, ter Kuile F, Maelankari L, Chongstruphajaisiddhi T, Napononratkoon L, Tangkichot S, et al. Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study. *Journal of Infectious Diseases* 1994;169(3):595–603. DOI: 10.1093/infdis/169.3.595

References to studies excluded from this review

Balocco 1992  {published data only}
Balocco R, Bonati M. Mefloquine prophylaxis against malaria for female travellers of childbearing age. *Lancet* 1992;340(8814):309–10.

Briand 2015  {published data only}
Briand V, Escolano S, Journot V, Massoughodji A. Cot M, Tubert-Bitter P. Mefloquine versus sulfadoxine-pyrimethamine for intermittent preventive treatment in pregnancy: a joint analysis on efficacy and tolerability. *American Journal of Tropical Medicine and Hygiene* 2015;93(2):300–4.

Denoeud-Ndam 2012  {published data only}
Denoeud-Ndam L, Clément MC, Briand V, Akakpo J, Agnouso VK, Atadokpédé F, et al. Tolerability of mefloquine intermittent preventive treatment for malaria in HIV-infected pregnant women in Benin. *Journal of Acquired Immune Deficiency Syndromes* 2012;61(1):64–72.

Nosten 1990 THA  {published data only}
Nosten F, Karbwang J, White NJ, Honeymoon, Na Bangchang K, Bunnag D, et al. Mefloquine antimalarial prophylaxis in pregnancy: dose finding and pharmacokinetic study. *British Journal of Clinical Pharmacology* 1990;30(1):79–85.

Phillips-Howard 1998  {published data only}
Phillips-Howard PA, Steffen R, Kerr L, Vanhauwere B, Schildknecht J, Fuchs E, et al. Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy. *Journal of Travel Medicine* 1998;5(3):121–6.

Schlagenhauf 2012  {published data only}
Schlagenhauf P, Blumentals WA, Suter P, Regep L, Vital-Durand G, Schaerer MT, et al. Pregnancy and fetal outcomes after exposure to mefloquine in the pre- and periconception period and during pregnancy. *Clinical Infections Diseases* 2012;54(11):e124–31.

Smoak 1997  {published data only}
Smoak BL, Witter JY, Keep IW, Cowan J, Chantelois JL. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen. *Journal of Infectious Diseases* 1992;176(3):831–3.

Stekete 1996 MAL  {published data only}
Stekete RW, Wirima JJ, Hightower AW, Slutsker L, Heymann DL, Breman JG. The effect of malaria and malaria prevention in pregnancy on offspring birthweight, prematurity, and intraterine growth retardation in rural Malawi. *American Journal of Tropical Medicine and Hygiene* 1996;55(Suppl 1):33–41.

Stekete 1999 RW, Wirima JJ, Slutsker L, Breman JG, Heymann DL. Comparability of treatment groups and risk factors for parasitemia at the first antenatal clinic visit in a study of malaria treatment and prevention in pregnancy in rural
Malawi. *American Journal of Tropical Medicine and Hygiene* 1996;55(Suppl 1):17–23.
Stekete RW, Wirima JJ, Slutsker L, Heymann DL, Breman JG. The problem of malaria and malaria control in pregnancy in sub-Saharan Africa. *American Journal of Tropical Medicine and Hygiene* 1996;55(Suppl 1):2–7.
Stekete RW, Wirima JJ, Slutsker L, Khoromana CO, Heymann DL, Breman JG. Malaria treatment and prevention in pregnancy: indications for use and adverse events associated with use of chloroquine or mefloquine. *American Journal of Tropical Medicine and Hygiene* 1996;55(Suppl 1):59–6.

Akinyotu 2015 NIG (published data only)

References to ongoing studies

Aubouy 2007

Aubouy A, Fiev N, Bertin G, Ságbó JC, Kossoú H, Kindle-Gazard D, et al. Dramatically decreased therapeutic efficacy of chloroquine and sulfadoxine-pyrimethamine, but not mefloquine, in southern Benin. *Tropical Medicine & International Health* 2007;12(7):886–94. [PUBMED: 17596256]

Ayisi 2003

Ayisi JG, van Eijk AM, ter Kuile FO, Koleczak MS, Otieno JA, Misore AO, et al. The effect of dual infection with HIV and malaria on pregnancy outcomes in western Kenya. *AIDS* 2003;17:585–94.

Bardaji 2008

Bardaji A, Sigauque B, Bruni L, Romagosa C, Sanz S, Mabunda S, et al. Clinical malaria in African pregnant women. *Malaria Journal* 2008;7:27.

Bardaji 2012

Bardaji A, Bassat Q, Alonso PL, Menendez C. Intermittent preventive treatment of malaria in pregnant women and infants: making best use of the available evidence. *Expert Opinion in Pharmacotherapy* 2012;13(12):1719–36.

Brabin 1983

Brabin BJ. An analysis of malaria in pregnancy in Africa. *Bulletin of the World Health Organization* 1983;61(6):1005–16.

Briand 2009

Briand V, Bottero J, Noel H, Masse V, Cordel H, Guerra J, et al. Intermittent treatment for the prevention of malaria during pregnancy in Benin: a randomized, open-label equivalence trial comparing sulfadoxine-pyrimethamine with mefloquine. *Journal of Infectious Diseases* 2009;200(6):991–1001.

Carrara 2009

Carrara VI, Zwang J, Ashley EA, Price RN, Stepniewska K, Barens M, et al. Changes in the treatment responses to artesunate-mefloquine on the northwestern border of Thailand during 13 years of continuous deployment. *PLoS ONE* 2009;4(2):e4551.

CDC 2016

Centers for Disease Control and Prevention. *Yellow Book - Malaria*, Chapter 3. *Travelers’ Health*. Available from wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria (accessed 13 February 2018).

CDC 2017

Centers for Disease Control and Prevention. CDC Malaria Maps. Available from https://www.cdc.gov/malaria/travelers/about/malaria/ (accessed 13 February 2018).

Desai 2007

Desai M, ter Kuile FO, Nosten F, McGready R, Asaemo K, Brabin B, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infectious Diseases* 2007;7(2):93–104.

Desai 2018

Desai M, Hill J, Fernandes S, Walker P, Pell C, Gutman J, et al. Prevention of malaria in pregnancy. *Lancet Infect Diseases* 2018 Jan 30 Epub ahead of print. DOI: 10.1016/S1473-3099(18)30064-1

FDA 2004

US Food, Drug Administration. Lariam-brand of mefloquine hydrochloride. 2004. Available from www.accessdata.fda.gov/drugsatfda_docs/label/2008/ 019591s024s025lbl.pdf (accessed 1 December 2014).

Gamble 2006

Gamble C, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy. *Cochrane Database of Systematic Reviews* 2006, Issue 2. DOI: 10.1002/14651858.CD003755.pub2

References to ongoing studies

Akinnyotu 2015 NIG (published data only (unpublished sought but not used))

A comparative study of mefloquine and SP as prophylaxis against malaria in pregnant HIV-infected patients. Ongoing study September 2015.

Additional references

Ataide 2014

Ataide R, Mayor A, Rogerson SJ. Malaria, primigravidae, and antibodies: knowledge gained and future perspectives. *Trends in Parasitology* 2014;30(2):85–94.

Aubouy 2007

Aubouy A, Fiev N, Bertin G, Ságbó JC, Kossoú H, Kindle-Gazard D, et al. Dramatically decreased therapeutic efficacy of chloroquine and sulfadoxine-pyrimethamine, but not mefloquine, in southern Benin. *Tropical Medicine & International Health* 2007;12(7):886–94. [PUBMED: 17596256]

Ayisi 2003

Ayisi JG, van Eijk AM, ter Kuile FO, Koleczak MS, Otieno JA, Misore AO, et al. The effect of dual infection with HIV and malaria on pregnancy outcomes in western Kenya. *AIDS* 2003;17:585–94.
Mefloquine for preventing malaria in pregnant women (Review)

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Gamble 2007
Gamble C, Ekwaru PJ, Garner P, ter Kuile FO. Insecticide-treated nets for the prevention of malaria in pregnancy: a systematic review of randomised controlled trials. *PLoS Medicine* 2007;4(5):e107.

Gonzalez 2012
Gonzalez R, Hellgren U, Greenwood B, Menéndez C. Mefloquine safety and tolerability in pregnancy: a systematic literature review. *Malaria Journal* 2012;11(1):75.

Gonzalez 2013
González R, Hellgren U, Greenwood B, Menéndez C. Mefloquine safety and tolerability in pregnancy: a systematic literature review. *Malaria Journal* 2013;12(1):75. DOI: 10.1186/1475-2875-13-75

Gonzalez 2014
Gonzalez R, Hellgren U, Greenwood B, Menendez C. Mefloquine safety and tolerability in pregnancy: a systematic literature review. *Malaria Journal* 2014;13(1):75.

GRADEpro GDT 2015 [Computer program]
McMaster University (developed by Evidence Prime). GRADEpro GDT. www.gradeworkinggroup.org/. Version accessed 6 August 2017. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Guyatt 2004
Guyatt HL, Snow RW. Impact of malaria during pregnancy on low birth weight in sub-Saharan Africa. *Clinical Microbiology Reviews* 2004;17(4):760–9.

Higgins 2011
Higgins JPT, Altman DG, Sterne JAC, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration.

Iriemenam 2012
Iriemenam NC, Shah M, Gatei W, van Eijk AM, Ayis J, Kariuki S, et al. Temporal trends of sulfadoxine-pyrimethamine (SP) drug-resistance molecular markers in Plasmodium falciparum parasites from pregnant women in western Kenya. *Malaria Journal* 2012;11(1):134.

Kayentao 2013
Kayentao A, Garner P, van Eijk AM, Naidoo I, Roper C, Mulokoti A, et al. Intermittent preventive treatment for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine and risk of low birth weight in Africa: systematic review and meta-analysis. *JAMA* 2013;309(6):594-604. DOI: 10.1001/jama.2012.216231

Lee 2017
Lee SJ, ter Kuile FO, Price RN, Luxemburger C, Nosten F. Adverse effects of mefloquine for the treatment of uncomplicated malaria in Thailand: a pooled analysis of 19, 850 individual patients. *PLoS ONE* 2017;12(2):e0168780. DOI: 10.1371/journal.pone.0168780

MacArthur 2001
MacArthur J, Stennes GM, Macheso A, Kolczak MS, Green MD, Ali D, et al. Efficacy of mefloquine and sulfadoxine-pyrimethamine for the treatment of uncomplicated *Plasmodium falciparum* infection in Machinga District, Malawi, 1998. *American Journal of Tropical Medicine and Hygiene* 2001;65(6):679–84.

Menendez 2010
Menendez C, Bardaji A, Sigauque B, Sanz S, Aponte JJ, Mabunda S, et al. Malaria prevention with IPTp during pregnancy reduces neonatal mortality. *PLoS ONE* 2010;5(2):9438.

Menéndez 2008
Menéndez C, Bardaji A, Sigauque B, Romagosa C, Sanz S, Serra-Casas E, et al. A randomized placebo-controlled trial of intermittent preventive treatment in pregnant women in the context of insecticide treated nets delivered through the antenatal clinic. *PLoS ONE* 2008;3(4):e1934.

Menéndez 2011
Menéndez C, Serra-Casas E, Seabill MD, Sanz S, Nhabomba A, Bardaji A, et al. HIV and placental infection modulate the appearance of drug-resistant *Plasmodium falciparum* in pregnant women who receive intermittent preventive treatment. *Clinical Infections Diseases* 2011;52(1):41–8.

Mockenhaupt 2008
Mockenhaupt FP, Bedu-Addo G, Eggelte TA, Hommerich L, Holmberg V, von Oertzen, C, et al. Rapid increase in the prevalence of sulfadoxine-pyrimethamine resistance among *Plasmodium falciparum* isolated from pregnant women in Ghana. *Journal of Infections Diseases* 2008;198(10):1545–9.

Nosten 1999
Nosten F, Vincenti M, Simpson J, Ye P, Thwai KL, de Vries A, et al. The effects of mefloquine treatment in pregnancy. *Clinical Infections Diseases* 1999;28(4):808–15.

Nosten 2000
Nosten F, van Vugt M, Price R, Luxemburger C, Thway KL, Brockman A, et al. Effects of artesunate-mefloquine combination on incidence of Plasmodium falciparum malaria and mefloquine resistance in western Thailand: a prospective study. *Lancet* 2000;356(9226):297–302.

Oduola 1987
Oduola AM, Milhous WK, Salako LA, Walker O, Desjardins RE. Reduced in-vitro susceptibility to mefloquine in West African isolates of Plasmodium falciparum. *Lancet* 1987;2(8571):1304–5.

Pekyi 2016
PREGACT Study Group, Pekyi D, Ampromfi AA, Tinto H, Traoré-Coulibaly M, Thaïta MC, et al. Four artemisinin-based treatments in African pregnant women with malaria. *New England Journal of Medicine* 2016;374(10):913–27. DOI: 10.1056/NEJMoa1508606
Mefloquine for preventing malaria in pregnant women (Review)

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WHO MPAC 2013
World Health Organization. Malaria Policy Advisory
Committee and Secretariat. Malaria Policy Advisory
Committee to the WHO: conclusions and recommendations
of September 2013 meeting. Malaria Journal 2013;12:346.
[PUBMED: 24359206]

References to other published versions of this review

González 2015
González R, Boerma RS, Sinclair D, Aponte JJ, ter Kuile
FO, Menéndez C. Mefloquine for preventing malaria in
pregnant women. Cochrane Database of Systematic Reviews
2015, Issue 1. DOI: 10.1002/14651858.CD011444
* Indicates the major publication for the study
## Characteristics of included studies

**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 |
| **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;
**Briand 2009 BEN**  (Continued)

| Risk of 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)** | High risk | No blinding was reported, and safety outcomes are likely to be influenced by lack of blinding |
| **Blinding of outcome assessment (detection bias)** | 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)** | 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)** | 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. |
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: 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)
Denoeud-Ndam 2014a BEN  (Continued)

- 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

| 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) | High risk          | The trial blinded only the microscopist who evaluated blood smears |
| Blinding of outcome assessment (detection bias) | 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) | 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) | 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 |
### Denoeud-Ndam 2014a BEN

| 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)
- **Inclusion criteria:** HIV-infected pregnant women of all gravities 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. 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

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Continued

- 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 A119-3-01528

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) | High risk          | The trial blinded only the microscopist who evaluated blood smears                    |
| All outcomes                                              |                    |                                                                                      |
| Blinding of outcome assessment (detection bias)           | 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 |
| Efficacy                                                  |                    |                                                                                      |
| Blinding of outcome assessment (detection bias)           | 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 |
| Safety                                                    |                    |                                                                                      |
| Incomplete outcome data (attrition bias)                  | Low risk           | Missing outcome data were balanced in numbers across groups.                           |
| All outcomes                                              |                    |                                                                                      |
### Denoeud-Ndam 2014b BEN (Continued)

| 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  
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

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**Mefloquine for preventing malaria in pregnant women (Review)**  
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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

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 accord- |
### Allocation concealment (selection bias)

| Risk Level | Description |
|------------|-------------|
| Low        | 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)

| Outcome | Risk Level | Description |
|---------|------------|-------------|
| All outcomes | High risk | 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)

| Outcome | Risk Level | Description |
|---------|------------|-------------|
| 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. |
| 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)

| Outcome | Risk Level | Description |
|---------|------------|-------------|
| 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)

| Risk Level | Description |
|------------|-------------|
| Low        | Not observed. Protocol available |

### Other bias

| Risk Level | Description |
|------------|-------------|
| Low        | The study appears to be free of other sources of bias. |
**Methods**

Trial design: individually randomized, double-blind, placebo-controlled trial of 3 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. 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

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**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

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**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 trimethoprim 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

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**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)
- 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” |
| Bias Type                                                   | Risk Level | Notes                                                                                                                                 |
|------------------------------------------------------------|------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Blinding of participants and personnel (performance bias) | 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 tablets in shape and colour |
| Blinding of outcome assessment (detection bias)            | Low risk   | Quote: “Investigators, laboratory staff, care providers, and study participants were blinded to intervention throughout the study”                                                                |
| Blinding of outcome assessment (detection bias)            | Low risk   | Quote: “Investigators, laboratory staff, care providers, and study participants were blinded to intervention throughout the study”                                                                |
| Incomplete outcome data (attrition bias)                   | 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.                                                                                                                                             |
### 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
- 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)
### Nosten 1994 THA

(Continued)

| Risk of 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) | 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)   | Unclear risk       | Not explained                                                                          |
| Blinding of outcome assessment (detection bias)   | Unclear risk       | Not explained                                                                          |
| Incomplete outcome data (attrition bias)          | 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.
| 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                                                                                                                                                                                                                     |
| Schlegenauf 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  
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 |
## 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]   |
| 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]   |
| 24 AEs: headache                          | 2              | 6272                | Risk Ratio (M-H, Random, 95% CI)    | 0.70 [0.25, 1.94]   |

## 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)
- **Risk Ratio (M-H, Fixed, 95% CI)**: 0.51 [0.29, 0.89]

### 4 Placental malaria (PCR)
- **Risk Ratio (M-H, Fixed, 95% CI)**: 0.28 [0.14, 0.57]

### 5 Mean haemoglobin at delivery
- **Mean Difference (IV, Random, 95% CI)**: 0.07 [-0.32, 0.46]

### 6 Maternal anaemia at delivery (< 9.5 g/dL)
- **Risk Ratio (M-H, Fixed, 95% CI)**: 0.94 [0.73, 1.20]

### 7 Maternal severe anaemia at delivery
- **Risk Ratio (M-H, Fixed, 95% CI)**: 0.93 [0.41, 2.08]

### 8 Cord blood parasitaemia
- **Risk Ratio (M-H, Fixed, 95% CI)**: 0.28 [0.14, 0.57]

### 9 Mean birth weight
- **Mean Difference (IV, Random, 95% CI)**: -0.32 [-0.96, 0.32]

### 10 Low birth weight
- **Risk Ratio (M-H, Fixed, 95% CI)**: 0.51 [0.29, 0.89]

### 11 Prematurity
- **Risk Ratio (M-H, Random, 95% CI)**: 1.07 [0.58, 1.96]

### 12 SAEs during pregnancy
- **Risk Ratio (M-H, Fixed, 95% CI)**: 0.93 [0.41, 2.08]

### 13 Spontaneous abortions and stillbirths
- **Risk Ratio (M-H, Random, 95% CI)**: 1.12 [0.42, 2.98]

### 14 Congenital malformations
- **Risk Ratio (M-H, Fixed, 95% CI)**: 0.61 [0.22, 1.67]

### 15 Maternal mortality
- **Risk Ratio (M-H, Fixed, 95% CI)**: 0.90 [0.26, 3.16]

### 16 Neonatal mortality
- **Risk Ratio (M-H, Fixed, 95% CI)**: 1.06 [0.28, 4.07]

### 17 Mother-to-child transmission HIV
- **Risk Ratio (M-H, Fixed, 95% CI)**: 4.30 [0.49, 37.49]

### 18 AEs: vomiting
- **Risk Ratio (M-H, Random, 95% CI)**: 13.43 [3.31, 54.54]

### 19 AEs: fatigue/weakness
- **Risk Ratio (M-H, Random, 95% CI)**: 2.95 [0.26, 32.93]

### 20 AEs: dizziness
- **Risk Ratio (M-H, Random, 95% CI)**: 16.34 [0.39, 684.99]

### 21 AEs: headache
- **Risk Ratio (M-H, Random, 95% CI)**: 0.76 [0.28, 2.10]

#### 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] |
| 16 AEs: vomiting | 1 | 139 | Risk Ratio (M-H, Fixed, 95% CI) | 13.43 [3.31, 54.54] |
**Comparison 4. Mefloquine versus placebo**

| Outcome or subgroup title | No. of studies | No. of participants | 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 1.1. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 1 Clinical malaria episodes during pregnancy.**

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine

Outcome: 1 Clinical malaria episodes during pregnancy

| Study or subgroup | log [Rate Ratio] (SE) | Rate Ratio (IV, Fixed, 95% CI) | Weight | Rate Ratio (IV, Fixed, 95% CI) |
|-------------------|-----------------------|---------------------------------|--------|--------------------------------|
| Briand 2009 BEN   | -0.42 (0.42)          | 8.7 %                           | 0.66 [0.29, 1.50] |
| Gonzalez 2014a BEN GAB MOZ TAN | -0.17 (0.13) | 91.3 %                           | 0.84 [0.65, 1.09] |
| **Total (95% CI)** |                        | **100.0 %**                      | **0.83 [0.65, 1.05]** |

Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² =0.0%
Test for overall effect: Z = 1.54 (P = 0.12)
Test for subgroup differences: Not applicable
Analysis 1.2. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 2 Maternal peripheral parasitaemia at delivery.

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine
Outcome: 2 Maternal peripheral parasitaemia 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           | 11/675      | 24/671                     | 22.3 %     | 0.46 [ 0.22, 0.92 ] |
| Gonzalez 2014a BEN GAB MOZ TAN | 88/2737   | 63/1372                    | 77.7 %     | 0.70 [ 0.51, 0.96 ] |
| **Total (95% CI)**        | **3412**    | **2043**                   | **100.0 %**| **0.65 [ 0.48, 0.86 ]** |

Total events: 99 (Mefloquine), 87 (Sulfadoxine-pyrimethamine)
Heterogeneity: Chi² = 1.19, df = 1 (P = 0.28); I² = 16%
Test for overall effect: Z = 2.97 (P = 0.0030)
Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine
Outcome: 3 Placental malaria

| 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           | 11/163      | 29/656                     | 37.3 %     | 1.53 [ 0.78, 2.99 ] |
| Gonzalez 2014a BEN GAB MOZ TAN | 119/2568  | 72/1281                    | 62.7 %     | 0.82 [ 0.62, 1.10 ] |
| **Total (95% CI)**        | **2731**    | **1937**                   | **100.0 %**| **1.04 [ 0.58, 1.86 ]** |

Total events: 130 (Mefloquine), 101 (Sulfadoxine-pyrimethamine)
Heterogeneity: Tau² = 0.12; Chi² = 2.74, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable
### Analysis 1.4. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 4 Mean haemoglobin at delivery.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine

Outcome: 4 Mean haemoglobin at delivery

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Mean Difference | Weight | Mean Difference |
|-------------------|------------|---------------------------|----------------|--------|----------------|
| Briand 2009 BEN (1) | 735 11.4 (1.63) | 730 11.3 (1.62) | 0.10 [-0.07, 0.27] |
| Gonzalez 2014a BEN GAB MOZ TAN | 2743 11.1 (1.5) | 1380 11.1 (1.6) | 0.10 [0.00, 0.20] |
| **Total (95% CI)** | **3478** | **2110** | **100.0 % 0.10 [ 0.01, 0.19 ]** |

Heterogeneity: $\chi^2 = 0.0, df = 1 (P = 1.00); I^2 = 0.0$

Test for overall effect: $Z = 2.26 (P = 0.024)$

Test for subgroup differences: Not applicable

(1) Denominators based on low birth weight outcome
Analysis 1.5. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 5 Maternal anaemia at delivery.

Review: Mefloquine for preventing malaria in pregnant women
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 (1) | 103/626   | 129/640                   |             | 23.2 % | 0.82 [0.65, 1.03] |
| Gonzalez 2014a BEN GAB MOZ TAN (2) | 541/2804 | 317/1399                   |             | 76.8 % | 0.85 [0.75, 0.96] |
| **Total (95% CI)** | **3430**  | **2039**                  |             | **100.0 %** | **0.84 [0.76, 0.94]** |

Total events: 644 (Mefloquine), 446 (Sulfadoxine-pyrimethamine)
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0.0%
Test for overall effect: Z = 3.07 (P = 0.0022)
Test for subgroup differences: Not applicable

(1) Anemia at delivery was defined as haemoglobin < 10 g/dl.
(2) Unpublished data. These were obtained by contacting the authors. In the original paper anaemia was defined as haemoglobin < 11 g/dl.
### Analysis 1.6. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 6 Severe maternal anaemia at delivery.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine

Outcome: 6 Severe maternal anaemia at delivery

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|------------|---------------------------|-------------------------------|--------|-------------------------------|
| Briand 2009 BEN   | 19/626     | 15/640                    | 34.1 % 1.29 [0.66, 2.53]      |        |                               |
| Gonzalez 2014a BEN GAB MOZ TAN (1) | 72/2804 | 46/1399                   | 65.9 % 0.78 [0.54, 1.12]      |        |                               |
| **Total (95% CI)** | **3430**   | **2039**                  | **100.0 % 0.93 [0.58, 1.48]** | **4**  |                               |

Total events: 91 (Mefloquine), 61 (Sulfadoxine-pyrimethamine)

Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 1.70$, df = 1 ($P = 0.19$); $I^2 = 41$

Test for overall effect: $Z = 0.31$ ($P = 0.75$)

Test for subgroup differences: Not applicable

(1) Unpublished data. These were obtained by contacting the authors. In the original paper severe anaemia was defined as haemoglobin<7g/dl.
### Analysis 1.7. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 7 Cord blood parasitaemia.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine

Outcome: 7 Cord blood parasitaemia

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|------------------|------------|---------------------------|-----------------------------|--------|-----------------------------|
| Briand 2009 BEN  | 2/653      | 9/652                     | 0.22 [0.05, 1.02]           | 43.7 % |                             |
| Gonzalez 2014a BEN GAB MOZ TAN | 6/2667 | 4/1337                     | 0.75 [0.21, 2.66]           | 56.3 % |                             |
| **Total (95% CI)** | 3320      | 1989                      | 0.44 [0.13, 1.46]           | 100.0 % |                             |

Total events: 8 (Mefloquine), 13 (Sulfadoxine-pyrimethamine)

Heterogeneity: $\tau^2 = 0.25$, $\chi^2 = 1.49$, df = 1 ($P = 0.22$); $I^2 = 33$

Test for overall effect: $Z = 1.34$ ($P = 0.18$)

Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine

Outcome: 8 Cord blood anaemia

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|------------------|------------|---------------------------|-----------------------------|--------|-----------------------------|
| Gonzalez 2014a BEN GAB MOZ TAN | 353/2672 | 170/1334                   | 1.04 [0.87, 1.23]           | 100.0 % |                             |
| **Total (95% CI)** | 2672      | 1334                      | 1.04 [0.87, 1.23]           | 100.0 % |                             |

Total events: 353 (Mefloquine), 170 (Sulfadoxine-pyrimethamine)

Heterogeneity: not applicable

Test for overall effect: $Z = 0.41$ ($P = 0.68$)

Test for subgroup differences: Not applicable
**Analysis 1.9. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 9 Mean birth weight.**

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine

Outcome: 9 Mean birth weight

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Mean Difference | Weight | Mean Difference |
|-------------------|------------|--------------------------|----------------|--------|----------------|
| Briand 2009 BEN (1) | 535 3036 (418) | 530 3018 (439) | 29.9 % 18.00 [ -33.49, 69.49 ] |
| Gonzalez 2014a BEN GAB MOZ TAN | 2778 2997.4 (535.5) | 1398 3001.5 (517.8) | 70.1 % -4.10 [ -37.76, 29.56 ] |
| **Total (95% CI)** | **3313** | **1928** | **100.0 % 2.52 [ -25.66, 30.69 ]** |

Heterogeneity: Chi$^2 = 0.50$, df = 1 ($P = 0.48$); $I^2 = 0.0$

Test for overall effect: $Z = 0.18$ ($P = 0.86$)

Test for subgroup differences: Not applicable

(1) Denominators based on low birth weight outcome
Analysis 1.10. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 10 Low birth weight.

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine
Outcome: 10 Low birth weight

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------------------------|------------|--------|------------|
| Briand 2009 BEN   | 59/735     | 72/730                    | 30.3 %     |        | 0.81 [ 0.59, 1.13 ] |
| Gonzalez 2014a BEN GAB MOZ TAN | 360/2778 | 177/1398 | 69.7 % | 1.02 [ 0.87, 1.21 ] |
| **Total (95% CI)** | **3513** | **2128** | **100.0 %** | **0.95 [ 0.78, 1.17 ]** |

Total events: 419 (Mefloquine), 249 (Sulfadoxine-pyrimethamine)
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 1.48$, df = 1 (P = 0.22); $I^2 = 33%$
Test for overall effect: $Z = 0.44$ (P = 0.66)
Test for subgroup differences: Not applicable
### Analysis 1.11. Comparison of Mefloquine versus sulfadoxine-pyrimethamine, Outcome 11 Low birth weight by gravidity.

**Review:** Mefloquine for preventing malaria in pregnant women

**Comparison:** Mefloquine versus sulfadoxine-pyrimethamine

**Outcome:** Low birth weight by gravidity

| 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 |
| **1 Primigravidae** |            |                           |            |        |            |
| Briand 2009 BEN   | 29/193     | 35/195                    |            | 11.3 % | 0.84 [0.53, 1.31] |
| Gonzalez 2014a BEN GAB MOZ T AN (1) | 133/798 | 59/390 |            | 25.8 % | 1.10 [0.83, 1.46] |
| **Subtotal (95% CI)** | **991** | **585** |            | **37.1 %** | **1.02 [0.80, 1.30]** |
| **Total events:** | 162 (Mefloquine), 94 (Sulfadoxine-pyrimethamine) | | | | |
| Heterogeneity: | Chi² = 1.03, df = 1 (P = 0.31); I² = 3% |
| Test for overall effect: | Z = 0.17 (P = 0.86) |
| **2 Multigravidae** |            |                           |            |        |            |
| Briand 2009 BEN   | 30/542     | 37/535                    |            | 12.1 % | 0.80 [0.50, 1.28] |
| Gonzalez 2014a BEN GAB MOZ T AN | 227/1980 | 118/1008 |            | 50.8 % | 0.98 [0.79, 1.21] |
| **Subtotal (95% CI)** | **2522** | **1543** |            | **62.9 %** | **0.94 [0.78, 1.14]** |
| **Total (95% CI)** | **3513** | **2128** |            | **100.0 %** | **0.97 [0.84, 1.13]** |
| **Total events:** | 419 (Mefloquine), 249 (Sulfadoxine-pyrimethamine) | | | | |
| Heterogeneity: | Chi² = 1.85, df = 3 (P = 0.60); I² = 0.0% |
| Test for overall effect: | Z = 0.36 (P = 0.72) |
| Test for subgroup differences: | Chi² = 0.25, df = 1 (P = 0.62), I² = 0.0% |

(1) Low birth weight data by gravidity from Gonzalez et al were provided by the authors (unpublished results).
### Analysis 1.12. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 12 Prematurity.

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 1 Mefloquine versus sulfadoxine-pyrimethamine  
**Outcome:** 12 Prematurity

| 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   | 3/637          | 5/625                         | 6.4 %                     | 0.59 [0.14, 2.45] |
| Gonzalez 2014a BEN GAB MOZ TAN | 118/2245 | 56/1133 | 93.6 %                     | 1.06 [0.78, 1.45] |
| **Total (95% CI)** | **2882**       | **1758**                      | **100.0 %**               | **1.03 [0.76, 1.40]** |

Total events: 121 (Mefloquine), 61 (Sulfadoxine-pyrimethamine)  
Heterogeneity: Chi² = 0.63, df = 1 (P = 0.43); I² = 0.0%  
Test for overall effect: Z = 0.21 (P = 0.83)  
Test for subgroup differences: Not applicable

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

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 1 Mefloquine versus sulfadoxine-pyrimethamine  
**Outcome:** 13 Malaria in first year of life

| Study or subgroup | log [Rate Ratio] (SE) | Rate Ratio IV,Fixed 95% CI | Weight | Rate Ratio IV,Fixed 95% CI |
|-------------------|------------------------|---------------------------|--------|---------------------------|
| Gonzalez 2014a BEN GAB MOZ TAN | -0.02623786 (0.08677885) | 100.0 % | 0.97 [0.82, 1.15] |
| **Total (95% CI)** | **100.0 %** | **0.97 [0.82, 1.15]** |

Heterogeneity: not applicable  
Test for overall effect: Z = 0.30 (P = 0.76)  
Test for subgroup differences: Not applicable
Analysis 1.14. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 14 Hospital admissions in first year of life.

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine
Outcome: 14 Hospital admissions in first year of life

```
Study or subgroup      log [Rate Ratio] (SE)   Rate Ratio   Weight   Rate Ratio
                      IV,Fixed,95% CI          IV,Fixed,95% CI
Gonzalez 2014a BEN GAB MOZ T AN  -0.06969752 (0.11394933)  100.0 %  0.93 [ 0.75, 1.17 ]
Total (95% CI)        100.0 %  0.93 [ 0.75, 1.17 ]
```

Heterogeneity: not applicable
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine
Outcome: 15 SAEs during pregnancy

```
| Study or subgroup | Mefloquine n/N | Sulfadoxine-pyrimethamine n/N | Risk Ratio | Weight | Risk Ratio |
|-------------------|----------------|-------------------------------|------------|--------|------------|
| Gonzalez 2014a BEN GAB MOZ T AN | 275/3113       | 140/1561                      | 100.0 %    | 0.98 [ 0.81, 1.20 ] |
Total (95% CI)     | 3113           | 1561                          | 100.0 %    | 0.98 [ 0.81, 1.20 ] |
```

Total events: 275 (Mefloquine), 140 (Sulfadoxine-pyrimethamine)
Heterogeneity: not applicable
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable
Analysis 1.16. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 16 Stillbirths and abortions.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: Mefloquine versus sulfadoxine-pyrimethamine

Outcome: 16 Stillbirths and abortions

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio (M-H,Fixed) 95% CI | Weight % | Risk Ratio (M-H,Fixed) 95% CI |
|-------------------|------------|---------------------------|-------------------------------|----------|-------------------------------|
| Briand 2009 BEN   | 25/781     | 16/764                    | 1.53 [0.82, 2.84]             | 17.8 %   |                               |
| Gonzalez 2014a BEN GAB MOZ TAN | 126/3113 | 56/1561                  |                               | 82.2 %   | 1.13 [0.83, 1.54]             |
| **Total (95% CI)** | 3894       | 2325                      |                               | 100.0 %  | 1.20 [0.91, 1.58]             |

Total events: 151 (Mefloquine), 72 (Sulfadoxine-pyrimethamine)

Heterogeneity: $\chi^2 = 0.74, df = 1 (P = 0.39); I^2 = 0.0$

Test for overall effect: $Z = 1.29 (P = 0.20)$

Test for subgroup differences: Not applicable
Analysis 1.17. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 17 Congenital malformations.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine

Outcome: 17 Congenital malformations

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio M-H Random 95% CI | Weight | Risk Ratio M-H Random 95% CI |
|------------------|------------|---------------------------|-----------------------------|--------|-------------------------------|
| Brand 2009 BEN   | 8/780      | 4/765                     | 31.3 % 1.96 [0.59, 6.49]    |        |                               |
| Gonzalez 2014a BEN GAB MOZ TAN | 25/2913 | 15/1473                  | 68.7 % 0.84 [0.45, 1.59]    |        |                               |
| **Total (95% CI)** | **3693**  | **2238**                 | **100.0 % 1.10 [0.51, 2.37]** |        |                               |

Total events: 33 (Mefloquine), 19 (Sulfadoxine-pyrimethamine)

Heterogeneity: $\tau^2 = 0.12; \text{Ch}^2 = 1.50, \text{df} = 1 (P = 0.22); I^2 = 33\%$

Test for overall effect: $Z = 0.24 (P = 0.81)$

Test for subgroup differences: Not applicable
**Analysis 1.18. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 18 Maternal mortality.**

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine

Outcome: 18 Maternal mortality

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|------------|---------------------------|-------------------------------|--------|-------------------------------|
| Briand 2009 BEN (1) | 5/781 | 0/764 | 33.6 % | 10.76 [0.60, 194.27] |
| Gonzalez 2014a BEN GAB MOZ TAN | 9/3113 | 4/1561 | 66.4 % | 1.13 [0.35, 3.66] |
| **Total (95% CI)** | **3894** | **2325** | **100.0 %** | **2.41 [0.27, 21.23]** |

Total events: 14 (Mefloquine), 4 (Sulfadoxine-pyrimethamine)

Heterogeneity: $\tau^2 = 1.50$, $\chi^2 = 2.18$, df = 1 ($P = 0.14$); $I^2 = 54\%$

Test for overall effect: $Z = 0.79$ ($P = 0.43$)

Test for subgroup differences: Not applicable

(1) Denominators based on stillbirths and abortions
### Analysis 1.19. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 19 Neonatal mortality.

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 1 Mefloquine versus sulfadoxine-pyrimethamine  
**Outcome:** 19 Neonatal mortality

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio (95% CI) | Weight | Risk Ratio (95% CI) |
|-------------------|------------|---------------------------|---------------------|--------|---------------------|
| Briand 2009 BEN (1) | 11/738     | 12/722                    | 22.7% | 0.90 [0.40, 2.02]  |
| Gonzalez 2014a BEN GAB MOZ TAN | 62/3113 | 31/1561 | 77.3% | 1.00 [0.65, 1.54]  |
| **Total (95% CI)** | **3851** | **2283** | **100.0%** | **0.98 [0.67, 1.43]** |

Heterogeneity: Chi$^2 = 0.06$, df = 1 ($P = 0.81$); $I^2 = 0.0%$

Test for overall effect: $Z = 0.11$ ($P = 0.91$)

Test for subgroup differences: Not applicable

(1) Data obtained by contacting the authors

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

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 1 Mefloquine versus sulfadoxine-pyrimethamine  
**Outcome:** 20 Infant mortality

| Study or subgroup | log [Rate Ratio] (SE) | Rate Ratio (95% CI) | Weight |
|-------------------|-----------------------|---------------------|--------|
| Gonzalez 2014a BEN GAB MOZ TAN | -0.00059042 (0.21374669) | 100.0% | 1.00 [0.66, 1.52] |
| **Total (95% CI)** | **100.0%** | **1.00 [0.66, 1.52]** |

Heterogeneity: not applicable

Test for overall effect: $Z = 0.00$ ($P = 1.0$)

Test for subgroup differences: Not applicable
Analysis 1.21. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 21 AEs: vomiting.

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine
Outcome: 21 AEs: vomiting

| Study or subgroup     | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-----------------------|------------|---------------------------|-----------------------------|--------|-----------------------------|
| Briand 2009 BEN       | 437/802    | 93/799                    | 41.2 %                      | 4.68   | 3.83, 5.72                  |
| Gonzalez 2014a BEN GAB MOZ TAN | 962/3112 | 100/1559                  | 58.8 %                      | 4.82   | 3.96, 5.87                  |
| **Total (95% CI)**    | **3914**   | **2358**                  | **100.0 %**                 | **4.76** | **4.13, 5.49**              |

Total events: 1399 (Mefloquine), 193 (Sulfadoxine-pyrimethamine)
Heterogeneity: $\chi^2 = 0.04$, df = 1 ($P = 0.84$); $I^2 = 0.0$
Test for overall effect: $Z = 21.47$ ($P < 0.00001$)
Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine
Outcome: 22 AEs: fatigue/weakness

| Study or subgroup     | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|-----------------------|------------|---------------------------|-----------------------------|--------|-----------------------------|
| Briand 2009 BEN       | 321/802    | 106/799                   | 53.5 %                      | 3.02   | 2.48, 3.67                  |
| Gonzalez 2014a BEN GAB MOZ TAN | 211/3112 | 14/1559                   | 46.5 %                      | 7.55   | 4.41, 12.92                 |
| **Total (95% CI)**    | **3914**   | **2358**                  | **100.0 %**                 | **4.62** | **1.80, 11.85**            |

Total events: 532 (Mefloquine), 120 (Sulfadoxine-pyrimethamine)
Heterogeneity: $\tau^2 = 0.42$; $\chi^2 = 10.88$, df = 1 ($P = 0.00097$); $I^2 = 91$
Test for overall effect: $Z = 3.19$ ($P = 0.0014$)
Test for subgroup differences: Not applicable
### Analysis 1.23. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 23 AEs: dizziness.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 1 Mefloquine versus sulfadoxine-pyrimethamine

Outcome: 23 AEs: dizziness

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio M-H Random 95% CI | Weight | Risk Ratio M-H Random 95% CI |
|-------------------|------------|---------------------------|-----------------------------|--------|-----------------------------|
| Briand 2009 BEN   | 403/802    | 107/799                   | 49.4 % 3.75 [ 3.11, 4.53 ] |        |                             |
| Gonzalez 2014a BEN GAB MOZ TAN | 1080/3112 | 115/1559                  | 50.6 % 4.70 [ 3.92, 5.65 ] |        |                             |
| **Total (95% CI)** | **3914**   | **2358**                 | 100.0 % 4.21 [ 3.36, 5.27 ] |        |                             |

Total events: 1483 (Mefloquine), 222 (Sulfadoxine-pyrimethamine)

Heterogeneity: $\tau^2 = 0.02$, $\chi^2 = 2.95$, df = 1 ($P = 0.09$); $I^2 = 66\%$

Test for overall effect: $Z = 12.47$ ($P < 0.00001$)

Test for subgroup differences: Not applicable
### Analysis 1.24. Comparison 1 Mefloquine versus sulfadoxine-pyrimethamine, Outcome 24 AEs: headache.

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 1 Mefloquine versus sulfadoxine-pyrimethamine  
**Outcome:** 24 AEs: headache

| Study or subgroup | Mefloquine | Sulfadoxine-pyrimethamine | Risk Ratio MJ | Weight | Risk Ratio MJ |
|-------------------|------------|---------------------------|---------------|--------|---------------|
| Briand 2009 BEN   | 9/802      | 23/799                    | 43.6 %        | 0.39   | 0.39 [ 0.18, 0.84 ] |
| Gonzalez 2014a BEN GAB MOZ TAN | 254/3112 | 115/1559 | 56.4 % | 1.11 | 1.11 [ 0.90, 1.37 ] |

**Total (95% CI)**  
3914 / 2358  
100.0 %  
0.70 [ 0.25, 1.94 ]  

Heterogeneity: Tau² = 0.46; Chi² = 6.66, df = 1 (P = 0.01); I² = 85%  
Test for overall effect: Z = 0.68 (P = 0.50)  
Test for subgroup differences: Not applicable

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

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 2 Mefloquine plus cotrimoxazole versus cotrimoxazole  
**Outcome:** 1 Clinical malaria episodes during pregnancy

| Study or subgroup | log [Rate Ratio] (SE) | Rate Ratio MJ | Weight | Rate Ratio MJ |
|-------------------|----------------------|---------------|--------|---------------|
| Gonzalez 2014b KEN MOZ TAN | -0.28 (0.43) | 100.0 % | 0.76 | 0.76 [ 0.33, 1.76 ] |

**Total (95% CI)**  
100.0 %  
0.76 [ 0.33, 1.76 ]  

Heterogeneity: not applicable  
Test for overall effect: Z = 0.65 (P = 0.51)  
Test for subgroup differences: Not applicable
### Analysis 2.2. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 2 Maternal peripheral parasitaemia at delivery (PCR).

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 2 Mefloquine plus cotrimoxazole versus cotrimoxazole  
**Outcome:** 2 Maternal peripheral parasitaemia at delivery (PCR)

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|---------------------------|---------------|------------|--------|-----------|
|                   | n/N                       | n/N           | M-H,Fixed,95% CI | M-H,Fixed,95% CI |
| Denoeud-Ndam 2014a BEN | 5/106                     | 8/114         | 23.5 %       | 0.67 [ 0.23, 1.99 ] |
| Gonzalez 2014b KEN MOZ TAN | 12/385                    | 25/384        | 76.5 %       | 0.48 [ 0.24, 0.94 ] |
| **Total (95% CI)** | **491**                   | **498**       | **100.0 %**  | **0.52 [ 0.30, 0.93 ]** |

Total events: 17 (Mefloquine+cotrimoxazole), 33 (Cotrimoxazole)  
Heterogeneity: Chisq = 0.27, df = 1 (P = 0.60); I² = 0.0%  
Test for overall effect: Z = 2.22 (P = 0.027)  
Test for subgroup differences: Not applicable

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

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 2 Mefloquine plus cotrimoxazole versus cotrimoxazole  
**Outcome:** 3 Placental malaria (blood smear)

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|---------------------------|---------------|------------|--------|-----------|
|                   | n/N                       | n/N           | M-H,Fixed,95% CI | 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 %**  | **0.51 [ 0.29, 0.89 ]** |

Total events: 17 (Mefloquine+cotrimoxazole), 33 (Cotrimoxazole)  
Heterogeneity: Chisq = 0.07, df = 1 (P = 0.79); I² = 0.0%  
Test for overall effect: Z = 2.39 (P = 0.017)  
Test for subgroup differences: Not applicable
## Analysis 2.4. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 4 Placental malaria (PCR).

**Review:** Mefloquine for preventing malaria in pregnant women

**Comparison:** 2 Mefloquine plus cotrimoxazole versus cotrimoxazole

**Outcome:** 4 Placental malaria (PCR)

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|---------------------------|---------------|------------|--------|------------|
|                   | n/N                       | n/N           | M-H,Fixed 95% CI | M-H,Fixed 95% CI |
| Denoeud-Ndam 2014a | 0/105                     | 5/103         | 16.4 %      | 0.09   | [0.00, 1.59] |
| Gonzalez 2014b KEN MOZ TAN | 9/388                  | 28/381        | 83.6 %      | 0.32   | [0.15, 0.66] |
| **Total (95% CI)** | 493                       | 484           | 100.0 %     | 0.28   | [0.14, 0.57] |

Total events: 9 (Mefloquine+cotrimoxazole), 33 (Cotrimoxazole)

Heterogeneity: $\chi^2 = 0.71$, df = 1 ($P = 0.40$); $I^2 = 0.0$

Test for overall effect: $Z = 3.53$ ($P = 0.00041$)

Test for subgroup differences: Not applicable
Analysis 2.5. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 5 Mean haemoglobin at delivery.

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole
Outcome: 5 Mean haemoglobin at delivery

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Mean Difference | Weight | Mean Difference |
|------------------|--------------------------|--------------|----------------|--------|----------------|
|                  | N           | Mean(SD)    | N           | Mean(SD) | IV,Random,95% CI | IV,Random,95% CI |
| Denoeud-Ndam 2014a BEN | 96 | 11.1 (1.4) | 108 | 10.8 (1.5) | 43.1 % | 0.30 [-0.10, 0.70 ] |
| Gonzalez 2014b KEN MOZ TAN | 479 | 11.2 (2.1) | 484 | 11.3 (2.2) | 56.9 % | -0.10 [-0.37, 0.17 ] |
| Total (95% CI) | 575 | 792 | 100.0 % | 0.07 [-0.32, 0.46 ] |

Heterogeneity: Tau^2 = 0.05; Chi^2 = 2.65, df = 1 (P = 0.10); I^2 =62%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole
Outcome: 6 Maternal anaemia at delivery (< 9.5 g/dL)

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|------------------|--------------------------|--------------|------------|--------|-----------|
|                  | n/N                     | n/N          | M-H,Fixed,95% CI | M-H,Fixed,95% CI |
| Denoeud-Ndam 2014a BEN | 12/96 | 20/108 | 17.7 % | 0.68 [ 0.35, 1.31 ] |
| Gonzalez 2014b KEN MOZ TAN (1) | 87/495 | 88/498 | 82.3 % | 0.99 [ 0.76, 1.30 ] |
| Total (95% CI) | 591 | 606 | 100.0 % | 0.94 [ 0.73, 1.20 ] |

Total events: 99 (Mefloquine+cotrimoxazole), 108 (Cotrimoxazole)
Heterogeneity: Chi^2 = 1.13, df = 1 (P = 0.29); I^2 =12%
Test for overall effect: Z = 0.50 (P = 0.61)
Test for subgroup differences: Not applicable
Analysis 2.7. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 7 Maternal severe anaemia at delivery.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole

Outcome: 7 Maternal severe anaemia at delivery

| Study or subgroup                  | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio M-H,Fixed | Weight | Risk Ratio M-H,Fixed |
|-----------------------------------|--------------------------|---------------|----------------------|--------|----------------------|
| Denoeud-Ndam 2014a BEN            | 0/96                     | 0/108         | Not estimable        |        |                      |
| Gonzalez 2014b KEN MOZ TAN        | 11/479                   | 12/484        | 100.0 %              | 0.93   | [0.41, 2.08]         |
| **Total (95% CI)**                | 575                      | 592           | 100.0 %              | 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)
Test for subgroup differences: Not applicable
Analysis 2.8. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 8 Cord blood parasitaemia.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole

Outcome: 8 Cord blood parasitaemia

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|--------------------------|---------------|------------|--------|------------|
| n/N               | n/N                      | M-H,Fixed,95% CI | M-H,Fixed,95% CI |
| Denoeud-Ndam 2014a BEN (1) | 0/117 | 0/116 | Not estimable |
| Gonzalez 2014b KEN MOZ TAN | 1/471 | 3/462 | 100.0 % | 0.33 [0.03, 3.13] |

**Total (95% CI)**

588 578 100.0 % 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)

Test for subgroup differences: Not applicable

(1) Denominators for this outcome were assumed based on the flow diagram.

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

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole

Outcome: 9 Mean birth weight

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Mean Difference | Weight | Mean Difference |
|-------------------|--------------------------|---------------|----------------|--------|----------------|
| N Mean(SD) | N Mean(SD) | IV,Random,95% CI | IV,Random,95% CI |
| Denoeud-Ndam 2014a BEN | 119 2856 (454) | 126 2889 (478) | 27.5 % | -33.00 [-149.70, 83.70 ] |
| Gonzalez 2014b KEN MOZ TAN | 489 3036.3 (570.6) | 486 3059.3 (575.5) | 72.5 % | -23.00 [-94.94, 48.94 ] |

**Total (95% CI)**

608 612 100.0 % -25.75 [-86.99, 35.49]

Heterogeneity: Tau² = 0.0, Chi² = 0.02, df = 1 (P = 0.89); I² =0.0%

Test for overall effect: Z = 0.82 (P = 0.41)

Test for subgroup differences: Not applicable

Mefloquine for preventing malaria in pregnant women (Review)
### Analysis 2.10. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 10 Low birth weight.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole

Outcome: 10 Low birth weight

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|--------------------------|---------------|------------|--------|------------|
| n/N | n/N | M-H,Fixed,95% CI | M-H,Fixed,95% CI |
|-------------------|--------------------------|---------------|------------|--------|------------|
| Denoeud-Ndam 2014a BEN | 24/119 | 26/126 | 35.4 % | 0.98 [ 0.60, 1.60 ] | |
| Gonzalez 2014b KEN MOZ TAN | 61/489 | 46/486 | 64.6 % | 1.32 [ 0.92, 1.89 ] | |
| **Total (95% CI)** | **608** | **612** | **100.0 %** | **1.20 [ 0.89, 1.60 ]** |

Total events: 85 (Mefloquine+cotrimoxazole), 72 (Cotrimoxazole)

Heterogeneity: Chi$^2$ = 0.92, df = 1 (P = 0.34); I$^2$ =0.0%

Test for overall effect: Z = 1.21 (P = 0.23)

Test for subgroup differences: Not applicable
### Analysis 2.11. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 11 Prematurity.

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 2 Mefloquine plus cotrimoxazole versus cotrimoxazole  
**Outcome:** 11 Prematurity

| Study or subgroup       | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------------|--------------------------|---------------|------------|--------|------------|
|                         | n/N                      | n/N           | M-H,Random,95% CI |         | 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           | 100.0 %   | 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 = 32%  
Test for overall effect: Z = 0.22 (P = 0.82)  
Test for subgroup differences: Not applicable

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

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 2 Mefloquine plus cotrimoxazole versus cotrimoxazole  
**Outcome:** 12 SAEs during pregnancy

| Study or subgroup       | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------------|--------------------------|---------------|------------|--------|------------|
|                         | n/N                      | n/N           | M-H,Fixed,95% CI |         | M-H,Fixed,95% CI |
| Denoeud-Ndam 2014a BEN  | 9/146                    | 10/146        | 12.0 %    | 0.90 [ 0.38, 2.15 ] |
| Gonzalez 2014b KEN MOZ TAN | 48/523                  | 74/532        | 88.0 %    | 0.66 [ 0.47, 0.93 ] |
| **Total (95% CI)**     | 669                      | 678           | 100.0 %   | 0.69 [ 0.50, 0.95 ] |

Total events: 57 (Mefloquine+cotrimoxazole), 84 (Cotrimoxazole)  
Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² =0.0%  
Test for overall effect: Z = 2.30 (P = 0.022)  
Test for subgroup differences: Not applicable

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**Mefloquine for preventing malaria in pregnant women (Review)**

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

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|---------------------------|---------------|------------|--------|------------|
|                   | n/N                       | n/N           | M-H,Random,95% CI |        | M-H,Random,95% CI |
| Denoeud-Ndam 2014a BEN | 12/146                   | 6/146         | 42.5% 2.00 [0.77, 5.19] | 42.5% 2.00 [0.77, 5.19] |
| Gonzalez 2014b KEN MOZ TAN | 20/523              | 28/532        | 57.5% 0.73 [0.41, 1.27] | 57.5% 0.73 [0.41, 1.27] |
| Total (95% CI) | 669                      | 678           | 100.0% 1.12 [0.42, 2.98] | 100.0% 1.12 [0.42, 2.98] |

Total events: 32 (Mefloquine+cotrimoxazole), 34 (Cotrimoxazole)
Heterogeneity: Tau² = 0.35, Chi² = 3.22, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable

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Mefloquine for preventing malaria in pregnant women (Review)
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Analysis 2.14. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 14 Congenital malformations.

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole
Outcome: 14 Congenital malformations

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Weight | Risk Ratio M-H,Fixed 95% CI |
|-------------------|--------------------------|---------------|--------|----------------------------|
| Denoeud-Ndam 2014a BEN | 1/146 | 2/146 | 20.2 % | 0.50 [ 0.05, 5.45 ] |
| Gonzalez 2014b KEN MOZ TAN | 5/505 | 8/515 | 79.8 % | 0.64 [ 0.21, 1.94 ] |
| **Total (95% CI)** | **651** | **661** | **100.0 %** | **0.61 [ 0.22, 1.67 ]** |

Total events: 6 (Mefloquine+cotrimoxazole), 10 (Cotrimoxazole)
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0.0%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole
Outcome: 15 Maternal mortality

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Weight | Risk Ratio M-H,Fixed 95% CI |
|-------------------|--------------------------|---------------|--------|----------------------------|
| Denoeud-Ndam 2014a BEN | 1/146 | 2/146 | 33.5 % | 0.50 [ 0.05, 5.45 ] |
| Gonzalez 2014b KEN MOZ TAN | 2/523 | 4/532 | 66.5 % | 0.51 [ 0.09, 2.76 ] |
| **Total (95% CI)** | **669** | **678** | **100.0 %** | **0.51 [ 0.13, 2.01 ]** |

Total events: 3 (Mefloquine+cotrimoxazole), 6 (Cotrimoxazole)
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0.0%
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable
Analysis 2.16. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 16 Neonatal mortality.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole

Outcome: 16 Neonatal mortality

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|--------------------------|---------------|------------|--------|------------|
|                   | n/N                      | n/N           | M-H,Fixed, 95% CI |        | M-H,Fixed, 95% CI |
| Denoeud-Ndam 2014a BEN | 4/129                   | 3/130         | 23.1 %     | 1.34 [ 0.31, 5.88 ] |
| Gonzalez 2014b KEN MOZ TAN | 13/488                  | 10/492        | 76.9 %     | 1.31 [ 0.58, 2.96 ] |
| **Total (95% CI)** | **617**                  | **622**       | **100.0 %** | **1.32 [ 0.65, 2.69 ]** |

Total events: 17 (Mefloquine+cotrimoxazole), 13 (Cotrimoxazole)

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0.0%

Test for overall effect: Z = 0.76 (P = 0.45)

Test for subgroup differences: Not applicable
### Analysis 2.17. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 17 Mother-to-child transmission HIV.

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 2 Mefloquine plus cotrimoxazole versus cotrimoxazole  
**Outcome:** 17 Mother-to-child transmission HIV  

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|---------------------------|---------------|------------|--------|------------|
|                   | n/N                       | n/N           | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Denoeud-Ndam 2014a BEN | 1/80                      | 1/84          | 5.0 % | 0.07, 16.50 | 1.05 |
| Gonzalez 2014b KEN MOZ TAN | 36/420                    | 19/435        | 95.0 % | 1.14, 3.37 | 1.96 |
| Total (95% CI) | 500                        | 519           | 100.0 % | 1.13, 3.25 | 1.92 |

Total events: 37 (Mefloquine+cotrimoxazole), 20 (Cotrimoxazole)  
Heterogeneity: $\chi^2 = 0.19$, df = 1 ($P = 0.66$); $I^2 = 0.0\%$  
Test for overall effect: $Z = 2.41$ ($P = 0.016$)  
Test for subgroup differences: Not applicable

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

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 2 Mefloquine plus cotrimoxazole versus cotrimoxazole  
**Outcome:** 18 AEs: vomiting  

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|---------------------------|---------------|------------|--------|------------|
|                   | n/N                       | n/N           | M-H,Random,95% CI |        | M-H,Random,95% CI |
| Denoeud-Ndam 2014a BEN | 50/146                    | 0/146         | 380 % | 6.29, 1621.68 | 101.00 |
| Gonzalez 2014b KEN MOZ TAN | 125/523                   | 16/532        | 62.0 % | 4.79, 13.18 | 7.95 |
| Total (95% CI) | 669                        | 678           | 100.0 % | 1.40, 311.66 | 20.88 |

Total events: 175 (Mefloquine+cotrimoxazole), 16 (Cotrimoxazole)  
Heterogeneity: $\tau^2 = 3.00$, $\chi^2 = 3.90$, df = 1 ($P = 0.05$); $I^2 = 74\%$  
Test for overall effect: $Z = 2.20$ ($P = 0.028$)  
Test for subgroup differences: Not applicable
### Analysis 2.19. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 19 AEs: fatigue/weakness.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole

Outcome: 19 AEs: fatigue/weakness

| Study or subgroup | Mefloquine+ cotrimoxazole | Cotrimoxazole | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|-----------------------------|---------------|--------------------------------|--------|--------------------------------|
| n/N               | n/N                         |               |                                |        |                                |
| Denoeud-Ndam 2014a BEN | 30/146                      | 3/146         | 48.5% 10.00 [3.12, 32.04]     |        |                                |
| Gonzalez 2014b KEN MOZ TAN (1) | 11/523                      | 12/532        | 51.5% 0.93 [0.42, 2.09]       |        |                                |
| **Total (95% CI)** | **669**                     | **678**       | **100.0% 2.95 [0.26, 32.93]** |        |                                |

Total events: 41 (Mefloquine+ cotrimoxazole), 15 (Cotrimoxazole)

Heterogeneity: $\tau^2 = 2.77$; $\chi^2 = 11.60$, df = 1 ($P = 0.00066$); $I^2 = 91$

Test for overall effect: $Z = 0.88$ ($P = 0.38$)

Test for subgroup differences: Not applicable

(1) Unpublished data. These data were obtained by contacting the authors.
## Analysis 2.20. Comparison 2 Mefloquine plus cotrimoxazole versus cotrimoxazole, Outcome 20 AEs: dizziness.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole

Outcome: 20 AEs: dizziness

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|--------------------------|---------------|--------------------------------|--------|-------------------------------|
| Denoeud-Ndam 2014a BEN | 52/146 | 0/146 | 43.3 % | 105.00 [ 6.54, 1685.03 ] |
| Gonzalez 2014b KEN MOZ TAN | 155/523 | 40/532 | 56.7 % | 3.94 [ 2.85, 5.46 ] |
| **Total (95% CI)** | **669** | **678** | **100.0 %** | **16.34 [ 0.39, 684.99 ]** |

Total events: 207 (Mefloquine+cotrimoxazole), 40 (Cotrimoxazole)

Heterogeneity: $\tau^2 = 6.38$, $Chi^2 = 7.28$, df = 1 ($P = 0.01$); $I^2 = 86\%$

Test for overall effect: $Z = 1.47$ ($P = 0.14$)

Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 2 Mefloquine plus cotrimoxazole versus cotrimoxazole

Outcome: 21 AEs: headache

| Study or subgroup | Mefloquine+cotrimoxazole | Cotrimoxazole | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|--------------------------|---------------|--------------------------------|--------|-------------------------------|
| Denoeud-Ndam 2014a BEN | 1/146 | 4/146 | 17.7 % | 0.25 [ 0.03, 2.21 ] |
| Gonzalez 2014b KEN MOZ TAN | 38/523 | 40/532 | 82.3 % | 0.97 [ 0.63, 1.48 ] |
| **Total (95% CI)** | **669** | **678** | **100.0 %** | **0.76 [ 0.28, 2.10 ]** |

Total events: 39 (Mefloquine+cotrimoxazole), 44 (Cotrimoxazole)

Heterogeneity: $\tau^2 = 0.28$, $Chi^2 = 1.43$, df = 1 ($P = 0.23$); $I^2 = 30\%$

Test for overall effect: $Z = 0.53$ ($P = 0.60$)

Test for subgroup differences: Not applicable
Analysis 3.1. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 1 Maternal peripheral parasitaemia at delivery (PCR).

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 3 Mefloquine versus cotrimoxazole
Outcome: 1 Maternal peripheral parasitaemia at delivery (PCR)

| Study or subgroup | Mefloquine | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------------|------------|--------|------------|
|                   | n/N        | n/N           | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Denoeud-Ndam 2014b BEN | 1/48      | 5/50          | 100.0 % | 0.21 [ 0.03, 1.72 ] |
| **Total (95% CI)** | **48** | **50** | **100.0 %** | **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)
Test for subgroup differences: Not applicable
### Analysis 3.2. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 2 Placental malaria (PCR).

**Review:** Mefloquine for preventing malaria in pregnant women  
**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 | 0.73 [0.13, 4.15] | 100.0 % | 0.73 [0.13, 4.15] |

Total (95% CI)  
Total events: 2 (Mefloquine), 3 (Cotrimoxazole)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.36 (P = 0.72)  
Test for subgroup differences: Not applicable

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

**Review:** Mefloquine for preventing malaria in pregnant women  
**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 | 0.35 [0.01, 8.30] | 100.0 % | 0.35 [0.01, 8.30] |

Total (95% CI)  
Total events: 0 (Mefloquine), 1 (Cotrimoxazole)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.65 (P = 0.51)  
Test for subgroup differences: Not applicable
### Analysis 3.4. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 4 Mean haemoglobin at delivery.

Review: Mefloquine for preventing malaria in pregnant women  
Comparison: 3 Mefloquine versus cotrimoxazole  
Outcome: 4 Mean haemoglobin at delivery

| Study or subgroup | Mefloquine | Cotrimoxazole | Mean Difference | Weight | Mean Difference |
|-------------------|------------|---------------|----------------|--------|----------------|
| Denoeud-Ndam 2014b BEN | 47 11.2 (1.4) | 53 11.3 (1.5) | -0.10 [-0.67, 0.47] | 100.0 % | -0.10 [-0.67, 0.47] |

Heterogeneity: not applicable  
Test for overall effect: Z = 0.34 (P = 0.73)  
Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women  
Comparison: 3 Mefloquine versus cotrimoxazole  
Outcome: 5 Maternal anaemia at delivery (< 9.5 g/dL)

| Study or subgroup | Mefloquine | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------------|------------|--------|------------|
| Denoeud-Ndam 2014b BEN | 4/47 | 5/53 | 0.90 [0.26, 3.16] | 100.0 % | 0.90 [0.26, 3.16] |

Total events: 4 (Mefloquine), 5 (Cotrimoxazole)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.16 (P = 0.87)  
Test for subgroup differences: Not applicable
### Analysis 3.6. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 6 Mean birth weight.

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 3 Mefloquine versus cotrimoxazole  
**Outcome:** Mean birth weight

| Study or subgroup         | Mefloquine | Cotrimoxazole | Mean Difference (IV/Fixed, 95% CI) | Weight | Mean Difference (IV/Fixed, 95% CI) |
|---------------------------|------------|---------------|-----------------------------------|--------|-----------------------------------|
| Denoeud-Ndam 2014b BEN    | 56         | 64            | -102.00 [-255.52, 51.52]          | 100.0% | -102.00 [-255.52, 51.52]          |
| **Total (95% CI)**        | 56         | 64            | 100.0%                            |        | 100.0%                            |

**Test for overall effect:** $Z = 1.30$ (P = 0.19)  
**Test for subgroup differences:** Not applicable

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

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 3 Mefloquine versus cotrimoxazole  
**Outcome:** Low birth weight

| Study or subgroup         | Mefloquine | Cotrimoxazole | Risk Ratio (M-H, Fixed, 95% CI) | Weight | Risk Ratio (M-H, Fixed, 95% CI) |
|---------------------------|------------|---------------|--------------------------------|--------|--------------------------------|
| Denoeud-Ndam 2014b BEN    | 8/56       | 6/64          | 1.52 [0.56, 4.13]               | 100.0% | 1.52 [0.56, 4.13]               |
| **Total (95% CI)**        | 56         | 64            | 100.0%                          |        | 100.0%                          |

**Total events:** 8 (Mefloquine), 6 (Cotrimoxazole)  
**Heterogeneity:** not applicable  
**Test for overall effect:** $Z = 0.83$ (P = 0.41)  
**Test for subgroup differences:** Not applicable
### Analysis 3.8. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 8 Prematurity.

Review: Mefloquine for preventing malaria in pregnant women  
Comparison: 3 Mefloquine versus cotrimoxazole  
Outcome: 8 Prematurity

| Study or subgroup | Mefloquine | Cotrimoxazole | Risk Ratio | Weight |
|-------------------|------------|---------------|------------|--------|
|                   | n/N        | n/N           | M-H,Fixed,95% CI |        |
| Denoeud-Ndam 2014b | 5/60       | 5/65          | 100.0 %   | 1.08 [ 0.33, 3.56 ] |
| **Total** (95% CI) | 60         | 65            | 100.0 %   | 1.08 [ 0.33, 3.56 ] |

Total events: 5 (Mefloquine), 5 (Cotrimoxazole)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.13 (P = 0.90)  
Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women  
Comparison: 3 Mefloquine versus cotrimoxazole  
Outcome: 9 SAEs during pregnancy

| Study or subgroup | Mefloquine | Cotrimoxazole | Risk Ratio | Weight |
|-------------------|------------|---------------|------------|--------|
|                   | n/N        | n/N           | M-H,Fixed,95% CI |        |
| Denoeud-Ndam 2014b | 4/68       | 4/72          | 100.0 %   | 1.06 [ 0.28, 4.07 ] |
| **Total** (95% CI) | 68         | 72            | 100.0 %   | 1.06 [ 0.28, 4.07 ] |

Total events: 4 (Mefloquine), 4 (Cotrimoxazole)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.08 (P = 0.93)  
Test for subgroup differences: Not applicable
### Analysis 3.10. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 10 Stillbirths.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 3 Mefloquine versus cotrimoxazole

Outcome: 10 Stillbirths

| 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 | 4/67           | 1/72               | 100.0 %                     | 4.30 [ 0.49, 37.49 ] |
| **Total (95% CI)** | **67**         | **72**             | **100.0 %**                 | **4.30 [ 0.49, 37.49 ]** |

Total events: 4 (Mefloquine), 1 (Cotrimoxazole)
Heterogeneity: not applicable
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 3 Mefloquine versus cotrimoxazole

Outcome: 11 Spontaneous abortions

| 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 | 1/67           | 1/72               | 100.0 %                     | 1.07 [ 0.07, 16.84 ] |
| **Total (95% CI)** | **67**         | **72**             | **100.0 %**                 | **1.07 [ 0.07, 16.84 ]** |

Total events: 1 (Mefloquine), 1 (Cotrimoxazole)
Heterogeneity: not applicable
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable
### Analysis 3.12. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 12 Congenital malformations.

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 3 Mefloquine versus cotrimoxazole  
**Outcome:** 12 Congenital malformations

| Study or subgroup | Mefloquine | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------------|------------|--------|------------|
| n/N               | n/N        |               | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Denoeud-Ndam 2014b BEN | 2/67       | 2/72          | 1.07 [0.16, 7.41] | 100.0% | 1.07 [0.16, 7.41] |
| **Total (95% CI)** | **67**     | **72**        | **100.0%** | **1.07 [0.16, 7.41]** |

Total events: 2 (Mefloquine), 2 (Cotrimoxazole)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.07 (P = 0.94)  
Test for subgroup differences: Not applicable

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

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 3 Mefloquine versus cotrimoxazole  
**Outcome:** 13 Maternal mortality

| Study or subgroup | Mefloquine | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------------|------------|--------|------------|
| n/N               | n/N        |               | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Denoeud-Ndam 2014b BEN | 0/67       | 0/72          | Not estimable |        | Not estimable |
| **Total (95% CI)** | **67**     | **72**        | Not estimable |        | Not estimable |

Total events: 0 (Mefloquine), 0 (Cotrimoxazole)  
Heterogeneity: not applicable  
Test for overall effect: not applicable  
Test for subgroup differences: Not applicable
### Analysis 3.14. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 14 Neonatal mortality.

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 3 Mefloquine versus cotrimoxazole  
**Outcome:** 14 Neonatal mortality

| 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 | 1/63 | 1/66 | 1.05 [0.07, 16.39] | 100.0 | 1.05 [0.07, 16.39] |
| **Total (95% CI)** | 63 | 66 | 100.0 | 1.05 [0.07, 16.39] |

Total events: 1 (Mefloquine), 1 (Cotrimoxazole)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.03 (P = 0.97)  
Test for subgroup differences: Not applicable

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

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 3 Mefloquine versus cotrimoxazole  
**Outcome:** 15 Infant deaths after 7 days

| 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 | 2/63 | 1/66 | 2.10 [0.19, 22.54] | 100.0 | 2.10 [0.19, 22.54] |
| **Total (95% CI)** | 63 | 66 | 100.0 | 2.10 [0.19, 22.54] |

Total events: 2 (Mefloquine), 1 (Cotrimoxazole)  
Heterogeneity: not applicable  
Test for overall effect: Z = 0.61 (P = 0.54)  
Test for subgroup differences: Not applicable
Analysis 3.16. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 16 AEs: vomiting.

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 3 Mefloquine versus cotrimoxazole
Outcome: 16 AEs: vomiting

| Study or subgroup | Mefloquine n/N | Cotrimoxazole n/N | Risk Ratio M-H,Fixed,95% CI | Weight |
|------------------|---------------|-------------------|-----------------------------|--------|
| Denoeud-Ndam 2014b BEN | 25/67 | 2/72 | 13.43 [3.31, 54.54] | 100.0% |
| **Total (95% CI)** | 67 | 72 | 13.43 [3.31, 54.54] | 100.0% |

Total events: 25 (Mefloquine), 2 (Cotrimoxazole)
Heterogeneity: not applicable
Test for overall effect: Z = 3.63 (P = 0.00028)
Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women
Comparison: 3 Mefloquine versus cotrimoxazole
Outcome: 17 AEs: fatigue/weakness

| Study or subgroup | Mefloquine n/N | Cotrimoxazole n/N | Risk Ratio M-H,Fixed,95% CI | Weight |
|------------------|---------------|-------------------|-----------------------------|--------|
| Denoeud-Ndam 2014b BEN | 13/67 | 2/72 | 6.99 [1.64, 29.81] | 100.0% |
| **Total (95% CI)** | 67 | 72 | 6.99 [1.64, 29.81] | 100.0% |

Total events: 13 (Mefloquine), 2 (Cotrimoxazole)
Heterogeneity: not applicable
Test for overall effect: Z = 2.63 (P = 0.0087)
Test for subgroup differences: Not applicable
### Analysis 3.18. Comparison 3 Mefloquine versus cotrimoxazole, Outcome 18 AEs: dizziness.

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 3 Mefloquine versus cotrimoxazole  
**Outcome:** 18 AEs: dizziness

| Study or subgroup | Mefloquine | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------------|------------|--------|------------|
|                   | n/N        | n/N           | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Denoeud-Ndam 2014b BEN | 24/67      | 0/72          | 100.0 % | 52.60 [3.26, 848.24] |

**Total (95% CI)**  
67 72  
**Total events:** 24 (Mefloquine), 0 (Cotrimoxazole)  
**Heterogeneity:** not applicable  
**Test for overall effect:** Z = 2.79 (P = 0.0052)  
**Test for subgroup differences:** Not applicable

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

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 3 Mefloquine versus cotrimoxazole  
**Outcome:** 19 AEs: headache

| Study or subgroup | Mefloquine | Cotrimoxazole | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------------|------------|--------|------------|
|                   | n/N        | n/N           | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Denoeud-Ndam 2014b BEN | 0/67      | 2/72          | 100.0 % | 0.21 [0.01, 4.39] |

**Total (95% CI)**  
67 72  
**Total events:** 0 (Mefloquine), 2 (Cotrimoxazole)  
**Heterogeneity:** not applicable  
**Test for overall effect:** Z = 1.00 (P = 0.32)  
**Test for subgroup differences:** Not applicable
## Analysis 4.1. Comparison 4 Mefloquine versus placebo, Outcome 1 Maternal peripheral parasitaemia during pregnancy.

### Review: Mefloquine for preventing malaria in pregnant women

### Comparison: 4 Mefloquine versus placebo

### Outcome: 1 Maternal peripheral parasitaemia during pregnancy

| Study or subgroup | Mefloquine | Placebo | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------|------------|--------|-----------|
|                   | n/N        | n/N     | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Nosten 1994 THA    | 5/171      | 37/168  |                     | 100.0% | 0.13 [0.05, 0.33] |
| **Total (95% CI)**| **171**    | **168** |                     | 100.0% | 0.13 [0.05, 0.33] |

Total events: 5 (Mefloquine), 37 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 4.35 (P = 0.000013)

Test for subgroup differences: Not applicable

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

### Review: Mefloquine for preventing malaria in pregnant women

### Comparison: 4 Mefloquine versus placebo

### Outcome: 2 Placental malaria

| Study or subgroup | Mefloquine | Placebo | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------|------------|--------|-----------|
|                   | n/N        | n/N     | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Nosten 1994 THA    | 0/111      | 3/109   |                     | 100.0% | 0.14 [0.01, 2.68] |
| **Total (95% CI)**| **111**    | **109** |                     | 100.0% | 0.14 [0.01, 2.68] |

Total events: 0 (Mefloquine), 3 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable

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

**Review:** Mefloquine for preventing malaria in pregnant women

**Comparison:** 4 Mefloquine versus placebo

**Outcome:** 3 Mean birth weight

| Study or subgroup | Mefloquine | Placebo | Mean Difference | Weight | Mean Difference |
|-------------------|------------|---------|----------------|--------|----------------|
|                   | N Mean(SD)| N Mean(SD)| IV,Fixed,95% CI| IV,Fixed,95% CI|
| Nosten 1994 THA (1) | 146 2877 (433) | 144 2957 (475) | 100.0 % -80.00 [ -184.65, 24.65 ] |
| **Total (95% CI)** | 146 | 144 | 100.0 % -80.00 [ -184.65, 24.65 ] |

Heterogeneity: not applicable

Test for overall effect: Z = 1.50 (P = 0.13)

Test for subgroup differences: Not applicable

(1) Denominators from live births

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

**Review:** Mefloquine for preventing malaria in pregnant women

**Comparison:** 4 Mefloquine versus placebo

**Outcome:** 4 Low birth weight

| Study or subgroup | Mefloquine n/N | Placebo n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-------------------|---------------|-------------|---------------------------|--------|---------------------------|
| Nosten 1994 THA   | 24/146        | 17/144      | 1.39 [ 0.78, 2.48 ]       | 100.0 % | 1.39 [ 0.78, 2.48 ]       |
| **Total (95% CI)** | 146           | 144         | 100.0 % 1.39 [ 0.78, 2.48 ] |

Total events: 24 (Mefloquine), 17 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.12 (P = 0.26)

Test for subgroup differences: Not applicable
### Analysis 4.5. Comparison 4 Mefloquine versus Placebo, Outcome 5 Prematurity.

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 4 Mefloquine versus placebo  
**Outcome:** 5 Prematurity

| Study or subgroup | Mefloquine | Placebo | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|---------|------------|--------|------------|
|                  | n/N        | n/N     | M-H,Fixed 95% CI | M-H,Fixed 95% CI |
| Nosten 1994 THA   | 4/102      | 8/97    | 100.0 %     | 0.48 [ 0.15, 1.53 ] |

**Total (95% CI):** 102 97 100.0 % 0.48 [ 0.15, 1.53 ]

- **Total events:** 4 (Mefloquine), 8 (Placebo)  
- **Heterogeneity:** not applicable  
- **Test for overall effect:** Z = 1.25 (P = 0.21)  
- **Test for subgroup differences:** Not applicable

### Analysis 4.6. Comparison 4 Mefloquine versus Placebo, Outcome 6 Stillbirths.

**Review:** Mefloquine for preventing malaria in pregnant women  
**Comparison:** 4 Mefloquine versus placebo  
**Outcome:** 6 Stillbirths

| Study or subgroup | Mefloquine | Placebo | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|---------|------------|--------|------------|
|                  | n/N        | n/N     | M-H,Fixed 95% CI | M-H,Fixed 95% CI |
| Nosten 1994 THA   | 11/159     | 4/152   | 100.0 %     | 2.63 [ 0.86, 8.08 ] |

**Total (95% CI):** 159 152 100.0 % 2.63 [ 0.86, 8.08 ]

- **Total events:** 11 (Mefloquine), 4 (Placebo)  
- **Heterogeneity:** not applicable  
- **Test for overall effect:** Z = 1.69 (P = 0.091)  
- **Test for subgroup differences:** Not applicable
### Analysis 4.7. Comparison 4 Mefloquine versus placebo, Outcome 7 Spontaneous abortions.

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 4 Mefloquine versus placebo

Outcome: 7 Spontaneous abortions

| Study or subgroup | Mefloquine | Placebo | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|---------|------------|--------|------------|
| n/N              | n/N        | M-H,Fixed,95% CI |          |        | M-H,Fixed,95% CI |
| Nosten 1994 THA | 1/159      | 2/152   | 0.48 [0.04, 5.22] | 100.0 % | 0.48 [0.04, 5.22] |

Total (95% CI) 159 152

Total events: 1 (Mefloquine), 2 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.61 (P = 0.54)

Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria in pregnant women

Comparison: 4 Mefloquine versus placebo

Outcome: 8 Congenital malformations

| Study or subgroup | Mefloquine | Placebo | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|---------|------------|--------|------------|
| n/N              | n/N        | M-H,Fixed,95% CI |          |        | M-H,Fixed,95% CI |
| Nosten 1994 THA | 4/159      | 1/152   | 3.82 [0.43, 33.83] | 100.0 % | 3.82 [0.43, 33.83] |

Total (95% CI) 159 152

Total events: 4 (Mefloquine), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.21 (P = 0.23)

Test for subgroup differences: Not applicable
### Analysis 4.9. Comparison 4 Mefloquine versus placebo, Outcome 9 Maternal mortality.

Review: Mefloquine for preventing malaria in pregnant women  
Comparison: 4 Mefloquine versus placebo  
Outcome: 9 Maternal mortality

| Study or subgroup | Mefloquine | Placebo | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------|------------|--------|-----------|
|                   | n/N        | n/N     | M-H,Fixed,95% CI | M-H,Fixed,95% CI |
| Nosten 1994 THA (1) | 1/171 | 0/168 | 100.0 % | 2.95 [0.12, 71.85] |
| **Total (95% CI)** | 171 | 168 | 100.0 % | 2.95 [0.12, 71.85] |

Total events: 1 (Mefloquine), 0 (Placebo)  
Heterogeneity: not applicable  
Test for overall effect: $Z = 0.66$ ($P = 0.51$)  
Test for subgroup differences: Not applicable

(1) Denominators based on included participants

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

Review: Mefloquine for preventing malaria in pregnant women  
Comparison: 4 Mefloquine versus placebo  
Outcome: 10 Infant mortality

| Study or subgroup | Mefloquine | Placebo | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------|------------|--------|-----------|
|                   | n/N        | n/N     | M-H,Fixed,95% CI | M-H,Fixed,95% CI |
| Nosten 1994 THA | 25/144 | 24/144 | 100.0 % | 1.04 [0.63, 1.74] |
| **Total (95% CI)** | 144 | 144 | 100.0 % | 1.04 [0.63, 1.74] |

Total events: 25 (Mefloquine), 24 (Placebo)  
Heterogeneity: not applicable  
Test for overall effect: $Z = 0.16$ ($P = 0.88$)  
Test for subgroup differences: Not applicable
APPENDICES

Appendix 1. Search strategies

| Search set | CIDG Register | 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                | -     |
| 9          | -             | 5 and 8               | 5 and 8               | 5 and 8               | -     |

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.
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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.

INDEX TERMS

Medical Subject Headings (MeSH)

*Insecticide-Treated Bednets; Abortion, Spontaneous [chemically induced; epidemiology]; Africa South of the Sahara [epidemiology]; Antimalarials [adverse effects; *therapeutic use]; Dizziness [chemically induced; epidemiology]; Drug Combinations; Drug Therapy, Combination; HIV Infections [complications]; Infant, Low Birth Weight; Malaria [epidemiology; *prevention & control]; Mefloquine [adverse effects; *therapeutic use]; Parasitemia [epidemiology]; Pregnancy Complications, Parasitic [epidemiology; *prevention & control]; Pyrimethamine [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic; Sulfadoxine [adverse effects; therapeutic use]; Thailand [epidemiology]; Trimethoprim, Sulfamethoxazole Drug Combination [therapeutic use]; Vomiting [chemically induced; epidemiology]

MeSH check words

Female; Humans; Pregnancy