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Intermittent preventive treatment regimens for malaria in HIV-positive pregnant women (Review)

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[Intervention Review]

Intermittent preventive treatment regimens for malaria in HIV-positive pregnant women

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ABSTRACT

Background

Malaria and HIV infection overlap geographically in sub-Saharan Africa and share risk factors. HIV infection increases malaria's severity, especially in pregnant women. The World Health Organization (WHO) recommends intermittent preventive treatment in pregnancy (IPTp) with sulphadoxine-pyrimethamine (SP) for pregnant women living in areas of stable malaria transmission. However, HIV-positive women on daily cotrimoxazole prophylaxis (recommended for prevention of opportunistic infections in people with HIV) cannot receive SP due to adverse drug interactions, so malaria prevention in this vulnerable population currently relies on daily cotrimoxazole prophylaxis alone. This review is based on a new protocol and provides an update to the 2011 Cochrane Review that evaluated alternative drugs for IPTp to prevent malaria in HIV-positive women.

Objectives

To compare the safety and efficacy of intermittent preventive treatment regimens for malaria prevention in HIV-positive pregnant women.

Search methods

We searched CENTRAL, MEDLINE, Embase, three other databases, and two trial registries to 31 January 2024. To identify relevant additional studies or unpublished work, we checked references and contacted study authors and other researchers working on malaria and HIV.

Selection criteria

We included randomized controlled trials (RCTs) comparing any intermittent preventive treatment regimen for preventing malaria in HIV-positive pregnant women against daily cotrimoxazole prophylaxis alone, placebo, current or previous standard of care, or combinations of these options. By 'standard of care' we refer to the country's recommended drug regimen to prevent malaria in pregnancy among HIV-positive women, or the treatment that a trial's research team considered to be the standard of care.

Data collection and analysis

Review authors, in pairs, independently screened all records identified by the search strategy, applied inclusion criteria, assessed risk of bias in included trials, and extracted data. We contacted trial authors when additional information was required. 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). We assessed the certainty of the evidence using the GRADE approach for what we considered to be the main comparisons and outcomes.

Main results

We included 14 RCTs, with a total of 4976 HIV-positive pregnant women initially randomized. All trials assessed the efficacy and safety of one antimalarial used as IPTp (mefloquine, dihydroartemisinin/piperaquine, SP, or azithromycin) with or without daily cotrimoxazole, compared to daily cotrimoxazole alone, placebo, or a standard of care regimen. We grouped the trials into nine comparisons. Our main comparison evaluated the current standard of care (daily cotrimoxazole) with another drug regimen (mefloquine or dihydroartemisinin/piperaquine) versus daily cotrimoxazole with or without placebo. In this comparison, two trials evaluated mefloquine and three evaluated dihydroartemisinin/piperaquine. We conducted meta-analyses that included trials evaluating dihydroartemisinin/piperaquine plus cotrimoxazole, and trials that evaluated mefloquine plus cotrimoxazole, as we considered there to be no qualitative or quantitative heterogeneity among trials for most outcomes. We considered drug-related adverse events and HIV-related outcomes to be drug-specific.

Daily cotrimoxazole prophylaxis plus another drug regimen (mefloquine or dihydroartemisinin/piperaquine) probably results in lower risk of maternal peripheral parasitaemia at delivery (RR 0.62, 95% CI 0.41 to 0.95; 2406 participants, 5 trials; moderate-certainty evidence). It results in little or no difference in maternal anaemia cases at delivery (RR 0.98, 95% CI 0.90 to 1.07; 2417 participants, 3 trials; high-certainty evidence). It probably results in a decrease in placental malaria measured by blood smear (RR 0.54, 95% CI 0.31 to 0.93; 1337 participants, 3 trials; moderate-certainty evidence), and probably results in little or no difference in low birth weight (RR 1.16, 95% CI 0.95 to 1.41; 2915 participants, 5 trials; moderate-certainty evidence). There is insufficient evidence to ascertain whether daily cotrimoxazole prophylaxis plus another drug regimen affects the risk of cord blood parasitaemia (RR 0.27, 95% CI 0.04 to 1.64; 2696 participants, 5 trials; very low-certainty evidence).

Daily cotrimoxazole prophylaxis plus another drug regimen probably results in little or no difference in foetal loss (RR 1.03, 95% CI 0.73 to 1.46; 2957 participants, 5 trials; moderate-certainty evidence), and may result in little or no difference in neonatal mortality (RR 1.21, 95% CI 0.68 to 2.14; 2706 participants, 4 trials; low-certainty evidence).

Due to the probability of an increased risk of mother-to-child HIV transmission and some adverse drug effects noted with mefloquine, we also looked at the results for dihydroartemisinin/piperaquine specifically.

Dihydroartemisinin/piperaquine plus daily contrimoxazole probably results in little to no difference in maternal peripheral parasitaemia (RR 0.59, 95% CI 0.31 to 1.11; 1517 participants, 3 trials; moderate-certainty evidence) or anaemia at delivery (RR 0.95, 95% CI 0.82 to 1.10; 1454 participants, 2 trials; moderate-certainty evidence), but leads to fewer women having placental malaria when measured by histopathologic analysis (RR 0.67, 95% CI 0.50 to 0.90; 1570 participants, 3 trials; high-certainty evidence). The addition of dihydroartemisinin/piperaquine to daily cotrimoxazole probably made little to no difference to rates of low birth weight (RR 1.13, 95% CI 0.87 to 1.48; 1695 participants, 3 trials), foetal loss (RR 1.14, 95% CI 0.68 to 1.90; 1610 participants, 3 trials), or neonatal mortality (RR 1.03, 95% CI 0.39 to 2.72; 1467 participants, 2 trials) (all moderate-certainty evidence). We found low-certainty evidence of no increased risk of gastrointestinal drug-related adverse events (RR 1.42, 95% CI 0.51 to 3.98; 1447 participants, 2 trials) or mother-to-child HIV transmission (RR 1.54, 95% CI 0.26 to 9.19; 1063 participants, 2 trials).

Authors' conclusions

Dihydroartemisinin/piperaquine and mefloquine added to daily cotrimoxazole seem to be efficacious in preventing malaria infection in HIV-positive pregnant women compared to daily cotrimoxazole alone. However, increased risk of HIV transmission to the foetus and poor drug tolerability may be barriers to implementation of mefloquine in practice. In contrast, the evidence suggests that dihydroartemisinin/piperaquine does not increase the risk of HIV mother-to-child transmission and is well tolerated.

PLAIN LANGUAGE SUMMARY

Drugs to prevent malaria in HIV-positive pregnant women

Key messages

• For HIV-positive pregnant women, adding an antimalarial drug (such as mefloquine or dihydroartemisinin/piperaquine) to usual infection-prevention treatment for people with HIV (daily cotrimoxazole):

- probably reduces the risk of the mother being infected with malaria when she delivers her baby;

- probably reduces malarial infection in the placenta;

- probably does not affect the risk of losing the baby before delivery or after birth, or of the baby having a low birthweight.

• Although mefloquine, when added to daily cotrimoxazole, probably reduces the risk of malaria infection in HIV-positive women, it probably increases the risk of mother-to-child HIV transmission and may have a higher risk of negative drug reactions.

• Dihydroartemisinin/piperaquine, when added to daily cotrimoxazole, probably reduces the risk of malaria in the placenta of HIV-positive pregnant women. It probably makes no difference to the risk of low birth weight or losing the baby before or after birth, or the risk of minor side effects, such as vomiting.

Why is malaria prevention in HIV-positive pregnant women important?

HIV-positive pregnant women are vulnerable to malaria. Having both malaria and HIV can make malaria worse in pregnancy, increasing the risk of health complications for women and their babies. Daily intake of a drug called cotrimoxazole is recommended to prevent infections in people with HIV, including pregnant women, in many countries where malaria is common. The drug that is recommended to prevent malaria in pregnancy, sulfadoxine-pyrimethamine, cannot be taken by women on cotrimozaxole because of potential negative interactions between the two drugs.

What did we want to find out?

We wanted to know if antimalarial drugs currently available are effective and safe when used for preventing malaria in HIV-positive pregnant women. This is an update of a Cochrane Review published in 2011.

What did we do?

We searched for studies that investigated the benefits and harms of antimalarial drugs used for prevention of malaria among HIV-positive pregnant women. We combined the results of these studies.

What did we find?

We found 14 studies with 4976 HIV-positive pregnant women. The studies were conducted between 2002 and 2023 in sub-Saharan African countries: Benin, Central African Republic, Gabon, Malawi, Mozambique, Nigeria, Kenya, Tanzania, Togo, Uganda, and Zambia. The studies tested nine comparisons of different drug regimens.

What are our main results?

Adding an anti-malarial drug such as mefloquine or dihydroartemisinin/piperaquine to daily cotrimoxazole probably reduces the risk of malaria infection in the mother's blood at delivery and in the placenta. It probably does not increase or decrease the risk of having a baby with low birth weight, or of losing the baby before or after birth. It probably does not increase or decrease the mother's risk of anaemia (i.e. low level of iron in the blood). We do not know if it has any effect on the risk of malarial parasites in the baby's umbilical cord.

Although mefloquine probably reduces the risk of malarial infection, it probably increases the risk of mother-to-child HIV transmission and may be more likely to cause negative drug-related effects, when compared to daily cotrimoxazole alone.

When we looked separately at the studies that evaluated dihydroartemisinin/piperaquine, we found that dihydroartemisinin/piperaquine added to daily cotrimoxazole probably does not reduce the presence of the *Plasmodium* parasites in the mother's blood at delivery or her risk of anaemia, but it reduces malarial infection in the placenta. It probably does not increase or decrease the risk of low birth weight, or of losing the baby before or after birth. Dihydroartemisinin/piperaquine plus daily cotrimoxazole may not increase the risk of mother-to-child HIV transmission, compared to daily cotrimoxazole alone, and may not increase the risk of negative side effects from taking the drug.

What are the limitations of the evidence?

In terms of routine preventive treatment for HIV-positive women (daily cotrimoxazole) plus any other drug (mefloquine or dihydroartemisinin/piperaquine), we are confident in the evidence regarding maternal anaemia at delivery. We are moderately confident in the evidence regarding presence of parasites in the mother's blood and placenta, babies born with low birth weight, and stillbirths and spontaneous abortions. It is possible that people in one of the studies were aware of who had received each drug regimen, which could have affected the study results. We are less confident in our results for presence of parasites in the cord blood and the risk of the baby dying after birth, because the results from the studies varied widely.

In terms of routine preventive treatment (daily cotrimoxazole) plus dihydroartemisinin/piperaquine specifically, we are confident in the evidence regarding malaria infection detected by the presence of parasites in the mother's placenta. We are moderately confident in the evidence regarding presence of parasites in the mother's blood, maternal anaemia at delivery, babies born with low birth weight, stillbirths and spontaneous abortions, and infant deaths. We are less confident in our results for the drug's side effects, and HIV transmission from mother to baby.

How up to date is this evidence?

The review authors searched for studies up to 31 January 2024.

SUMMARY OF FINDINGS

Summary of findings 1. Daily cotrimoxazole with another antimalarial drug regimen (mefloquine or dihydroartemisinin/piperaquine) versus cotrimoxazole with or without placebo for malaria prophylaxis during pregnancy among HIV-positive women

Population: HIV-positive pregnant women

Setting: sub-Saharan Africa (Benin, Gabon, Kenya, Malawi, Mozambique, Tanzania, and Uganda)

Intervention: daily cotrimoxazole with another antimalarial drug regimen (mefloquine or dihydroartemisinin/piperaquine (DHA-PPQ))

Comparison: daily cotrimoxazole with or without placebo

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with daily cotrimoxazole with or without placebo	Risk with daily cotrimoxazole with another drug regimen (mefloquine or DHA-PPQ)				
Maternal peripheral parasitaemia at delivery (amplification techniques)	46 per 1000	29 per 1000 (19 to 44)	RR 0.62 (0.41 to 0.95)	2406 (5 RCTs)	⊕⊕⊕⊖ MODERATE [a]	Daily cotrimoxazole prophylaxis with another drug regimen (mefloquine or DHA-PPQ) probably results in lower maternal peripheral parasitaemia at delivery measured by amplification techniques.
Maternal anaemia at delivery	470 per 1000	461 per 1000 (423 to 503)	RR 0.98 (0.90 to 1.07)	2417 (3 RCTs)	⊕⊕⊕⊕ HIGH	Daily cotrimoxazole prophylaxis with another drug regimen (mefloquine or DHA-PPQ) results in little or no difference in maternal anaemia cases at delivery.
Placental malaria (blood smear)	52 per 1000	28 per 1000 (16 to 48)	RR 0.54 (0.31 to 0.93)	1337 (3 RCTs)	⊕⊕⊕⊖ MODERATE [a]	Daily cotrimoxazole prophylaxis with another drug regimen (mefloquine or DHA-PPQ) probably results in a decrease in placental malaria measured by blood smear.
Low birth weight (< 2500 g)	111 per 1000	128 per 1000 (105 to 156)	RR 1.16 (0.95 to 1.41)	2915 (5 RCTs)	⊕⊕⊕⊖ MODERATE [b]	Daily cotrimoxazole prophylaxis with another drug regimen (mefloquine or DHA-PPQ) probably results in little or no difference in low birth weight.
Cord blood parasitaemia (blood smear)	4 per 1000	1 per 1000 (0 to 6)	RR 0.27 (0.04 to 1.64)	2696 (5 RCTs)	⊕⊖⊖⊖ VERY LOW [b,c]	We do not know if daily cotrimoxazole prophylaxis with another drug regimen (mefloquine or DHA-PPQ) results

						in a difference in cord blood parasitaemia measured by blood smear.
Foetal loss	41 per 1000	42 per 1000 (30 to 60)	RR 1.03 (0.73 to 1.46)	2957 (5 RCTs)	⊕⊝⊝⊝ MODERATE [b]	Daily cotrimoxazole prophylaxis with another drug regimen (mefloquine or DHA-PPQ) probably results in little or no difference in foetal loss.
Neonatal mortality	15 per 1000	19 per 1000 (10 to 33)	RR 1.21 (0.68 to 2.14)	2706 (4 RCTs)	⊕⊕⊝⊝ LOW [c]	Daily cotrimoxazole prophylaxis with another drug regimen (mefloquine or DHA-PPQ) may result in little or no difference in neonatal mortality.

*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; **DHA-PPQ**: dihydroartemisinin-piperaquine; **HIV**: human immunodeficiency virus; **g:** grams; **PCR**: polymerase chain reaction; **RR**: risk ratio; **RCT:** randomized controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

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

[a]Downgraded by 1 level for imprecision: CIs include appreciable benefit to no important benefit
[b]Downgraded by 1 level due to risk of bias: one of the studies is at serious risk of bias
[c]Downgraded by 2 levels due to imprecision: CIs range from large benefit to moderate harm

Summary of findings 2. Daily cotrimoxazole plus dihydroartemisinin/piperaquine versus cotrimoxazole with placebo for malaria prophylaxis during pregnancy among HIV-positive women

Population: HIV-positive pregnant women

Setting: sub-Saharan Africa (Gabon, Kenya, Malawi and Mozambique)

Intervention: daily cotrimoxazole with dihydroartemisinin/piperaquine (DHA-PPQ)

Comparison: daily cotrimoxazole with placebo

Outcomes	Anticipated absolute effects (95% CI)	Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with daily cotrimoxazole with placebo	Risk with daily cotrimoxazole with DHA-PPQ				
Maternal peripheral parasitaemia at delivery (amplification techniques)	33 per 1000	19 per 1000 (10 to 37)	RR 0.59 (0.31 to 1.11)	1517 (3 RCTs)	⊕⊕⊕⊖ MODERATE [a]	Daily cotrimoxazole prophylaxis with DHA-PPQ probably results in little or no difference in maternal peripheral parasitaemia at delivery measured by amplification techniques.
Maternal anaemia at delivery	525 per 1000	499 per 1000 (431 to 578)	RR 0.95 (0.82 to 1.10)	1454 (2 RCTs)	⊕⊕⊕⊖ MODERATE [b]	Daily cotrimoxazole prophylaxis with DHA-PPQ probably results in little or no difference in maternal anaemia delivery.
Placental malaria (histopathologic analysis)	121 per 1000	81 per 1000 (60 to 109)	RR 0.67 (0.50 to 0.90)	1570 (3 RCTs)	⊕⊕⊕⊕ HIGH	Daily cotrimoxazole prophylaxis results in fewer women with placental malaria measured by histopathologic analysis.
Low birth weight (< 2500 g)	106 per 1000	120 per 1000 (92 to 157)	RR 1.13 (0.87 to 1.48)	1695 (3 RCTs)	⊕⊕⊕⊖ MODERATE [c]	Daily cotrimoxazole prophylaxis with DHA-PPQ probably results in little or no difference in low birth weight
Foetal loss	33 per 1000	38 per 1000 (23 to 63)	RR 1.14 (0.68 to 1.90)	1610 (3 RCTs)	⊕⊕⊕⊖ MODERATE [c]	Daily cotrimoxazole prophylaxis with DHA-PPQ probably results in little or no difference in foetal loss
Neonatal mortality	11 per 1000	11 per 1000 (4 to 29)	RR 1.03 (0.39 to 2.72)	1467 (2 RCTs)	⊕⊕⊕⊖ MODERATE [c]	Daily cotrimoxazole prophylaxis with DHA-PPQ probably results in little or no difference in neonatal mortality.
Adverse events: gastrointestinal disorders after 1st IPTp dose	33 per 1000	47 per 1000 (17 to 131)	RR 1.42 (0.51 to 3.98)	1447 (2 RCTs)	⊕⊕⊖⊖ LOW[c,d]	Daily cotrimoxazole prophylaxis with DHA-PPQ may result in little or no difference in gastrointestinal disorders after 1st IPTp dose.
Mother-to-child transmision of HIV	4 per 1000	6 per 1000 (1 to 34)	RR 1.54 (0.26 to 9.19)	1063 (2 RCTs)	⊕⊕⊖⊖ LOW[e]	Daily cotrimoxazole prophylaxis with DHA-PPQ may result in little or no difference in mother-to-child transmission of HIV.

*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; **DHA-PPQ**: dihydroartemisinin-piperaquine; **HIV**: human immunodeficiency virus; **g:** grams; **PCR**: polymerase chain reaction; **RR**: risk ratio; **RCT:** randomized controlled trial

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.

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[a]Downgraded by 1 level due to imprecision: CIs are very wide and range from large benefit to little harm
[b]Downgraded by 1 level due to inconsistency: trials showed moderate heterogeneity
[c]Downgraded by 1 level due to imprecision: CIs are very wide and range from large benefit to considerable harm
[d]Downgraded by 1 level due to inconsistency: trials showed substancial heterogeneity
[e]Downgraded by 2 levels due to imprecision: CIs are very wide and range from large benefit to large harm

BACKGROUND

Description of the condition

Malaria

Malaria is an infectious disease caused by the *Plasmodium* species parasite and transmitted by the bite of the *Anopheles* mosquito. It constitutes one of the leading causes of morbidity and mortality in the world, particularly in low- and middle-income countries, with pregnant women and children under 5 years of age being the most vulnerable populations. According to the World Health Organization (WHO), around 249 million cases of malaria and 608,000 deaths occurred in 2022 worldwide (WHO 2023). The WHO African region bears the largest burden of malaria morbidity, with 233 million cases (94% of all cases) in 2022. An estimated 12.7 million women were exposed to malaria infection during pregnancy in sub-Saharan Africa in 2022 (WHO 2023).

Malaria infection in pregnancy is associated with deleterious consequences for the woman, her foetus, and the newborn child. Malaria in pregnancy is known to increase the risk of maternal death, spontaneous abortion, stillbirth, foetal growth restriction, preterm birth, and low birth weight. Foetal growth restriction, preterm birth and low birth weight are major risk factors for perinatal, neonatal, and infant morbidity and mortality (Desai 2007; Moore 2017; Saito 2020). Women who suffered from malaria in pregnancy gave birth to about 872,000 children with low birth weight in sub-Saharan Africa in 2018 (16% of all children with low birth weight in the region) (WHO 2022a). Primigravidae are most at risk for malaria in pregnancy and for its related adverse pregnancy outcomes (Tran 2020).

Human immunodeficiency virus (HIV)

HIV infection is characterized by a gradual loss of lymphocytes CD4+ T-cells and imbalance in CD4+ T-cell homeostasis, with progressive impairment of immunity (Vidya Vijayan 2017). Nearly 68% of the world's HIV-positive population lives in sub-Saharan Africa, where 350 million people are exposed to malaria (WHO 2017). An estimated 20 million HIV-positive individuals in sub-Saharan Africa live in malaria-endemic areas, and among them, over 12 million are women of reproductive age (UNAIDS 2019). Given the geographical overlap, a substantial number of coinfections occur in sub-Saharan Africa where malaria and HIV are concentrated (UNAIDS 2016; WHO 2016). In this region, the prevalence of malaria and HIV coinfection among pregnant women has been estimated to vary from 0.94% to 37%, depending on the country. A meta-analysis performed in 2016 revealed an overall pooled prevalence of 12% of malaria and HIV coinfection among pregnant women (Kwenti 2018; Naing 2016).

Synergistic interactions between both infections have been described, particularly in pregnant women. During pregnancy, malaria and HIV coinfection increase the risk of adverse pregnancy outcomes (Figueroa-Romero 2024). In particular, pregnant women with both infections are more likely to have symptomatic malaria infections, high parasite density, placental malaria infection, anaemia, and infants with low birth weight, when compared to women infected with malaria only (González 2012). There is also evidence suggesting that placental and clinical malaria episodes may increase the risk of mother-to-child transmission of HIV (WHO 2017). Finally, it has been reported that HIV infection reduces the efficacy of antimalarial drugs (Kamya 2012). Thus, prevention of malaria in pregnancy among HIV-positive women constitutes a global health priority (González 2016).

Description of the intervention

To prevent malaria in pregnancy, the WHO recommends that pregnant women living in malaria-endemic countries receive intermittent preventive treatment in pregnancy (IPTp) with sulphadoxine-pyrimethamine (SP), and use of long-lasting insecticide-treated nets (LLINs), in addition to receiving prompt diagnosis and effective treatment of malaria cases (WHO 2012). The WHO recommends that IPTp-SP be given at each monthly antenatal care visit, starting as early as possible in the second trimester.

On the other hand, daily cotrimoxazole prophylaxis is currently recommended in HIV-positive individuals to prevent opportunistic infections regardless of their count of CD4+ cells, and it also has a proven antimalarial effect (WHO 2016). Daily cotrimoxazole prophylaxis is currently the standard of care for malaria prevention among HIV-positive pregnant women in many malaria-endemic countries.

Due to the risk of sulfonamide-induced adverse drug reactions (González 2016; Kwenti 2018; WHO 2017), IPTp-SP is contraindicated in women receiving daily cotrimoxazole prophylaxis. Thus, the women most vulnerable to malaria, those who are HIV-positive, cannot receive the recommended IPTp drug.

Alternative drugs to SP are being evaluated for prevention of malaria among HIV-positive women on daily cotrimoxazole prophylaxis. A placebo-controlled trial has demonstrated that three doses of IPTp with mefloquine had a significant impact on improving malaria prevention and maternal health through reduction in hospital admissions in HIV-positive pregnant women (González 2014). However, mefloquine was not well tolerated, and most importantly, it was associated with a two-fold increase in the frequency of mother-to-child transmission of HIV, thus limiting its potential to be used for IPTp.

Dihydroartemisinin/piperaquine is an artemisinin-based combination therapy (ACT) recommended by the WHO for treatment of uncomplicated malaria in adults and children from the age of six months (WHO 2015). Studies in Kenya and Uganda comparing IPTp with SP versus IPTp with dihydroartemisinin/piperaquine in pregnant women not infected with HIV showed that the drug could be a promising alternative to SP (Desai 2015; Kakuru 2016). A meta-analysis of 11 studies evaluating repeated doses of dihydroartemisinin/piperaquine for the prevention and treatment of malaria concluded that monthly dihydroartemisinin/piperaquine is well tolerated and may be effective for IPTp, although the study did not assess its effects in pregnant women therefore additional data in pregnancy are needed (Gutman 2017).

How the intervention might work

The use of drugs to prevent malaria ('chemoprevention') in pregnancy is thought to work through the clearance or suppression of asymptomatic malaria infections in the mother and the placenta (White 2005). However, this reduction in the number of *Plasmodium* parasites in the blood ('parasitaemia') may be insufficient to justify recommendations for widespread prophylactic prescription, without subsequent tangible benefits for clinically important outcomes in the mother and her baby. Clinically important outcomes may include reductions in malaria episodes, risk of

anaemia, severe maternal illness, lower mortality rates, and improved birth weight.

The effects of malaria chemoprevention may depend on the local malaria epidemiology. In stable malaria transmission areas, mothers may have partial immunity to malaria, causing parasitaemia without clinical disease, but this may still produce detrimental effects such as anaemia and low birth weight (Mayor 2015). In contrast, where malaria transmission is seasonal or unstable, natural immunity may be lower and the main effects of chemoprevention may be a reduction in clinical episodes or severe illness (Ndam 2017). HIV infection is a potential effect modifier of malaria chemoprevention (Menéndez 2011). Many malaria-endemic areas also have a high prevalence of HIV infection among pregnant women, which has been shown to increase the risk of malaria infection (González 2012; Van Eijk 2003).

For women with and without HIV the use of LLINs 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 may modify the effect of IPTp.

Why it is important to do this review

Firstly, the current drug recommended by the WHO for preventing malaria during pregnancy (SP) cannot be given to HIV-positive women on daily cotrimoxazole prophylaxis due to potential adverse effects. Thus, even though IPTp-SP is a life-saving and cost-effective intervention (Sicuri 2010), it cannot be administered to HIV-positive women (Eisele 2012; Menéndez 2010; Ward 2007). Although daily cotrimoxazole may offer some protection (Manyando 2013), the most susceptible and vulnerable women to malaria may be currently the least protected (González 2016). No drug is currently recommended as IPTp for preventing malaria during pregnancy in HIV-positive women other than daily cotrimoxazole prophylaxis. Secondly, several clinical trials evaluating alternative drugs for IPTp to prevent malaria in HIV-positive women have been conducted since the first Cochrane Review on this topic was published (Mathanga 2011). Finally, updating this review will provide a synthesis of the scientific advances made on such an important research question and open perspectives on new studies to be undertaken to help find a safe and effective strategy for the prevention of malaria in HIV-positive pregnant women living in malaria-endemic areas.

OBJECTIVES

To compare the safety and efficacy of intermittent preventive treatment regimens for malaria prevention in HIV-positive pregnant women.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs)

Types of participants

HIV-positive pregnant women living in areas of stable malaria transmission.

Types of interventions

Intervention

Any antimalarial drug administered as intermittent preventive treatment of malaria during pregnancy (IPTp) (including sulphadoxine-pyrimethamine (SP) regardless of the number of doses, dihydroartemisinin/piperaquine, mefloquine, and others), with or without daily cotrimoxazole prophylaxis.

Control

Daily cotrimoxazole prophylaxis, placebo, previous or other standard of care, or combinations of these options. By standard of care, we refer to a country's recommended drug regimen to prevent malaria in pregnancy among HIV-positive women, or the treatment that the trial's research team considered to be the standard of care.

We accepted any cointervention, such as long-lasting insecticidal nets (LLINs) or administration of antiretroviral drugs, if it were used in the same way in the intervention and control arms of the trial.

Types of outcome measures

Primary outcomes

Maternal

- Maternal peripheral parasitaemia at delivery, measured by the presence of malaria parasites on thick and thin malaria smears by microscopy
- Maternal anaemia at delivery, as defined in the original studies

Foetal/infant

- Low birth weight, measured as birth weight < 2.5 kg in a liveborn

Secondary outcomes

Maternal

- Placental malaria, measured by the presence of malaria parasites in the placenta (assessed by histology or by polymerase chain reaction (PCR))
- Maternal peripheral parasitaemia during pregnancy, as defined in the original studies
- Clinical malaria episodes during pregnancy, as defined in the original studies
- Mean haemoglobin level (g/dL) at delivery
- Severe anaemia, as defined in the original studies

Foetal/infant

- Birth weight (kg or g)
- Cord blood parasitaemia
- Prematurity (< 37 weeks of gestation)
- Small for gestational age (having a birth weight lower than expected for its gestational age (below the 10th percentile of a specific reference population))

Safety

Severe adverse events

- Adverse pregnancy outcomes: foetal loss (stillbirths and/or miscarriages) and congenital malformations
- Severe adverse events (life-threatening events and severe events that require hospitalization) during pregnancy

- Maternal, infant, and neonatal mortality

Drug-related adverse events

- Headache
- Nausea
- Vomiting
- Dizziness
- Rash
- Fatigue
- Other adverse events leading to discontinuation of intervention

HIV-related

- Mother-to-child transmission of HIV
- Maternal viral load at delivery, measured as number of HIV-RNA copies/mL

All outcome data had to be collected at individual participant level in the original trials.

We reported outcomes according to the categories of maternal outcomes, foetal/infant outcomes, safety outcomes, and HIV-related outcomes. Within each of these subsections, we reported primary outcomes first followed by secondary outcomes.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, and in press). We described trials in progress in the Characteristics of ongoing studies table.

Electronic searches

We searched the following databases up to 31 January 2024, using the terms and strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register (included in Cochrane CENTRAL); Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1 of 12, January 2024), published in the Cochrane Library; PubMed (MEDLINE, from 1966); EMBASE (OVID, from 1947); the Latin American Caribbean Health Sciences Literature (LILIACS, from 1982); and the Malaria in Pregnancy Library (mip.wwarn.org). To identify trials in progress, we searched the WHO International Clinical Trial Registry Platform (ICTRP; https://apps.who.int/trialsearch/); ClinicalTrials.gov (www.clinicaltrials.gov); and the International Standard Randomized Controlled Trial Number (ISRCTN) registry (www.isrctn.com), on 31 January 2024.

Searching other resources

Researchers

We contacted study authors and researchers working on malaria and HIV to identify relevant ongoing or unpublished work. To identify relevant additional studies or unpublished work, we checked references.

Data collection and analysis

Selection of studies

All review authors, organized in pairs, scanned the identified trial abstracts to identify potentially relevant trials. We coded studies as 'retrieve' or 'do not retrieve'. We retrieved the full-text copies of trials deemed potentially eligible. Then, each pair of review authors independently screened a subset of the selected trials, applying the inclusion criteria to the full reports using an eligibility form. If some of the information needed to classify the study was missing, we attempted to contact the study authors for clarification. To resolve disagreements, the review authors discussed the matter to reach a consensus, and sent the study to a third review author if consensus was not reached. We illustrated the study screening process in a PRISMA flow diagram (Figure 1).

Figure 1. Study flow diagram

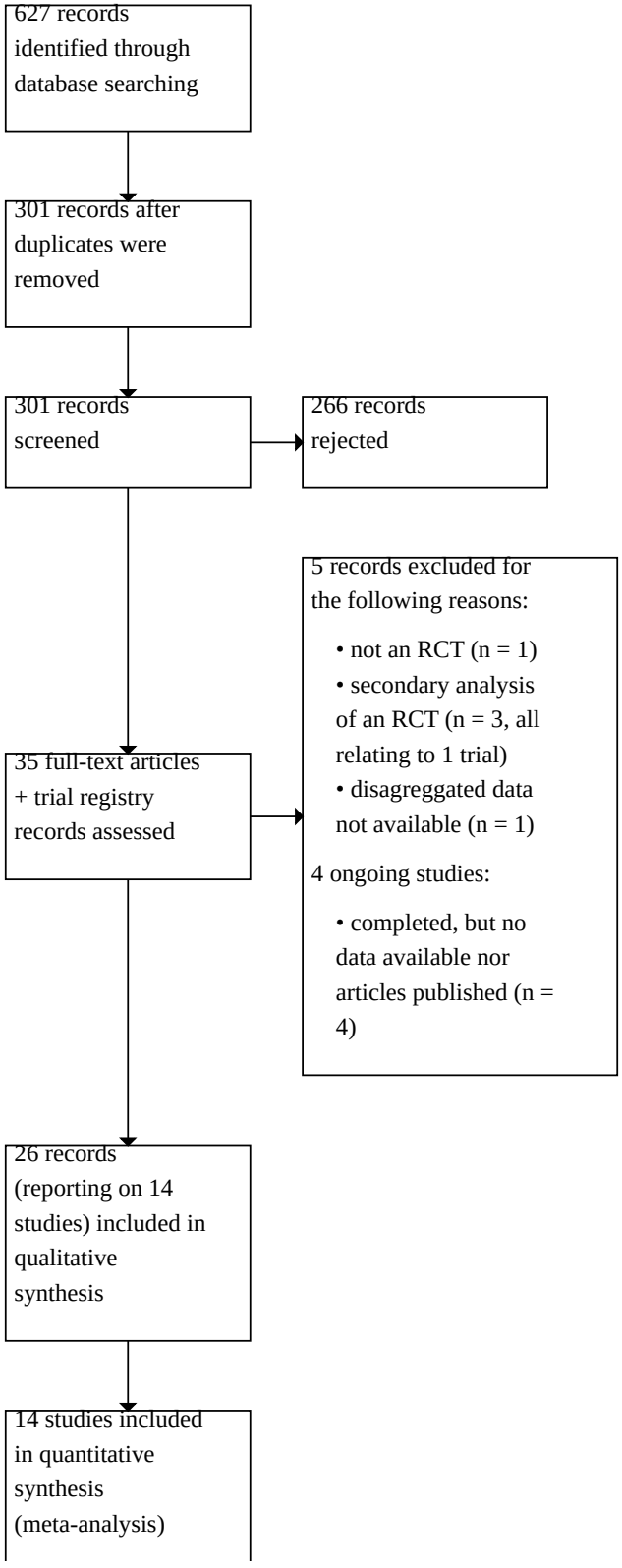


Figure 1. (Continued)

(meta-analysis)

Data extraction and management

We used a data extraction form to independently extract data on trial characteristics, including details about trial site, year, local malaria transmission estimates, national HIV prevalence, trial methods, participants, interventions, doses, and outcomes. Two review authors independently extracted data from each paper.

For dichotomous variables, we extracted data on the total number of participants randomized, number of participants that experienced outcomes, and the number analyzed. For continuous outcomes, we extracted data on the total number of participants analyzed, arithmetic means, standard deviations (SD), and the number of participants randomized. If the SD values were not reported, we derived them from standard errors (SE) and confidence intervals (CI).

Any review author who participated in any of the trials included in the review did not undertake the data extraction or risk of bias assessment of these trials.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each included trial using version 1 of the Cochrane risk of bias (RoB) tool for RCTs (Higgins 2011). We resolved any disagreement between authors' assessments by asking a third review author to decide. We assessed the risk of bias in seven domains: sequence generation (to assess possible selection bias), allocation concealment (to assess possible selecion bias), blinding of participants and trial personnel (to assess possible performance bias), blinding of outcome assessment (to evaluate possible detection bias), incomplete outcome data (to evaluate for possible attrition bias due to the amount, nature, and handling of incomplete outcome data), selective outcome reporting, and other potential sources of bias. For each domain, we assigned a judgement of low, high or unclear risk of bias. We judged the risk of bias for blinding according to 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) (new cases per person-years at risk), and continuous outcomes as mean differences (MDs). We presented all measures of effect with 95% CIs.

Unit of analysis issues

When conducting meta-analysis, we ensured that participants and cases in the control group were not counted more than once. We did not expect any unit of analysis issues as we anticipated studies would be individually randomized.

Dealing with missing data

We aimed to conduct the analysis according to the intention-to-treat principle. However, where 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 assumes that the participants for whom an outcome is available are representative of the original randomized participants. If data from the trial reports were unclear or missing, we attempted to contact the trial authors for additional information.

Assessment of heterogeneity

We assessed heterogeneity amongst the trials using the I^2 test. 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 (McKenzie 2023).

Based on the information in the data extraction forms, the review author team judged the similarity between the studies were similar in terms of participant inclusion criteria, inverventions, and outcomes. Therefore, meta-analyses were conducted.

Assessment of reporting biases

We had planned 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 analyzed data using Review Manager (RevMan Web 2023). We conducted meta-analysis when the RCTs we found were similar in terms of participant inclusion criteria, interventions, and outcomes. We used a fixed-effect model of meta-analysis unless heterogeneity was found. When we considered it clinically meaningful to combine the trials, but there was moderate, substantial, or considerable heterogeneity according to the I^2 test, we used the random-effects model for meta-analysis.

Subgroup analysis and investigation of heterogeneity

We had planned to explore potential sources of heterogeneity by conducting prespecified subgroup analyses to evaluate the contribution of differences in trial characteristics. We had planned to conduct subgroup analyses for the primary outcomes based on gravidity, CD4 counts, LLINs, and malaria transmission; however, the number of trials, their sample sizes, and the lack of disaggregated data made this impossible.

Sensitivity analysis

We had planned to conduct sensitivity analysis to restore the integrity of the randomization process, test the robustness of our results, and determine if the results were sensitive to the allocation of withdrawals and post-randomization exclusions. The approach we selected was to test how the results would have changed if all missing data caused by withdrawals and post-randomization exclusions had a positive or negative outcome. However, not all trials reported in detail the proportion of missing data and the

reasons for all exclusions in the evaluation of each outcome. It was therefore not possible to conduct sensitivity analysis consistently across all comparisons.

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of the evidence for what we considered to be the main comparison and key outcomes using the GRADE approach, and presented these assessments in a summary of findings table. When we decided to downgrade the certainty of evidence for an outcome, we provided our justification in footnotes. Review authors who were authors of any included studies did not assess the certainty of the evidence for outcomes that included data from their own studies.

RESULTS

Description of studies

Results of the search

The literature search, conducted up to 31 January 2024, yielded a total of 627 records. After removing duplicates, there were 301 records. We rejected 266 irrelevant records, and we assessed the remaining 35 full-text articles and trial registry records. We excluded five records: one study was not an RCT, one article was a secondary analysis of an RCT, and one RCT (reported in three records) did not have disaggregated data available. Four of the trial registry records related to ongoing studies potentially suitable for inclusion in the review. We contacted the authors of these studies about their results, but the authors either did not respond or the results were not available. We found that one published article and its corresponding trial registry record reported two different trials. Thus, we included 14 trials, reported in 26 records, in the review (Figure 1).

Included studies

We included 14 trials in the review; they were published in 15 articles and 11 trial registry records (see the Characteristics of included studies tables). The trials were conducted in various sub-Saharan African countries (i.e. Benin, Central African Republic, Gabon, Kenya, Malawi, Mozambique, Nigeria, Tanzania, Togo, Uganda, and Zambia), between 2002 and 2023, and enroled a total of 4976 HIV-positive pregnant women. Five trials compared the current standard of care for HIV-positive women (daily cotrimoxazole) with the standard of care plus the addition of an antimalarial, either mefloquine (Denoeud-Ndam 2014b; González 2014) or dihydroartemisinin/piperaquine (Barsosio 2024; González 2024; Natureeba 2017). Four trials compared the current standard of care with different IPTp options, either three doses of SP (Klement 2013; Manirakiza 2021; Manyando 2014) or mefloquine (Denoeud-Ndam 2014a). Four trials compared different IPTp options: two doses of IPTp-SP versus monthly SP (Filler 2006; Hamer 2007), mefloquine versus SP (Akinyotu 2018), and azithromycin versus SP (Akinyotu 2019). Finally, one trial compared SP with placebo (Menéndez 2008). HIV treatment was heterogeneous amongst the trials, but always consistent across both arms of each trial. More details can be found in the Characteristics of included studies table.

Thirteen of the trials recruited women of all gravidities (Akinyotu 2018; Akinyotu 2019; Barsosio 2024; Denoeud-Ndam 2014a; Denoeud-Ndam 2014b; González 2014; González 2024; Hamer 2007; Klement 2013; Manirakiza 2021; Manyando 2014; Menéndez 2008; Natureeba 2017); one enroled only women in their first or second pregnancy (Filler 2006). The age range was above 15 years in two trials (Filler 2006; Klement 2013), above 16 years in one trial (Natureeba 2017), above 18 years in four trials (Denoeud-Ndam 2014a; Denoeud-Ndam 2014b; Hamer 2007; Manirakiza 2021), and any age in seven trials (Akinyotu 2018; Akinyotu 2019; Barsosio 2024; González 2014; González 2024; Manyando 2014; Menéndez 2008). Gestational age at recruitment was 16 weeks or under in two trials (Akinyotu 2018; Akinyotu 2019), 12 to 28 weeks in one trial (Natureeba 2017), 14 to 28 weeks in one trial (Klement 2013), 16 to 28 weeks in seven trials (Barsosio 2024; Denoeud-Ndam 2014a; Denoeud-Ndam 2014b; Filler 2006; Hamer 2007; Manirakiza 2021; Manyando 2014), up to and including 28 weeks in three trials (González 2014; González 2024, Menéndez 2008).

Ongoing studies

The four ongoing studies we identified seem to be completed, but no data are available or published (NCT00132535; NCT00164255; NCT03431168 (PREMISE); PACTR201612001901313). See the Characteristics of ongoing studies table.

Excluded studies

We excluded three trials (Gill 2007; Luntamo 2010; Parise 1998), for the reasons stated above and detailed in the Characteristics of excluded studies table.

Risk of bias in included studies

See Figure 2 and Figure 3 for a summary of the risk of bias assessments. We have presented further details in the Characteristics of included studies table.

Figure 2. Risk of bias summary of individual included studies

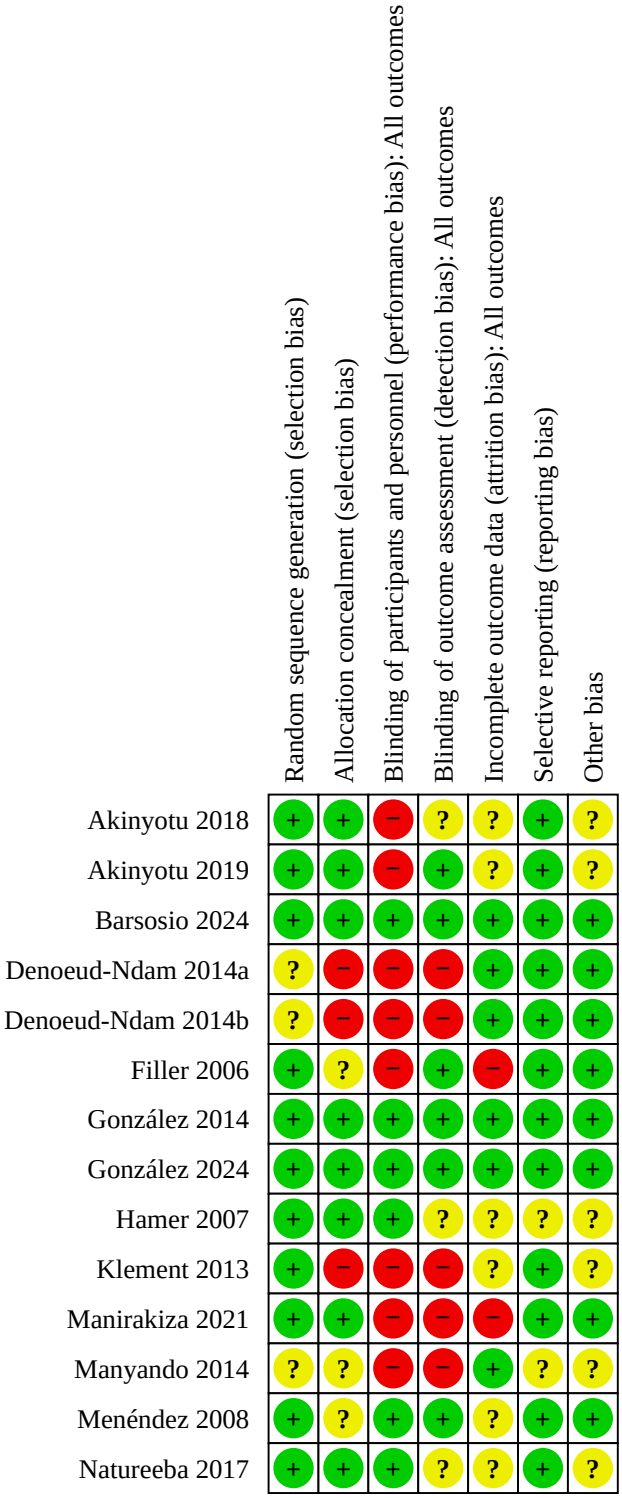
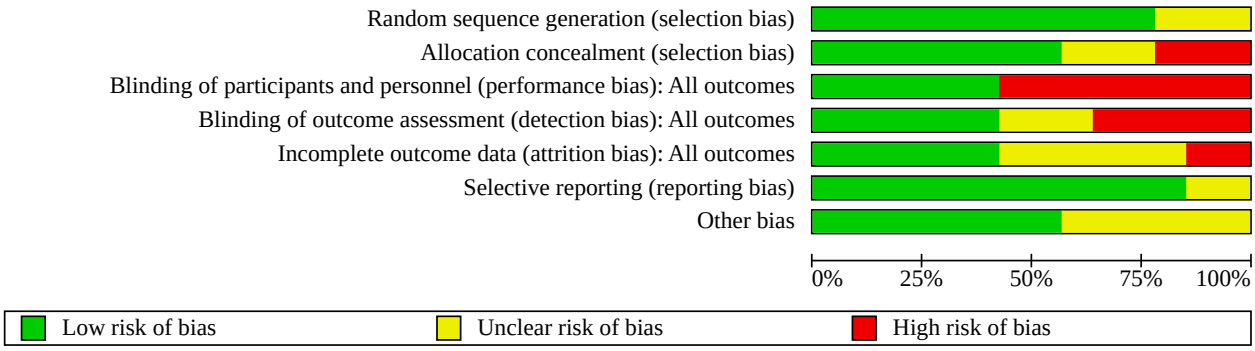


Figure 3. Risk of bias summary across included studies



Overall risk of bias

Three studies were at low overall risk of bias (Barsosio 2024; González 2014; González 2024), three were at unclear overall risk of bias (Hamer 2007; Menéndez 2008; Natureeba 2017), and the remaining eight were at high overall risk of bias (Akinyotu 2018; Akinyotu 2019; Denoeud-Ndam 2014a; Denoeud-Ndam 2014b; Filler 2006; Klement 2013; Manirakiza 2021; Manyando 2014).

Allocation

Random sequence generation

Eleven trials adequately described methods of sequence generation (Akinyotu 2018; Akinyotu 2019; Barsosio 2024; Filler 2006; González 2014; González 2024; Hamer 2007; Klement 2013; Manirakiza 2021; Menéndez 2008; Natureeba 2017). In three trials, we considered the risk of selection bias unclear as the randomization method was not described (Denoeud-Ndam 2014a; Denoeud-Ndam 2014b; Manyando 2014).

Allocation concealment

Eight trials described adequate methods of allocation concealment (Akinyotu 2018; Akinyotu 2019; Barsosio 2024; González 2014; González 2024; Hamer 2007; Manirakiza 2021; Natureeba 2017). In three trials, the risk of selection bias in this regard was unclear (Filler 2006; Manyando 2014; Menéndez 2008). We assessed three trials to be at high risk of bias as they reported that there was no concealment of allocation (Denoeud-Ndam 2014a; Denoeud-Ndam 2014b; Klement 2013).

Blinding

Six trials were double-blind and placebo-controlled (Barsosio 2024; González 2014; González 2024; Hamer 2007; Menéndez 2008; Natureeba 2017), and we assessed these as having low risk of performance bias. Eight trials were open label, and we assessed these as having a high risk of performance risk (Akinyotu 2018; Akinyotu 2019; Denoeud-Ndam 2014a; Denoeud-Ndam 2014b; Filler 2006; Klement 2013; Manirakiza 2021; Manyando 2014).

In six trials, we assessed the risk of detection bias for blinding of outcome assessment to be low (Akinyotu 2019; Barsosio 2024; Filler 2006; González 2014; González 2024; Menéndez 2008). In contrast, we deemed this risk to be high in five trials (Denoeud-Ndam 2014a; Denoeud-Ndam 2014b; Klement 2013; Manirakiza 2021; Manyando 2014), and unclear in three trials (Akinyotu 2018; Hamer 2007; Natureeba 2017).

Incomplete outcome data

We assessed the risk of attrition bias as low in six trials (Barsosio 2024; Denoeud-Ndam 2014a; Denoeud-Ndam 2014b; González 2014; González 2024; Manyando 2014), unclear in six trials (Akinyotu 2018; Akinyotu 2019; Hamer 2007; Klement 2013; Menéndez 2008; Natureeba 2017), and high in two trials (Filler 2006; Manirakiza 2021). In particular, the outcomes of clinical malaria episodes, adverse events, placental malaria, and low birth weight were affected by attrition bias in the studies with high and unclear risk.

Selective reporting

We considered the risk of reporting bias to be low in 12 trials, and unclear in two (Hamer 2007; Manyando 2014).

Other potential sources of bias

Eight included trials appeared to be free of other sources of bias (Barsosio 2024; Denoeud-Ndam 2014a; Denoeud-Ndam 2014b; Filler 2006; González 2014; González 2024; Manirakiza 2021; Menéndez 2008). We considered the risk of other potential sources of bias in the other six trials to be unclear (Akinyotu 2018; Akinyotu 2019; Hamer 2007; Klement 2013; Manyando 2014; Natureeba 2017).

Effects of interventions

See: **Summary of findings 1** Daily cotrimoxazole with another antimalarial drug regimen (mefloquine or dihydroartemisinin/piperaquine) versus cotrimoxazole with or without placebo for malaria prophylaxis during pregnancy among HIV-positive women; **Summary of findings 2** Daily cotrimoxazole plus dihydroartemisinin/piperaquine versus cotrimoxazole with placebo for malaria prophylaxis during pregnancy among HIV-positive women

Comparison 1: daily cotrimoxazole with any other drug regimen (mefloquine or dihydroartemisinin/piperaquine) versus daily cotrimoxazole with or without placebo (current standard of care)

We included five trials in this comparison to evaluate the current standard of care (daily cotrimoxazole) plus any other drug regimen (mefloquine in Denoeud-Ndam 2014a and González 2014, and dihydroartemisinin/piperaquine in Natureeba 2017, Barsosio 2024

and González 2024) versus daily cotrimoxazole with or without placebo. Of note, malaria risk in Uganda, Mozambique, and Gabon while the dihydroartemisinin/piperaquine trials were conducted was relatively low (González 2024; Natureeba 2017).

Some of the outcomes presented below were not reported in all five studies. Therefore, some of the results presented are repeatedly reported in comparisons 2 and 3, which focus on the effects of mefloquine and dihydroartemisinin/piperaquine plus daily cotrimoxazole versus placebo plus daily cotrimoxazole, respectively.

We conducted these joint meta-analyses of trials evaluating both dihydroartemisinin/piperaquine plus cotrimoxazole, and mefloquine plus cotrimoxazole as we considered there to be no qualitative or quantitative heterogeneity among trials for the efficacy and safety outcomes of mothers and their newborns (see Summary of findings 1). However, we excluded HIV-related outcomes and drug-related adverse events from this comparison since these are very specific to each drug administered and the results of meta-analysis could be misleading.

Maternal outcomes

Compared to those receiving daily cotrimoxazole alone, participants in the intervention group taking other antimalarial drugs were at 0.62 times lower risk of maternal peripheral parasitaemia at delivery as determined by amplification techniques (polymerase chain reaction (PCR) or loop-mediated isothermal amplification (LAMP)) (risk ratio (RR) 0.62, 95% CI 0.41 to 0.95; 2406 participants, 5 trials; I^2 = 0%; Analysis 1.1), but did not show differences when parasitaemia was determined by microscopy (RR 0.77, 95% CI 0.17 to 3.58; 1614 participants, 3 trials; I^2 = 33%; Analysis 1.2). Maternal anaemia (haemoglobin < 11 g/dL) was reported by three trials and showed no differences between study arms (RR 0.98, 95% CI 0.90 to 1.07; 2417 participants; 3 trials; I^2 = 21%; Analysis 1.3). Recipients of daily cotrimoxazole and mefloquine or dihydroartemisinin/piperaquine did not show significant differences in terms of placental malaria as determined by any test (RR 0.66, 95% CI 0.42 to 1.03; 2690 participants; 5 trials; I^2 =51%; Analysis 1.4), or specifically by amplification techniques (RR 0.45, 95% CI 0.09 to 2.19; 1171 participants; 3 trials; I^2 = 54%; Analysis 1.6), but did show lower risk in the studies measuring placental malaria by blood smear (RR 0.54, 95% CI 0.31 to 0.93; 1337 participants, 3 trials; I^2 = 0%; Analysis 1.5), or histopathologic analysis (RR 0.67, 95% CI 0.50 to 0.90; 1570 participants, 3 trials; I^2 = 27%; Analysis 1.7). One trial reported that women taking daily cotrimoxazole phrophylaxis plus dihydroartemisinin/piperaquine were at a lower risk of maternal peripheral parasitaemia during pregnancy than those taking cotrimoxazole prophylaxis alone (RR 0.46, 95% CI 0.28 to 0.77; 895 participants, 1 trial; heterogeneity: not applicable; Analysis 1.8).

There was no difference observed between groups in clinical malaria episodes during pregnancy (rate ratio 0.67, 95% CI 0.35 to 1.32; 3 trials; I^2 = 0%; Analysis 1.9). There was no difference observed between study arms for mean haemoglobin at delivery and severe anaemia (mean haemoglobin at delivery (in g/dL): MD -0.06, 95% CI -0.28 to 0.17; 2145 participants, 4 trials; I^2 = 46%; Analysis 1.10; maternal severe anaemia at delivery (haemoglobin < 7 g/dL): RR 1.21, 95% CI 0.73 to 1.98; 2621 participants; 4 trials; I^2 = 0%; Analysis 1.11).

Foetal/infant outcomes

No differences were observed in the prevalence of babies with low birth weight (RR 1.16, 95% CI 0.95 to 1.41, 2915 participants, 5 trials; I^2 = 0%; Analysis 1.12). However, a significant difference in mean birth weight of neonates was found indicating that children whose mothers took daily cotrimoxazole prohylaxis with or without placebo weighed more at birth (MD -46.90, 95% CI -85.96 to -7.54, 2718 participants, 4 trials; I^2 = 0%; Analysis 1.13). There was no evidence of a difference between groups in cases of cord blood parasitaemia detected by blood smear (RR 0.28, 95% CI 0.04 to 1.64; 2696 participants, 5 trials; I^2 = 0%; Analysis 1.14), and zero cases of cord blood parasitaemia were detected by LAMP in one study (190 participants; 1 study; Analysis 1.15). Prematurity rates were not different between interventions (RR 1.07, 95% CI 0.78 to 1.47; 2401 participants, 5 trials, I^2 = 18%; Analysis 1.16).

Safety outcomes

Severe adverse events during pregnancy were less frequent amongst those receiving IPTp plus daily cotrimoxazole than amongst those receiving daily cotrimoxazole with or without placebo (RR 0.77, 95% CI 0.60 to 0.97; 2797 participants, 4 trials; I^2 = 0%; Analysis 1.17). However, some adverse pregnancy outcomes reported in the trials were not different between study arms, including foetal loss (RR 1.03, 95% CI 0.73 to 1.46; 2957 participants, 5 trials; I^2 = 9%; Analysis 1.18), and congenital malformations (RR 0.90, 95% CI 0.51 to 1.58; 2904 participants, 5 trials; I^2 = 2%; Analysis 1.19). Analyses of maternal mortality (RR 0.85, 95% CI 0.27 to 2.65; 2787 participants, 4 trials; I^2 = 0%; Analysis 1.20), and neonatal mortality (RR 1.21, 95% CI 0.68 to 2.14; 2706 participants, 4 trials; I^2 = 0%; Analysis 1.21) did not reveal differences between groups since CI included the possibility of no effect of the intervention.

Comparison 2: mefloquine plus daily cotrimoxazole versus daily cotrimoxazole

Two trials were included in this comparison to evaluate the safety and efficacy of mefloquine plus daily cotrimoxazole versus daily cotrimoxazole alone as IPTp in HIV-positive pregnant women. One trial was conducted in Benin (Denoeud-Ndam 2014a), and one in Kenya, Mozambique, and Tanzania (González 2014).

Maternal outcomes

Recipients of both IPTp-mefloquine and daily cotrimoxazole had a 48% reduction in risk of maternal peripheral parasitaemia at delivery measured by PCR compared to recipients of daily cotrimoxazole alone (RR 0.52, 95% CI 0.30 to 0.93; 989 participants, 2 trials; I^2 = 0%; Analysis 2.1). There was no evidence of a difference between groups for maternal anaemia at delivery (mean haemoglobin at delivery (in g/dL) (RR 0.94, 95% CI 0.73 to 1.20; 1197 participants, 2 trials; I^2 = 12%; Analysis 2.2). The administration of IPTp-mefloquine and daily cotrimoxazole was associated with a 49% risk reduction in placental malaria measured by blood smear (RR 0.51, 95% CI 0.29 to 0.89; 1144 participants, 2 trials; I^2 = 0%; Analysis 2.3), and a 72% risk reduction in placental malaria measured by PCR (RR 0.28, 95% CI 0.14 to 0.57; 977 participants, 2 trials; I^2 = 0%; Analysis 2.4). Clinical malaria episodes during pregnancy were recorded by only one of the two trials, which did not observe differences in episodes between study arms (IRR 0.76, 95% CI 0.33 to 1.76; 371.3 person-year at risk; 1 trial; Analysis 2.5). Analyses of other maternal outcomes included in

this comparison did not provide evidence of a difference between groups (mean haemoglobin at delivery (in g/dL): MD 0.07, 95% CI -0.32 to 0.46; 1167 participants, 2 trials; I^2 = 62%; Analysis 2.6; maternal severe anaemia at delivery (haemoglobin < 7 g/dL): RR 0.93, 95% CI 0.41 to 2.08; 1167 participants, 2 trials; heterogeneity: not applicable; Analysis 2.7). In one trial (González 2014), anaemia was originally defined as haemoglobin < 11 g/dL, but we used the same definitions for this analysis.

Foetal/infant outcomes

All foetal and neonatal outcomes included in this comparison displayed wide CIs that did not demonstrate different effects between study arms: low birth weight (RR 1.20, 95% CI 0.89 to 1.60; 1220 participants, 2 trials; I^2 = 0%; Analysis 2.8, mean birth weight (MD -25.75 grams, 95% CI -86.99 to 35.49; 1220 participants, 2 trials; I^2 = 0%; Analysis 2.9), cord blood parasitaemia (RR 0.33, 95% CI 0.03 to 3.13; 1166 participants; 2 trials; heterogeneity: not applicable; Analysis 2.10)), and prematurity (RR 1.07, 95% CI 0.58 to 1.96; 824 participants, 2 trials; I^2 = 32%; Analysis 2.11).

Safety outcomes

Overall, there was less risk of severe adverse events occurring during pregnancy among the mefloquine plus daily cotrimoxazole group than among those receiving only cotrimoxazole (RR 0.69, 95% CI 0.50 to 0.95; 1347 participants, 2 trials; I^2 = 0%; Analysis 2.12). However, analyses of individual severe adverse events did not provide evidence for a difference between groups (spontaneous abortions and stillbirths: RR 1.12, 95% CI 0.42 to 2.98; 1347 participants, 2 trials; I^2 = 69%; Analysis 2.13; congenital malformations: RR 0.61, 95% CI 0.22 to 1.67; 1312 participants, 2 trials; I^2 = 0%; Analysis 2.14; maternal deaths: RR 0.51, 95% CI 0.13 to 2.01; 1347 participants, 2 trials; I^2 = 0%; Analysis 2.15; neonatal deaths: RR 1.32, 95% CI 0.65 to 2.69; 1239 participants, 2 trials; I^2 = 0%; Analysis 2.16). Because the two trials used different gestational age cut-offs to classify spontaneous abortions and stillbirths, we grouped the two outcomes into one analysis. Information on maternal mortality was only reported in the González 2014 article. This information was obtained from the authors of the other trial (Denoeud-Ndam 2014a) when the 2018 Cochrane review was written (González 2018).

Headache cases did not differ between groups, with the CIs including the possibility of no effect of the intervention compared to the control (RR 0.76, 95% CI 0.28 to 2.10; 1347 participants, 2 trials; I^2 = 30%; Analysis 2.17). Analyses of vomiting, dizziness and fatigue/weakness displayed substantial and considerable heterogeneity, as well as wide CIs. Though individual trials showed increases for these three types of drug-related adverse events, random-effects analyses showed an increase of vomiting among the IPTp-mefloquine group (RR 20.88, 95% CI 1.40 to 311.66; 1347 participants, 2 trials; I^2 = 74%; Analysis 2.18), but no evidence of a difference between groups was found for dizziness (RR 16.34, 95% CI 0.39 to 684.99; 1347 participants, 2 trials; I^2 = 86%; Analysis 2.19) or fatigue/weakness (RR 2.95, 95% CI 0.26 to 32.93; 1347 participants, 2 trials; I^2 = 91%; Analysis 2.20).

HIV-related outcomes

Recipients of mefloquine and daily cotrimoxazole were at 1.92 times greater risk of mother-to-child transmission of HIV than recipients of daily cotrimoxazole alone (RR 1.92, 95% CI 1.13 to 3.25; 1019 participants, 2 trials; I^2 = 0%; Analysis 2.21). There was no evidence of a difference between groups for undetectable maternal viral load at delivery (RR 0.93, 95% CI 0.81 to 1.08; 1220 participants, 2 trials; I^2 = 0%; Analysis 2.22).

Comparison 3: dihydroartemisinin-piperaquine plus daily cotrimoxazole versus placebo plus daily cotrimoxazole

Three trials conducted in Uganda, Kenya, Malawi, Mozambique and Gabon were included in this comparison of daily cotrimoxazole plus monthly dihydroartemisinin/piperaquine versus daily cotrimoxazole plus placebo in HIV-positive pregnant women (Barsosio 2024; González 2024; Natureeba 2017).

Maternal outcomes

Analyses of maternal peripheral parasitaemia at delivery and maternal anemia did not show evidence of differences between study arms (maternal peripheral parasitaemia at delivery measured by amplification techniques: RR 0.59, 95% CI 0.31 to 1.11; 1517 participants, 3 trials; I^2 = 22% Analysis 3.1; maternal peripheral parasitaemia at delivery measured by microscopy: RR 0.77, 95% CI 0.17 to 3.58; 1614 participants, 3 trials; I^2 = 33%; Analysis 3.2; maternal anaemia at delivery (< 11 g/dL): RR 0.95, 95% CI 0.82 to 1.10; 1454 participants; 2 trials; I^2 = 51%; Analysis 3.3). Placental malaria measured by any test was not found to be different between study arms (RR 0.79, 95% CI 0.42 to 1.49; 1571 participants; 3 trials; I^2 = 64%; Analysis 3.4). However, when placental malaria was measured by histopathologic analysis, results indicate that women taking daily cotrimoxazole prophylaxis plus dihydroartemisinin/piperaquine were at a lower risk compared to women taking placebo plus daily cotrimoxazole (RR 0.67, 95% CI 0.50 to 0.90; 1570 participants; 3 studies; I^2 = 27%; Analysis 3.5). One trial reported that women taking daily cotrimoxazole prophylaxis plus dihydroartemisinin/piperaquine were at a lower risk of maternal peripheral parasitaemia during pregnancy than those taking cotrimoxazole phrophylaxis alone (RR 0.46 0.44, 95% CI 0.28 to 0.77; 895 participants, 1 trial; heterogeneity: not applicable; Analysis 3.6). No evidence of a difference was found for clinical malaria episodes during pregnancy between the two study arms (Rate Ratio 0.56, 95% CI 0.19 to 1.67; 3 trials; I^2 = 0%; Analysis 3.7). Adding monthly dihydroartemisinin/piperaquine to daily cotrimoxazole did not show an effect on mean haemoglobin at delivery (MD -0.18, 95% CI -0.51 to 0.15; 978 participants; 2 trials; I^2 = 44%; Analysis 3.8), and maternal severe anaemia at delivery (< 7g/dL) (RR 1.42, 95% CI 0.75 to 2.67; 1454 participants; 2 trials; I^2 = 0%; Analysis 3.9).

Foetal/infant outcomes

The observed prevalence of babies with low birth weight (< 2500 g) was similar between the two study arms (RR 1.13, 95% CI 0.87 to 1.695; 197 participants, 3 trials; I^2 = 0%; Analysis 3.10). However, a decrease in mean birth weight was observed for the intervention group taking dihydroartemisinin/piperaquine plus cotrimoxazole (MD -61.39, 95% CI -112.11 to -10.68; 1498 participants; 2 trials; I^2 = 0%; Analysis 3.11). There was no evidence of a difference between groups in cases of cord blood parasitaemia detected by blood smear (RR 0.20, 95% CI 0.01 to 4.19; 1530 participants; 3 trials; heterogeneity: not applicable; Analysis 3.12), and no cases were detected by LAMP (190 participants; 1 trial; Analysis 3.13). Analysis of prematurity rate provided no evidence of differences between groups (RR 1.05, 95% CI 0.56 to 1.94; 1577 participants, 3 trials; I^2 = 42%; Analysis 3.14).

Safety outcomes

No evidence was found for a difference between groups with regard to severe adverse events during pregnancy (RR 0.88, 95% CI 0.61 to 1.25; 1450 participants, 2 trials; I^2 = 0%; Analysis 3.15). For the prevalence of foetal loss and congenital malformations, analyses revealed no differences across the two arms (foetal loss: RR 2.1.14, 95% CI 0.68 to 1.90; 1610 participants, 2 trials; I^2 = 0%; Analysis 3.16; congenital malformations: RR 1.10, 95% CI 0.39 to 3.06; 1592 participants, 2 trials; I^2 = 39%; Analysis 3.17). There was no evidence of differences between study arms regarding maternal mortality, which displayed wide CIs (RR 4.99, 95% CI 0.24 to 103.62; 1440 participants; 2 trials; heterogeneity: not applicable; Analysis 3.18), and neonatal mortality (RR 1.03, 95% CI 0.39 to 2.72; 1467 participants; 2 trials; I^2 =20%; Analysis 3.19).

Analyses on drug-related adverse events did not reveal evidence of an effect of the intervention compared to the control in the rate of headache (RR 1.60, 95% CI 0.62 to 4.10; 1447 participants, 2 trials; I^2 = 0%; Analysis 3.20), gastrointestinal disorders after first dose of IPTp (RR 1.42, 95% CI 0.51 to 3.98; 1447 participants, 2 trials; I^2 = 70%; Analysis 3.21), and dizziness after first dose of IPTp (RR 1.25, 95% CI 0.26 to 5.96; 1447 participants; 2 trials, I^2 = 52%; Analysis 3.22).

HIV-related outcomes

Analyses of HIV-related outcomes did not reveal any differences between women taking daily cotrimoxazole plus monthly dihydroartemisinin/piperaquine and women taking daily cotrimoxazole plus placebo (mother-to-child transmission of HIV: RR 1.54, 95% CI 0.26 to 9.19; 1063 participants; 2 trials; I^2 = 0%; Analysis 3.23; undetectable HIV viral load at delivery: RR 0.97, 95% CI 0.90 to 1.05; 620 participants; 1 trial; Analysis 3.24).

Comparison 4: two doses of sulfadoxine-pyrimethamine versus monthly sulfadoxine-pyrimethamine

Two trials were included in this comparison of monthly regimens of sulfadoxine-pyrimethamine (SP) to the then-standard 2-dose regimen given in the second and third trimesters. The studies, which enroled a total of 722 HIV-positive pregnant women, were conducted in Malawi and Zambia (Filler 2006 and Hamer 2007, respectively). This comparison was discussed in the previous version of this Cochrane review on IPTp regimens for malaria in HIV-positive pregnant women published in 2011 (Mathanga 2011).

Maternal outcomes

The proportion of maternal peripheral parasitaemia at delivery was significantly lower among those who received monthly SP than those on 2-dose SP (RR 0.26, 95% CI 0.15 to 0.45; 622 participants, 2 trials; I^2 = 0%; Analysis 4.1). Regarding rates of maternal anaemia at delivery, there was no evidence of a difference between the two study arms (RR 0.96, 95% CI 0.82 to 1.14; 604 participants, 2 trials; I^2 = 41%; Analysis 4.2). Results from the two trials show a 58% risk reduction of placental parasitaemia in women on the monthly SP regimen compared to those on 2-dose SP (RR 0.42, 95% CI 0.24 to 0.75; 612 participants, 2 trials; I^2 = 0%; Analysis 4.3). Only one of the two trials reported clinical malaria episodes during pregnancy (Hamer 2007). Results show a reduction in risk in the monthly SP group, but the CIs include the possibility of no difference in effects (RR 0.45, 95% CI 0.20 to 1.00; 387 participants, 1 trial; Analysis 4.4).

Results showed that women who received monthly SP had a higher haemoglobin level at delivery than those treated with 2-dose SP (MD 0.10 g/dL, 95% CI 0.07 to 0.13; 604 participants, 2 trials; I^2 = 0%; Analysis 4.5).

Foetal/infant outcomes

Rates of low birth weight (< 2500 g) were not different between those receiving monthly SP and those receiving 2-dose SP (RR 0.87, 95% CI 0.61 to 1.24; 624 participants, 2 trials; I^2 = 0%; Analysis 4.6). A mean difference in birth weight of 0.09 kg between the two groups was reported, with babies born to women on monthly SP having a higher mean birth weight (MD 0.09 kg, 95% CI 0.08 to 0.09; 624 participants, 2 trials; I^2 = 0%; Analysis 4.7). Regarding cord blood parasitaemia, no evidence was found for a difference between groups (RR 0.36, 95% CI 0.07 to 1.75; 359 participants, 1 trial; Analysis 4.8). There was no difference in the occurrence of premature births in either group (RR 0.98, 95% CI 0.82 to 1.17; 377 participants; 1 trial; Analysis 4.9).

Safety outcomes

Some safety outcomes included in this comparison were only reported by Hamer 2007 and provided no evidence of differences between groups (severe adverse events during pregnancy: RR 1.17, 95% CI 0.60 to 2.29; 456 participants, 1 trial; Analysis 4.10; spontaneous abortion: no events in either arm, RR not estimable; 456 participants, 1 trial; Analysis 4.11; stillbirth: RR 0.43, 95% CI 0.08 to 2.17; 394 participants, 1 trial; Analysis 4.12; maternal mortality: RR 3.11, 95% CI 0.13 to 75.86; 456 participants, 1 trial; Analysis 4.13). Both trials included reported neonatal mortality as an outcome, defined as death occurring within 28 or 30 days after birth (Filler 2006 and Hamer 2007, respectively). Meta-analysis did not reveal a difference between groups and showed considerable heterogeneity (RR 0.90, 95% CI 0.10 to 8.23; 640 participants, 2 trials; I^2 = 83%; Analysis 4.14).

HIV-related outcomes

Neither of the two included studies in this comparison assessed the impact of monthly SP on HIV parameters.

Comparison 5: daily cotrimoxazole versus three doses of sulfadoxine-pyrimethamine

We included three trials, conducted in Togo, the Central African Republic and Zambia, in this comparison of daily cotrimoxazole to three doses of SP (Klement 2013, Manirakiza 2021, and Manyando 2014, respectively).

Maternal outcomes

The rate of maternal peripheral parasitaemia during pregnancy was lower among women receiving daily cotrimoxazole than among those receiving three doses of SP (RR 0.59, 95% CI 0.37 to 0.96; 250 participants; 1 trial; Analysis 5.1). Maternal anaemia during delivery appeared to be less common among the 3-dose SP group than the daily cotrimoxazole group. However, evidence did not show a risk reduction since the CIs included the possibility of no different effects (RR 1.58, 95% CI 0.98 to 2.53; 362 participants; 2 trials; I^2 = 14%; Analysis 5.2). There was no difference between groups in rates of placental malaria determined by histology (RR 0.83, 95% CI 0.43 to 1.57; 131 participants; 1 trial; Analysis 5.3), nor when determined by microscopy or PCR (RR 0.56, 95% CI 0.20 to 1.61; 112 participants; 1 trial; Analysis 5.4). Episodes of clinical malaria during pregnancy

were not more frequent in the daily cotrimoxazole arm than in the 3-dose SP arm (RR 1.38, 95% CI 0.92 to 2.07; 362 participants; 2 trials; I^2 = 0%; Analysis 5.5). One trial reported data on mean maternal haemoglobin levels at delivery (in g/dL) without including a standard deviation. We therefore could not calculate the mean difference (MD not estimable; 250 participants; 1 trial; Analysis 5.6).

Foetal/infant outcomes

There was no difference found in prevalence of babies born with low birth weight between the cotrimoxazole alone and the 3-dose SP arms (RR 1.10, 95% CI 0.68 to 1.80; 392 participants, 3 trials; I^2 statistic = 0%; Analysis 5.7), nor in mean birth weight (MD -100.00 g, 95% CI -386.47 g to 186.47 g; 281 participants, 2 trials; heterogeneity: not applicable; Analysis 5.8). One trial included malaria in cord blood measured by rapid diagnostic tests as an outcome (Manirakiza 2021). There were no positive tests in either study arm (RR not estimable; 100 participants; 1 trial; Analysis 5.9). One trial reported data on congenital malaria, defined as symptoms attributable to malaria plus a positive thick blood smear in the newborn within the first seven days of life (Klement 2013). Analysis did not reveal a difference between study groups (RR 0.90, 95% CI 0.43 to 1.89; 231 participants, 1 trial; Analysis 5.10). All three trials reported prematurity as an outcome, but different definitions were used. Klement 2013 defined prematurity as a birth ≤ 34 weeks gestation, Manirakiza 2021 as < 37 weeks, and Manyando 2014 as ≤ 37 weeks. Meta-analysis did not reveal a difference between groups for prematurity rates (RR 0.91, 95% CI 0.54 to 1.55; 391 participants, 3 trials; I^2 = 6%; Analysis 5.11).

Safety outcomes

Women receiving daily cotrimoxazole had an increased risk of severe adverse events during pregnancy than women receiving three doses of SP (RR 1.83, 95% CI 1.06 to 3.15; 412 participants; 3 trials, I^2 = 0%; Analysis 5.12). Other safety outcomes included in this comparison did not show evidence of differences between study arms (spontaneous abortion: RR 0.40, 95% CI 0.06 to 2.65; 400 participants, 3 trials; I^2 = 0%; Analysis 5.13; stillbirth: RR 0.94, 95% CI 0.31 to 2.87; 400 participants, 3 trials; I^2 = 0%; Analysis 5.14; congenital malformations: RR 0.97, 95% CI 0.06 to 15.26; 277 participants, 2 trials; heterogeneity: not applicable; Analysis 5.15; maternal mortality: RR 2.95, 95% CI 0.12 to 71.79; 362 participants, 2 trials; heterogeneity: not applicable; Analysis 5.16; neonatal mortality: RR 3.79, 95% CI 0.43 to 33.43; 392 participants, 3 trials; I^2 = 0%; Analysis 5.17; infant mortality: RR 0.32, 95% CI 0.01 to 7.89; 231 participants, 1 trial; Analysis 5.18; adverse events (rash): RR 2.95, 95% CI 0.31 to 28.00; 250 participants, 1 trial; Analysis 5.19).

HIV-related outcomes

There was no evidence of a difference between interventions in mother-to-child transmission of HIV (RR 1.02, 95% CI 0.34 to 3.06; 310 participants, 2 trials; heterogeneity: not applicable; Analysis 5.20).

Comparison 6: mefloquine versus sulfadoxine-pyrimethamine

One trial conducted in Nigeria was included in this comparison of mefloquine versus SP as prophylaxis against malaria in pregnancy without daily cotrimoxazole prophylaxis (Akinyotu 2018).

Maternal outcomes

There was no evidence of a difference between mefloquine and SP for maternal peripheral parasitaemia at delivery (RR 0.70, 95% CI 0.26 to 1.85; 131 participants, 1 study; Analysis 6.1) and placental malaria measured by blood smear (RR 0.70, 95% CI 0.12 to 4.04; 131 participants, 1 study; Analysis 6.2).

Foetal/infant outcomes

There was no evidence of differences between interventions in the risk of low birth weight (RR 0.26, 95% CI 0.03 to 2.28; 131 participants, 1 study; Analysis 6.3) and prematurity (RR 0.35, 95% CI 0.07 to 1.67; 131 participants, 1 study; Analysis 6.4).

Safety outcomes

Regarding adverse events, reports of nausea were more frequent among women who took mefloquine compared to those who were assigned to take SP (RR 8.38, 95% CI 1.08 to 65.08; 131 participants, 1 study; Analysis 6.5). Headache (RR 0.15, 95% CI 0.02 to 1.18; 131 participants, 1 study; Analysis 6.6), vomiting (RR 0.35, 95% CI 0.01 to 8.41; 131 participants, 1 study; Analysis 6.7), and dizziness (RR 0.42, 95% CI 0.08 to 2.08; 131 participants, 1 study; Analysis 6.8) were reported more frequently by women taking SP, but the results of the meta-analysis include the possibility of no difference in effects. There was no evidence of an effect of mefloquine or SP on the frequency of gastric pain (RR 1.05, 95% CI 0.07 to 16.38; 131 participants, 1 study; Analysis 6.9).

HIV-related outcomes

No HIV-related outcomes were reported in Akinyotu 2018.

Comparison 7: azithromycin versus sulfadoxine-pyrimethamine

One trial performed in Nigeria compared azithromycin versus SP as prophylaxis against malaria in pregnancy (Akinyotu 2019). Overall, the study did not find differences between the interventions for the outcomes measured, which may be partly due to the small trial sample size.

Maternal outcomes

There was no evidence of an effect of azithromycin compared to SP for maternal peripheral parasitaemia at delivery measured by blood smear (RR 0.90, 95% CI 0.32 to 2.52; 123 participants, 1 study; Analysis 7.1), maternal anaemia at delivery (RR 1.16, 95% CI 0.53 to 2.52; 123 participants, 1 study; Analysis 7.2), placental malaria assessed by blood smear (RR 3.15, 95% CI 0.34 to 29.45; 123 participants, 1 study, Analysis 7.3), and number of clinical malaria episodes experienced during pregnancy (RR 1.44, 95% CI 0.84 to 2.47; 123 participants, 1 study; Analysis 7.4).

Foetal/infant outcomes

The trial measured the prevalence of babies born with low birth weight (< 2.5 kg) (RR 2.10, 95% CI 0.55 to 8.02; 123 participants, 1 study; Analysis 7.5), mean birth weight (in kg) (MD -0.06, 95% CI -0.17 to 0.05; 123 participants, 1 study; Analysis 7.6), and prematurity rate (RR 1.05, 95% CI 0.27 to 4.01; 123 participants, 1 study; Analysis 7.7), which indicated no evidence of effects of azithromycin over SP.

Safety outcomes

No severe adverse events, spontaneous abortions, stillbirths, congenital malformations, maternal deaths, or neonatal deaths were reported during follow-up of study participants in the trial evaluating this comparison (123 participants, 1 study; Analysis 7.8; Analysis 7.9; Analysis 7.10; Analysis 7.11; Analysis 7.12; Analysis 7.13). In terms of adverse events, CIs of effect estimates included the possibility of no effect of azithromycin compared to SP (headache: RR 0.17, 95% CI 0.02 to 1.41; 123 participants, 1 study; Analysis 7.14; nausea: RR 7.35, 95% CI 0.93 to 57.97; 123 participants, 1 study, Analysis 7.15; vomiting: RR 2.10, 95% CI 0.20 to 22.56; 123 participants, 1 study; Analysis 7.16; dizziness: RR 0.42, 95% CI 0.08 to 2.08; 123 participants, 1 study; Analysis 7.17; abdominal pain: RR 1.05, 95% CI 0.07 to 16.41; 123 participants, 1 study; Analysis 7.18).

HIV-related outcomes

No HIV-related outcomes were reported in Akinyotu 2019.

Comparison 8: mefloquine versus daily cotrimoxazole

One trial conducted in Benin provided data on this comparison of three doses of IPTp with mefloquine compared to daily cotrimoxazole prophylaxis (Denoeud-Ndam 2014b). The analyses based on results of this trial did not show differences in most of the outcomes probably due to the small number of observations. This comparison was presented in 2018 in a published Cochrane review on mefloquine for IPTp (González 2018).

Maternal outcomes

We found no evidence of an effect of mefloquine compared to daily cotrimoxazole prophylaxis on any of the malaria-related efficacy outcomes due to wide CIs (maternal peripheral parasitaemia at delivery measured by PCR: RR 0.21, 95% CI 0.03 to 1.72; 98 participants, 1 study; Analysis 8.1; maternal anaemia at delivery (RR 0.90, 95% CI 0.26 to 3.16; 100 participants, 1 study; Analysis 8.2; placental malaria measured by PCR: RR 0.73, 95% CI 0.13 to 4.15; 94 participants, 1 study; Analysis 8.3; placental malaria measured by blood smear: RR 0.35, 0.01 to 8.30; 108 participants, 1 study; Analysis 8.4); and mean haemoglobin at delivery (g/dL): MD -0.10, 95% CI -0.67 to 0.47; 100 participants, 1 study; Analysis 8.5).

Foetal/infant outcomes

Weight-related outcomes displayed wide CIs and provided no evidence of differences between groups (low birth weight (< 2500 g): RR 1.52, 95% CI 0.56 to 4.13; 120 participants, 1 study; Analysis 8.6; mean birth weight in grams: MD -102.00, 95% CI -255.52 to 51.52; 120 participants, 1 study; Analysis 8.7). There were no cases of cord blood parasitaemia detected among the study participants (140 participants, 1 study; Analysis 8.8). Prematurity rates were not different between study arms (RR 1.08, 95% CI 0.33 to 3.56; 125 participants, 1 study; Analysis 8.9).

Safety outcomes

The results include the possibility of no different effects across interventions with regard to SAEs (RR 1.06, 95% CI 0.28 to 4.07; 140 participants, 1 study; Analysis 8.10), spontaneous abortions (RR 1.07, 95% CI 0.07 to 16.84; 139 participants, 1 study; Analysis 8.11), stillbirths (RR 4.30, 95% CI 0.49 to 37.49; 139 participants, 1 study; Analysis 8.12), and congenital malformations (RR 0.54, 95% CI 0.05 to 5.79; 139 participants, 1 study; Analysis 8.13). There were no maternal deaths among the 139 trial participants (1 study; Analysis 8.14). No differences across groups were observed in terms of early neonatal deaths (< 7 days after birth) (RR 1.05, 95% CI 0.07 to 16.39; 129 participants, 1 study; Analysis 8.15). The small number of deaths among children ≥ 7 days up to 6 weeks of age led to wide CIs, and no differences were observed across groups (RR 2.10, 95% CI 0.19 to 22.54; 129 participants, 1 study; Analysis 8.16).

There was no evidence of a difference in frequency of headache across groups (RR 0.21, 95% CI 0.01 to 4.39; 139 participants, 1 study; Analysis 8.17). Analyses of other drug-related adverse events displayed wide CIs, but showed effects of mefloquine in increasing the frequency of vomiting (RR 13.43, 95% CI 3.31 to 54.54; 139 participants, 1 study; Analysis 8.18), dizziness (RR 52.60, 95% CI 3.26 to 848.24; 139 participants, 1 study; Analysis 8.19, and fatigue and weakness (RR 6.99, 95% CI 1.64 to 29.81; 139 participants, 1 study; Analysis 8.20).

HIV-related outcomes

The risk of mother-to-child transmission of HIV was investigated in the study included in this comparison (Denoeud-Ndam 2014b). The authors found no cases of mother-to-child transmission of HIV in either trial arm.

Comparison 9: sulfadoxine-pyrimethamine versus placebo

One trial conducted in Mozambique was included in this comparison to evaluate the safety and efficacy of two doses of SP versus placebo (Menéndez 2008).

Maternal outcomes

Two doses of SP were associated with a 73% reduction in the risk of maternal peripheral parasitaemia at delivery (RR 0.27, 95% CI 0.11 to 0.67; 199 participants, 1 study; Analysis 9.1). Maternal anaemia rates at delivery were not affected by the intake of SP compared to placebo when using PCV (packed cell volume) < 33% as the threshold for anaemia (RR 0.94, 95% CI 0.72 to 1.23; 200 participants, 1 study; Analysis 9.2), or when defining anaemia as haemoglobin < 120 g/L (RR 0.95, 95% CI 0.88 to 1.03; 135 participants, 1 study; Analysis 9.3). For acute placental infection measured by histology, the data showed a reduction in risk that did include the possibility of no difference in effects (RR 0.45, 95% CI 0.11 to 1.81; 178 participants, 1 study; Analysis 9.4). A 72% risk reduction of chronic placental infection measured by histology was observed (RR 0.28, 95% CI 0.11 to 0.68; 178 participants, 1 study; Analysis 9.5). We found no evidence of an effect of two doses of SP on mean levels of haemoglobin at delivery measured in g/L compared to placebo (MD 3.38, 95% CI -1.40 to 8.15; 135 participants, 1 study; Analysis 9.6).

Foetal/infant outcomes

There was no evidence of a difference between the SP and placebo groups in low birth weight (< 2500 g) (RR 1.17, 95% CI 0.63 to 2.17; 208 participants, 1 study; Analysis 9.7), mean birth weight (MD -43.71 g, 95% CI -253.05 to 165.63; 208 participants, 1 study; Analysis 9.8), and prematurity rate (RR 0.65, 95% CI 0.20 to 2.06; 208 participants, 1 study; Analysis 9.9).

Safety outcomes

The included trial assessed the impact of SP on safety outcomes for a combined overall sample of HIV-positive and uninfected women.

We requested disaggregated data by HIV-status, but this was not possible to retrieve for safety outcomes.

HIV-related outcomes

With regard to HIV-related health parameters, we found no evidence of SP changing the risk of mother-to-child transmission of HIV (RR 0.89, 95% CI 0.38 to 2.06; 153 participants, 1 study; Analysis 9.10), or impacting maternal viral load at delivery (≥ 10,000 copies/mL) (RR 1.21, 95% CI 0.48 to 3.00; 81 participants, 1 study; Analysis 9.11).

DISCUSSION

Summary of main results

See Summary of findings 1 and Summary of findings 2.

We included 14 randomized clinical trials in this review, which randomized a total of 4976 pregnant women. The trials evaluated nine comparisons. All trials assessed the efficacy and safety of one antimalarial used as IPTp (mefloquine, dihydroartemisinin/piperaquine, SP or azithromycin) with or without daily cotrimoxazole, compared to daily cotrimoxazole alone, placebo, or other standards of care.

Our main comparison, presented in Summary of findings 1, included five trials that evaluated the current standard of care (daily cotrimoxazole) with or without placebo versus daily cotrimoxazole with mefloquine or dihydroartemisinin/piperaquine; two trials evaluated mefloquine and three evaluated dihydroartemisinin/piperaquine. Daily cotrimoxazole prophylaxis with another drug regimen probably results in lower maternal peripheral parasitaemia at delivery (moderate-certainty evidence), and results in little or no difference in maternal anaemia cases at delivery (high-certainty evidence). Daily cotrimoxazole prophylaxis with another drug regimen (mefloquine or dihydroartemisinin/piperaquine) probably results in a decrease in placental malaria. This evidence was of moderate certainty; however, when looking only at trials evaluating dihydroartemisinin/piperaquine plus daily cotrimoxazole prophylaxis, the certainty of evidence was high for this finding (placental malaria measured by histopathologic analysis). Daily cotrimoxazole prophylaxis with another drug regimen (mefloquine or dihydroartemisinin/piperaquine) probably results in little or no difference in low birth weight or foetal loss (moderate-certainty evidence), and may result in little or no difference in neonatal mortality (low-certainty evidence).

When we looked at the two drugs separately, regarding tolerability, comparisons assessing differences between mefloquine plus daily cotrimozaxole and daily cotrimoxazole alone, mefloquine and SP, and mefloquine and daily cotrimoxazole, showed low-certainty evidence of significant associations of poor drug tolerability outcomes with mefloquine intake, with or without daily cotrimoxazole, compared to SP or daily cotrimoxazole alone. In contrast, the three studies on dihydroartemisinin/piperaquine plus daily cotrimoxazole versus placebo plus daily cotrimoxazole showed low-certainty evidence of no differences between study arms in the rate of drug-related adverse events. Likewise, moderate-certainty evidence showed cotrimoxazole plus mefloquine probably increases the risk of mother-to-child HIV transmission compared to cotrimoxazole alone, but low-certainty evidence suggested no evidence of a difference between dihydroartemisinin/piperaquine plus daily cotrimaxozole and daily cotrimaxozole alone for mother-to-child HIV transmission. Key results for dihydroartemisinin/piperaquine are presented in Summary of findings 2.

The studies included in the remaining comparisons, which looked at the effects of monthly versus two-dose SP, daily cotrimoxazole versus three-dose SP, azithromycin versus SP, and SP versus placebo, did not use the current standard of care for pregnant women (daily cotrimoxazole) in both trial arms. Two doses of SP were associated with a reduction in the risk of maternal peripheral parasitaemia at delivery and chronic placental infection compared to placebo. Monthly SP compared to two doses of SP during pregnancy showed a reduction in both maternal peripheral parasitaemia and placental parasitaemia at delivery. However, maternal peripheral parasitaemia during pregnancy was significantly lower among women receiving daily cotrimoxazole than among those receiving three doses of SP, while pregnant women receiving three doses of SP had a reduced risk of severe adverse events during pregnancy than women receiving daily cotrimoxazole. Notably, SP was not associated with a decreased risk of low birth weight in comparisons including SP in one trial arm verus cotrimoxazole, azithromycin or placebo in the other arm, despite the known benefits of SP on birth weight observed in trials among pregnant women not infected with HIV. Mother-to-child HIV transmission rates showed no differences between women receiving SP and daily cotrimoxazole. The results of the single trial comparing azithromycin versus SP did not find any differences between the interventions for the studied outcomes.

Overall completeness and applicability of evidence

This review included 14 trials conducted in sub-Saharan Africa between 2002 and 2023, which were published in 13 peer-reviewed articles. Five trials compared the current standard of care for malaria prevention among pregnant women (daily cotrimoxazole prophylaxis) with the addition of other antimalarial drugs in the intervention arm. For this reason, the results of these trials are the most helpful for informing decisions in settings with malaria transmission among pregnant women. Those five trials were conducted in Benin, Gabon, Kenya, Malawi, Mozambique, and Uganda, and enrolled 2981 women (Barsosio 2024; Denoeud-Ndam 2014a; González 2014; González 2024; Natureeba 2017). The findings of the published trials that compared dihydroartemisinin/piperaquine plus daily cotrimoxazole with placebo plus daily cotrimoxazole go in the same direction - except the one conducted in Uganda, which had a low sample size (200 women randomized) (Natureeba 2017) and did not show differences between groups for any outcome.

The use of mefloquine for the prevention of malaria in pregnancy was previously evaluated in a Cochrane review (González 2018). This review, as well as our findings, evidenced that preventing malaria with mefloquine reduced the risk of maternal parasitaemia at delivery and placental malaria among women. However, the risk of drug-related adverse events was more common among women receiving mefloquine, and mefloquine was found to increase the risk of mother-to-child HIV transmission in one trial (González 2014). This same trial showed a slight but significant increased viral load at delivery among women under mefloquine preventive treatment (according to protocol analysis). Mefloquine is currently recommended as malaria treatment and malaria chemoprevention for pregnant women of any gestational age travelling to malaria-endemic countries (CDC 2019). This drug is also recommended

for treatment of uncomplicated malaria episodes among the general population in combination with artesunate, regardless of HIV status, except for women in their first trimester (WHO 2022b). The 2022 WHO Guidelines for Malaria stated that there is continued availability of mefloquine as monotherapy in some countries, which is expected to shorten its therapeutic life as partner drug of artemisinin-based combination treatment (WHO 2022b). In 2013, the WHO Evidence Review Group (ERG) on IPTp met to assess the available evidence from trials evaluating mefloquine to prevent malaria. The WHO Malaria Policy Advisory Committee (MPAC) reviewed the ERG recommendations and agreed that mefloquine should not be recommended for malaria prevention during pregnancy, regardless of whether women are infected with HIV, given the increased risk of adverse events, the poor tolerability, and the risk of mother-to-child transmission of HIV (WHO MPAC 2013).

Regarding the three trials that evaluated dihydroartemisinin/piperaquine, the analyses found that adding monthly dihydroartemisinin/piperaquine to daily cotrimoxazole reduced the risk of placental infection (detected by histopathologic analysis in three trials) and maternal peripheral parasitaemia during pregnancy (detected by any test in one trial). Two of the trials evaluating intermittent preventive treatment with dihydroartemisinin/piperaquine (Barsosio 2024; González 2024) have recently been completed and have similar results regarding the drug safety and efficacy to prevent overall malaria infection in this group of women with HIV. The findings of these studies were presented to the Global Malaria Program (WHO) in February 2024 and are expected to guide future malaria prevention guidelines.

Certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach. We presented a summary of the evidence in Summary of findings 1 and Summary of findings 2. Where we judged the evidence to be low or very low certainty, this reflected our decreased confidence in the evidence due to risk of bias, imprecise results, or inconsistent results across trials.

For the main comparison looking at the current standard of care (daily cotrimoxazole) with or without placebo versus daily cotrimoxazole with mefloquine or dihydroartemisinin/piperaquine, the certainty of the evidence ranged from very low to high. We downgraded the certainty of evidence of some outcomes evaluated for risk of bias in one of the included studies (an open-label clinical trial, Denoeud-Ndam 2014a). The findings of maternal anaemia at delivery are of high certainty. We downgraded the results for peripheral maternal parasitaemia and placental malaria due to imprecision, while we downgraded low birth weight and foetal loss due to risk of bias; all of them are of moderate certainty. Analyses of severe adverse events during pregnancy and neonatal mortality were downgraded due to wide CIs ranging from considerable benefit to considerable harm of the intervention versus the standard of care (daily cotrimoxazole), and risk of bias in the case of severe adverse events only; both outcomes are of low certainty. Analysis results of cord blood parasitaemia were downgraded by one level for risk of bias, and by two levels of imprecision due to wide CIs ranging from large benefit to moderate harm; thus we have only very-low certainty evidence for this outcome.

Summary of findings 2, which summarizes a subset of the main comparison, the current standard of care (daily cotrimoxazole) with placebo versus daily cotrimoxazole with dihydroartemisinin/piperaquine, yielded higher levels of evidence, ranging from high to low certainty. The results for placental malaria were of high certainty. Analyses of maternal parasitaemia at delivery, maternal anemia at delivery, neonatal mortality, low birth weight, and foetal loss had moderate-certainty evidence. We downgraded the evidence by one level due to imprecision since CIs were very wide, or due to inconsistency across trials. We assessed the results for the gastrointestinal disorders after first intermittent preventive treatment dose as low certainty due to downgrading for both inconsistency and imprecision. Finally, we downgraded the certainty of the evidence for the analysis of mother-to-child transmission of HIV by two levels due to imprecision since the CIs were very wide and ranged from large benefit to large harm, thus evidence was of low certainty.

Potential biases in the review process

We were able to identify and access all relevant studies to fully undertake the screening process and extract data from the included studies. Review authors who were part of the authors' team in any of the included studies did not participate in the evaluation or data extraction of those studies. We consider it unlikely that the study selection process could have introduced any bias. We could have selected or prioritised different outcomes or measures for the review; for aspects of methodology that we changed post-protocol, please see Differences between protocol and review.

Agreements and disagreements with other studies or reviews

To the best of our knowledge, there are no reviews to compare with this Cochrane review other than the previous published version (Mathanga 2011). Only one of the nine comparisons presented in this review was included in the previous version. The results of that comparison (monthly versus standard two-dose sulfadoxine-pyrimethamine) are the same in both versions.

In addition, a prior Cochrane Review conducted by this same author team investigated the potential of mefloquine for the prevention of malaria in pregnancy among both women and women without HIV (González 2018), and concluded that it was efficacious, but that "the high proportion of mefloquine-related adverse events constitutes an important barrier to its effectiveness for malaria preventive treatment in pregnant women".

AUTHORS' CONCLUSIONS

Implications for practice

Mefloquine and dihydroartemisinin/piperaquine with daily cotrimoxazole have been evaluated in clinical trials for the prevention of malaria among HIV-positive pregnant women. Meta-analysis showed them to be efficacious in preventing malaria; however, one of the drugs, mefloquine, was associated with increased risk of HIV mother-to-child transmission and poor drug tolerability, which may be barriers to its implementation in practice.

The evidence evaluating dihydroartemisinin/piperaquine added to daily cotrimoxazole prophylaxis indicates that it reduces the risk of placental malaria in HIV-positive women compared to daily cotrimoxazole prophylaxis alone, and does not seem to increase the

risk of adverse events, which may make it an adequate drug for an intermittent preventive regimen for malaria in this population.

Implications for research

Further research is needed to elucidate the mechanisms that lead to a two-fold increased risk of mother-to-child transmission of HIV infection when mefloquine is used as an intermittent preventive regimen for malaria in HIV-positive pregnant women.

Dihydroartemisinin/piperaquine has previously been shown to be a promising candidate for intermittent preventive treatment of malaria in pregnancy among women without HIV in areas of high sulfadoxine-pyrimethamine resistance and stable malaria transmission, where it may be cost-effective when used in combination with long-lasting insecticidal nets. The studies in this review that evaluated dihydroartemisinin/piperaquine in women with HIV on cotrimoxazole prophylaxis indicate that it probably reduces malarial infection in the placenta of HIV-positive pregnant women in malaria-endemic countries. The cost-effectiveness of this strategy will need to be evaluated along with the study and surveillance of parasite development of resistance against the drug. Studies in regions of different malaria transmission intensities and seasonality might also be informative to guide and tailor recommendations for malaria prevention in women with HIV.

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Paul Garner, CIDG Editor
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Deirdre Walshe, CIDG
- Copy Editor (copy editing and production): Laura MacDonald, Cochrane Central Production Service;
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*Marty Chaplin is a member of CIDG, and provided peer-review comments on this article, but was not otherwise involved in the editorial process or decision-making for this article.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Akinyotu 2018

Study characteristics	
Methods	Single-blind, superiority RCT
Participants	142 HIV-positive pregnant women in South-West Nigeria Inclusion criteria • HIV-infected • ≥ 16 weeks of gestation • No history of use of mefloquine or SP prior to enrolment Exclusion criteria • Severe anaemia • Allergy to mefloquine or SP • Multiple pregnancy • Medical conditions such as hypertension or diabetes mellitus • Known psychiatric illness, seizure disorder, history of renal/hepatic disease • Febrile illness or symptomatic malaria at the time of recruitment
Interventions	3 monthly doses of SP as IPTp vs 3 monthly doses of mefloquine as IPTp (one dose administered each month for 3 months)

Akinyotu 2018 *(Continued)*

Outcomes	The primary outcome of the study was maternal peripheral parasitaemia at delivery. Secondary outcomes included placental parasitaemia, birth weight, prematurity, and drug-related adverse events.
Notes	All participants were given an LLIN at enrollment. All participants received a twice-daily fixed-dose of 200 mg of nevirapine, 300 mg of zidovudine, and 150 mg of lamivudine as per the facilities' prevention of mother-to-child HIV transmission protocol at the time of the study. In the first 2 weeks of administration, nevirapine was administered separately at a reduced dose of 200 mg daily to limit the risk of adverse effects.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated to receive SP or mefloquine using block randomization with a block size of 4 and 6 possible permutations (AABB, BBAA, ABAB, BABA, BAAB, and ABBA). NB: 2 study sites (one tertiary hospital), but no stratification
Allocation concealment (selection bias)	Low risk	The investigators were masked to allocation because the drugs were pre-packaged on the basis of the random numbers and they could not see the content.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial. Participants were not masked to treatment received because the investigational drugs were commercially available tablets that were easily differentiated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The laboratory technician reading the slides was masked to which treatment group each slide belonged. The paper does not discuss blinding of those assessing other outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of the 142 women enrolled, 131 (93.2%) women completed the study and were included in the primary endpoint analysis (4/71 women were lost to follow-up in the SP arm and 7/71 in the mefloquine arm).
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Unclear risk	Possible selection bias due to significant differences in participant's parity and occupation between treatment groups. It is not clear whether these differences were accounted for during data analysis. Adherence to treatment was not reported.

Akinyotu 2019

Study characteristics

Methods	Single-blind RCT
Participants	123 HIV-positive pregnant women in Nigeria Inclusion criteria • HIV-positive • Gestational age ≥ 16 weeks • No history of azithromycin or SP use 4 weeks prior to recruitment

Akinyotu 2019 *(Continued)*

	Exclusion criteria • Anaemia • Pre-existing medical conditions (other than HIV infection), allergy to SP or azithromycin • Non-consenting patients • Multiple gestations
Interventions	Single-dose azithromycin vs 3-dose SP for IPTp
Outcomes	The primary study outcome was malaria parasitaemia at delivery. The secondary outcomes included maternal peripheral parasitaemia during pregnancy, placental malaria, clinical malaria episodes during pregnancy, maternal anaemia, birth weight, prematurity, and drug-related adverse events.
Notes	All participants received an LLIN. All participants received routine care for HIV-infected women to prevent mother-to-child transmission of HIV.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were enrolled and allocated into study arms using block randomization (block size of 4).
Allocation concealment (selection bias)	Low risk	Allocation numbers and drugs were kept in opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no masking of the intervention drugs. Both drugs were self-administered and the dosing regimens for the drugs differed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome assessor was blinded to the allocation group and drug administered.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A total of 123 participants (87.9%) completed the study and 17 participants (12.1%) were lost to follow-up. It is unclear whether loss-to-follow-up was balanced between the study arms.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Unclear risk	Possible selection bias due to significant differences in participant's parity, gestational age at enrolment, and occupation between treatment groups. It is not clear whether these differences were accounted for during data analysis. Adherence to treatment was not reported.

Barsosio 2024

Study characteristics

Methods	Two-arm multicentre, individually randomized, placebo-controlled trial in 6 antenatal clinics in western Kenya (n = 3) and Malawi (n = 3) in areas with high-grade S-P resistance and perennial malaria transmission

Barsosio 2024 *(Continued)*

Participants	904 women living with HIV Inclusion crieria • Women living with HIV • Eligible for (or on) daily ART consisting of tenofovir, lamivudine, and dolutegravir • Had ultrasound confirmed viable singleton pregnancies between 16 and 28 weeks' gestation • Residents of study area • Willing to adhere to scheduled and unscheduled study visit procedures and deliver in a study clinic Exclusion criteria • Women with multiple pregnancies (e.g. twin pregnancies) • Known heart conditions • Advanced HIV disease at WHO clinical stages 3 and 4 • Confirmed or suspected tuberculosis disease • Known allergy or contraindication to dihydroartemisinin–piperaquine • HIV-negative or unknown HIV status
Interventions	Cotrimoxazole plus monthly dihydroartemisinin/piperaquine-IPTp vs cotrimoxazole plus monthly placebo-IPTp
Outcomes	The primary endpoint was the incidence of at least one *Plasmodium* infection detected in the peripheral (maternal) or placental (maternal) blood or tissue by PCR, microscopy, rapid diagnostic test, or placental histology (active infection) from 2 weeks after the first day of the first dose of the first course of dihydroartemisinin–piperaquine or placebo to delivery, inclusive. Key secondary efficacy endpoints included the individual components of the primary endpoint, clinical malaria, maternal haemoglobin concentrations, and anaemia measured in the third trimester and at delivery; maternal weight gain and mid-upper arm circumference measured at each scheduled monthly visit; and adverse pregnancy outcome, defined as a composite of either foetal loss (miscarriage or stillbirth), small vulnerable newborn or with low birthweight (< 2500 g), or preterm (< 37 weeks' gestation) or subsequent neonatal death by day 28, and the individual components of the composite adverse pregnancy outcome.
Notes	All participants received an LLIN.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Balanced randomization was done using computer-generated permuted block randomization stratified by site and HIV status.
Allocation concealment (selection bias)	Low risk	An independent statistician, not involved in the study, generated the randomization list for the trial pharmacists in Kenya and Malawi, who prepared sequentially numbered, sealed, opaque envelopes for each participant with the randomization assignments. Contained in each opaque envelope were the pre-packed investigational products for the entire study duration for that participant.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All investigators, laboratory staff, data analysts, and participants were masked to treatment assignment.
Blinding of outcome assessment (detection bias)	Low risk	All investigators, laboratory staff, data analysts, and participants were masked to treatment assignment.

Barsosio 2024 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very low number of losses in outcomes reported.
Selective reporting (reporting bias)	Low risk	None observed
Other bias	Low risk	No other biases identified

Denoeud-Ndam 2014a

Study characteristics	
Methods	One of 2 parallel, open-label, non-inferiority RCTs investigating cotrimoxazole prophylaxis vs mefloquine: the "cotrimoxazole mandatory" trial
Participants	292 HIV-positive pregnant women in 5 hospitals in Benin Inclusion criteria • HIV-positive • Aged ≥ 18 years • Living permanently in the study area • Gestational age between 16 and 28 weeks • Giving a written informed consent Exclusion criteria • Age < 18 years • History of a neuropsychiatric disorder • Severe kidney or liver disease • Serious adverse reactions to mefloquine, sulfa drugs, or quinine
Interventions	Daily cotrimoxazole vs daily cotrimoxazole plus 3 doses of mefloquine as IPTp
Outcomes	The primary outcome was proportion of placental malaria. Secondary outcomes were maternal peripheral parasitaemia during pregnancy and at delivery, maternal anaemia, cord blood malaria infection at delivery, low birth weight, preterm deliveries, spontaneous abortions, stillbirths, congenital anomalies, neonatal and infant mortality, adverse drug effects, and mother-to-child HIV transmission rate.
Notes	All participants received insecticide-treated bed nets. All women received ART to prevent mother-to-child transmission of HIV according to national guidelines. Women who were already under treatment before pregnancy continued with the same ART. In other cases, ART was prescribed immediately if HIV-infected pregnant women needed treatment for themselves, or at different times during pregnancy, according to the ongoing PMTCT guidelines: before June 2010, ART was recommended from 28 weeks of pregnancy; after June 2010, it was recommended from 14 weeks of pregnancy (Denoeud-Ndam 2013).
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Denoeud-Ndam 2014a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomization was stratified according to the study site and the number of previous pregnancies (primigravid vs multigravid). The randomization procedure used was not described.
Allocation concealment (selection bias)	High risk	Open-label, non-inferiority RCT based on the participants' immunodeficiency levels. Randomization was stratified according to the study site and the number of previous pregnancies (primigravid vs multigravid). The study co-ordination centre retained the master list and assigned treatments by phone.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This open-label trial was blinded only to the microscopists who evaluated blood smears.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This trial was blinded only to the microscopists who evaluated blood smears. Those assessing other outcomes, including adverse events, were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The reasons for exclusion are well explained and balanced.
Selective reporting (reporting bias)	Low risk	Not observed
Other bias	Low risk	Not observed

Denoeud-Ndam 2014b

Study characteristics	
Methods	One of 2 parallel open-label, non-inferiority RCTs investigating cotrimoxazole prophylaxis vs mefloquine: "cotrimoxazole not mandatory" trial
Participants	140 HIV-positive pregnant women in 5 hospitals in Benin Inclusion criteria • HIV-positive • Aged ≥ 18 years • Living permanently in the study area • Gestational age between 16 and 28 weeks • Giving a written informed consent Exclusion criteria • Age < 18 years • History of a neuropsychiatric disorder • Severe kidney or liver disease • Serious adverse reactions to mefloquine, sulfa drugs, or quinine
Interventions	Daily cotrimoxazole vs 3 doses of mefloquine as IPTp
Outcomes	The primary outcome was proportion of placental malaria. Secondary outcomes were maternal peripheral parasitaemia during pregnancy and at delivery, maternal anaemia, cord blood malaria infection at

Denoeud-Ndam 2014b *(Continued)*

	delivery, low birth weight, preterm deliveries, spontaneous abortions, stillbirths, congenital anomalies, neonatal and infant mortality, adverse drug effects, and mother-to-child HIV transmission rate.
Notes	All participants received insecticide-treated bed nets. All women received ART to prevent mother-to-child transmission of HIV according to national guidelines. Women who were already under treatment before pregnancy continued with the same ART. In other cases, ART was prescribed immediately if HIV pregnant women needed treatment for themselves, or at different times during pregnancy according to the ongoing PMTCT guidelines: before June 2010, ART was recommended from 28 weeks of pregnancy; after June 2010, it was recommended from 14 weeks of pregnancy (Denoeud-Ndam 2013).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Rrandomization was stratified according to the study site and the number of previous pregnancies (primigravid vs multigravida). The randomization procedure used was not described.
Allocation concealment (selection bias)	High risk	It is an open-label, noninferiority controlled trial based on the participants' immunodeficiency levels. Randomization was stratified according to the study site and the number of previous pregnancies (primigravid vs multigravid). The study co-ordination centre retained the master list and assigned treatments by phone.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This open-label trial was blinded only to the microscopists who evaluated blood smears.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This trial was blinded only to the microscopists who evaluated blood smears. Those assessing other outcomes, including adverse events, were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The reasons for exclusion are well explained and balanced.
Selective reporting (reporting bias)	Low risk	Not observed
Other bias	Low risk	Not observed

Filler 2006

Study characteristics

Methods	Non-blinded efficacy RCT
Participants	266 HIV-positive pregnant women in Malawi Inclusion criteria • Patients seeking antenatal care in Machinga District Hospital (Malawi) • First or second pregnancy • Gestational age between 16 and 28 weeks

Filler 2006 *(Continued)*

	Exclusion criteria • Women reporting a priori adverse drug reaction to sulfa-containing medications or quinine • > 28 weeks of gestation or < 16 weeks of gestation • Not pregnant • No foetal movement • Moving from the study area • Antimalarial or cotrimoxazole prophylaxis intake in last month • Prior intake of IPTp with SP • 2 or more prior pregnancies • < 15 years of age
Interventions	Monthly SP for IPTp vs 2-dose SP for IPTp (standard of care)
Outcomes	The primary outcome was placental malaria parasitaemia rates at delivery. Secondary outcomes were clinical malaria episodes during pregnancy, maternal peripheral parasitaemia at delivery, maternal anaemia, cord blood parasitaemia, low birth weight, prematurity, spontaneous abortions, stillbirths, and neonatal mortality.
Notes	Combination antiretroviral therapy was not routinely available in Malawi during the time of the trial. Single-dose nevirapine was given to all HIV-infected women at 32 weeks of gestation to self-administer once they entered active labour.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Enrolled women were randomized, by permuted blocks of random length, to 1 of 2 IPTp regimens, by HIV status.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Neither study participants nor clinicians were blinded to group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trained laboratory workers who assessed the primary outcome of placental malaria were blinded to the women's HIV status and treatment arm.
Incomplete outcome data (attrition bias) All outcomes	High risk	The study's main analysis excluded women who were reassigned from the 2-dose arm to the monthly SP arm. Study authors performed an intention-to-treat analysis, which analyzed data according to original arm assignments. However, findings of this intention-to-treat analysis are only reported for the principal outcome (placental malaria) and not for other outcomes such as clinical malaria episodes or adverse events.
Selective reporting (reporting bias)	Low risk	Not observed
Other bias	Low risk	Not observed

González 2014

Study characteristics	
Methods	An individually-randomized, double-blind, placebo-controlled, multicentre efficacy trial
Participants	1071 HIV-positive pregnant women receiving cotrimoxazole prophylaxis in selected antenatal care clinics in Tanzania, Mozambique, and Kenya Inclusion criteria • Pregnant women • Permanent residents in the study area • Gestational age equal or below 28 weeks • Positive HIV-test at recruitment • Absence of history of allergy to sulfa drugs and mefloquine • Absence of history of severe renal, hepatic, psychiatric, or neurological disease • Had not received mefloquine or halofantrine treatment in the preceding 4 weeks Exclusion criteria • Residence outside the study area or planning to move out in the following 10 months from enrollment • Gestational age at the first antenatal visit > 28 weeks of pregnancy • Known history of allergy to cotrimoxazole or mefloquine • Known history of severe renal, hepatic, psychiatric or neurological disease • Mefloquine or halofantrine treatment in the preceding 4 weeks • Participating in other intervention studies
Interventions	Cotrimoxazole plus mefloquine-IPTp vs cotrimoxazole plus placebo
Outcomes	The primary outcome of this study was maternal peripheral parasitaemia at delivery. Secondary outcomes included prevalence of placental *Plasmodium falciparum* infection, maternal anaemia, maternal viral load at delivery, cord blood parasitaemia, prevalence of low birth weight, prematurity rate, SAEs during pregancy, drug-related adverse events, and mother-to-child transmission of HIV.
Notes	All participants received an LLIN. All participants received antiretroviral drugs for prevention of mother-to-child HIV transmission according to national guidelines.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	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	The Pharmacy Department of the Hospital Clinic in Barcelona produced and safeguarded the computer-generated randomization list for each recruiting site until unblinding, and carried out the masking, labelling, and packaging of all study interventional drugs. Study number allocation for each participant was concealed in opaque sealed envelopes that were sequentially numbered and opened only after recruitment by study health personnel.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	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. The placebo tablets were identical to mefloquine tablets in shape and colour.

González 2014 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	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.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All excluded participants, at each stage of the trial, are counted in the flow chart (both ITT and ATP cohorts). All main outcomes for both endpoints are correctly reported in the article. Only infant data are missing (reported in another article with a different objective).
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	Not observed

González 2024

Study characteristics	
Methods	An individually-randomized, double-blind, placebo-controlled, multicentre efficacy trial
Participants	666 HIV-positive pregnant women attending the antenatal care clinic for the first time in their pregnancy in selected centres from Gabon and Mozambique Inclusion criteria • Permanent residence in the study area • Gestational age equal or below 28 weeks • HIV seropositive status • Agreement to deliver in the study site's maternity wards Exclusion criteria • Planning to move out of the study area in the following 10 months from enrolment • Known history of allergy to cotrimoxazole • Known history of allergy or other contraindications to dihydroartemisinin–piperaquine • Participation in other interventional studies
Interventions	Cotrimoxazole plus dihydroartemisinin/piperaquine-IPTp vs cotrimoxazole plus placebo
Outcomes	The primary outcome of this study was maternal peripheral parasitaemia at delivery. Secondary outcomes included prevalence of placental *Plasmodium falciparum* infection, maternal anaemia, maternal viral load at delivery, cord blood parasitaemia, prevalence of low birth weight, prematurity rate, SAEs during pregancy, drug-related adverse events, and mother-to-child transmission of HIV.
Notes	All participants received a LLIN and aniretroviral therapy (ART). In 2020, HIV/AIDS treatment guidelines were updated in the study countries, with first-line treatment changed from efavirenz-based ART regimens to dolutegravir-based regimens, following WHO recommendations. Participants received the ART regimen recommended at the time of enrolment throughout the study duration, as recommended by national guidelines.
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

González 2024 *(Continued)*

Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (1:1) to study groups, by block randomization of eight (to account for seasonality) and stratified by country.
Allocation concealment (selection bias)	Low risk	Allocation of participants to study groups was done centrally by the trial's sponsor (the Barcelona Institute for Global Health, ISGlobal, Barcelona, Spain). Study number allocation for each study participant was concealed in sealed opaque envelopes that were opened only after recruitment. Study drug tablets (dihydroartemisinin–piperaquine and placebo) were identically packaged.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study personnel, investigators, outcome assessors, data analysts, and participants remained masked to treatment assignment throughout the trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel, investigators, outcome assessors, data analysts, and participants remained masked to treatment assignment throughout the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary endpoint: peripheral blood samples were collected at delivery from 602 (90.4%) of 666 participants, thus contributing to the primary endpoint analysis; of those, 294 (of 332; 88.6%) women were in the intervention group and 308 women were in the control group (of 334; 92.2%). Per-protocol analysis: performed in 63.0% of the intervention group (209 of 332) and 66.5% (222 of 334) of the control group.
Selective reporting (reporting bias)	Low risk	Not observed
Other bias	Low risk	Not observed. There were comparable characteristics (including CD4 count) at baseline between arms and comparable compliance with cotrimoxazole in both arms.

Hamer 2007

Study characteristics	
Methods	A randomized, double-blind, placebo-controlled superiority trial
Participants	456 HIV-seropositive pregnant women in 3 district health clinics in Zambia Inclusion criteria • HIV-1 infection • All gravidities • Gestation of 16 to 28 weeks • Free of an acute illness requiring hospitalization • Willing to deliver at a study maternity clinic Exclusion criteria • Age < 18 years • Prior enrolment in this study • Residence outside of or intent to move out of the catchment areas of the clinics • Severe anaemia (haemoglobin level < 6 g/dL) • History of allergic reactions to sulfa drugs

Hamer 2007 *(Continued)*

	• Prior major pregnancy complications (e.g. breech presentation, severe pre-eclampsia, ≥ 2 caesarean sections) • Major illness likely to influence pregnancy outcomes
Interventions	Monthly SP for IPTp vs 2-dose SP for IPTp (standard of care)
Outcomes	The primary outcomes of this study were the prevalence of placental malaria infection and the prevalence of maternal peripheral parasitaemia at delivery. Secondary outcomes were clinical malaria during pregnancy, maternal anaemia, cord blood parasitaemia, birth weight, prematurity, spontaneous abortion, stillbirth, neonatal and infant death, and maternal death.
Notes	All participants were offered nevirapine for prevention of mother-to-child transmission of HIV.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed in blocks of 20 in 1 of 2 dosing schedules (IPTp every month vs twice during pregnancy).
Allocation concealment (selection bias)	Low risk	Randomization codes were retained by the study biostatistician and stored in a locked cabinet. This code was broken upon completion of data collection and preliminary blinded analyses.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study is a double-blind placebo-controlled trial. Participants were given a sealed package of study drugs, containing the same number of tablets (SP or placebo, prepared by Roche Pharmaceuticals).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear information provided in the methods section of the paper, but in their discussion the authors describe the clinical trial as "double-blind" avoiding "theoretical biases associated with the open-label designs".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of 456 women enrolled, 388 completed the study (35/224 women were lost to follow-up in the monthly SP arm and 32/232 in the 2-dose SP arm). Placental samples were collected from 361 participants (171/189 in the monthly SP arm and 189/200 in the 2-dose SP arm).
Selective reporting (reporting bias)	Unclear risk	Rates of mild adverse events were not shown.
Other bias	Unclear risk	Possible selection bias due to a difference in baseline characteristics between the two groups: a higher proportion of primigravidae enrolled in the arm receiving monthly SP for IPTp. It is not clear whether this difference was accounted for during data analysis.

Klement 2013

Study characteristics	
Methods	Open-label, non-inferiority RCT
Participants	250 HIV-positive pregnant women aged 15 to 45 years in 19 health centres in Togo Inclusion criteria • HIV-1 confirmed by serology through the national HIV testing program

Klement 2013 *(Continued)*

- Age ≥ 15 years
- Gestation of 14 to 28 weeks
- CD4 count ≥ 200 cells/µL
- Hemogobin level ≥ 7 g/dL

Exclusion criteria

- Allergy to cotrimoxazole or SP
- Ongoing cotrimoxazole or SP treatment

Interventions	Daily cotrimoxazole vs 3-dose SP for IPTp
Outcomes	The primary outcome measure was the incidence of clinical malaria during pregnancy. Secondary outcome measures were blood parasitaemia in women and newborn, placental malarial infection, maternal anaemia, birth weight, prematurity, pregnancy outcome (stillbirth, spontaneous abortion, congenital malformations, maternal and infant mortality), treatment tolerance, and mother-to-child transmission of HIV.
Notes	All pregnant women received an insecticide-treated bed net. Women with WHO HIV stage 1–2 with a CD4 count of > 200 cells/µL received 300 mg zidovudine twice daily from 28 weeks of gestation and single-dose nevirapine at labour, and women with WHO stage 3–4 HIV received ART mostly with stavudine, lamivudine, and nevirapine fixed-dose combination.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed in a 1:1 ratio using centralized random allocation tables.
Allocation concealment (selection bias)	High risk	This study was an open-label clinical trial.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was an open-label clinical trial.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was an open-label clinical trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	A placental sample was collected in 131 women: 74/126 in the CTXp group and 57/126 in the IPT with SP group. The study does not explain why placental tissue was not collected from all enroled women.
Selective reporting (reporting bias)	Low risk	Not observed. Many malarial indicators were analyzed (though some of them not clearly defined).
Other bias	Unclear risk	Possible selection bias due to differences in baseline characterstics between the two groups: differences in immunological and ART treatment status with lower median CD4 counts (391 cells/µL (range 200 to 1150 cells/µL) vs 467 cells/µL (range 200 to 1988 cells/µL); P = 0.02) and an accordingly higher proportion of women under ART in the CTXp group (25.4% vs 8.9%; P = 0.001).

Manirakiza 2021

Study characteristics	
Methods	A multicentre, open-label, superiority RCT comparing SP for IPTp with cotrimoxazole under real-life conditions
Participants	193 HIV-positive pregnant women at 4 maternity clinics in Bangui, Central African Republic Inclusion criteria • At least 18 years old • HIV-positive • Gestation of 16 to 28 weeks • CD4+ count ≥ 350 cells/mm^3 • No sign of WHO HIV stage 2, 3, or 4 • Agree to attend all antenatal care visits • Informed consent signed Exclusion criteria • Psychological instability • Known hypersensitivity to sulphonamides or dermatological diseases • Severe anaemia (haemoglobin level < 7g/dL) • Severe diseases requiring hospitalization
Interventions	Cotrimoxazole (administered once daily) vs SP forIPTp (3 curative doses spaced one month apart)
Outcomes	The primary outcome was placental parasitaemia. Secondary outcomes were maternal anaemia, incidence of malaria episodes during pregnancy, cord blood parasitaemia, prematurity, low birth weight, spontaneous abortions, stillbirths, neonatal mortality, occurrence of drug-related adverse events, and mother-to-child transmission of HIV.
Notes	All pregnant women received an insecticide-treated net. All participants received a preventive ART to reduce HIV mother-to-child transmission: (i) zidovudine from week 16 of amenorrhoea; (ii) zidovudine, lamivudine and nevirapine during labour and delivery, and (iii) zidovudine and lamivudine for 7 days after delivery.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization of women was centralized and stratified on maternity clinic and gravidity (primigravidae vs multigravidae). Randomization lists were generated using a 1:1 ratio.
Allocation concealment (selection bias)	Low risk	“Once a pregnant woman is confirmed to be eligible for the study, the field investigator will telephone the coordination staff at the Institut Pasteur of Bangui to indicate the gravid rank, and the site staff will assign women to a treatment arm according to the randomization list, respecting the chronological order of inclusion.”
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was an open-label clinical trial.
Blinding of outcome assessment (detection bias)	High risk	This study was an open-label clinical trial.

Manirakiza 2021 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	The primary end point was documented in only 112 of 193 randomized women. A substantial number of pregnant women in the study delivered at home during an imposed curfew or were lost to follow-up. This limitation occurred primarily because of a worsening sociopolitical crisis in the Central African Republic.
Selective reporting (reporting bias)	Low risk	Not observed
Other bias	Low risk	Not observed

Manyando 2014

Study characteristics	
Methods	Phase 3b, non-inferiority RCT
Participants	52 HIV-positive pregnant women in Zambia
Interventions	Cotrimoxazole as chemoprophylaxis vs 3 doses of SP as IPTp Inclusion criteria • HIV infection with CD4 count ≥ 200 cells/µL • Gestation of 16 to 28 weeks • Willingness to deliver at a study maternity clinic and to adhere to study requirements • No symptoms consistent with malaria at the time of recruitment Exclusion criteria • Previous history of unfavourable pregnancy outcome (pre-eclampsia, stillbirth, caesarean section) • Intent to move outside the study catchment area before delivery • Severe anaemia (haemoglobin level < 7g/dL) • History of allergy to sulpha drugs • History or presence of major illnesses likely to influence pregnancy outcomes (diabetes, severe renal or heart disease, active tuberculosis)
Outcomes	Reported study outcomes included low birth weight and prematurity rates, and SAEs during pregnancy (spontaneous abortions, stillbirths, congenital malformations, neonatal mortality, and maternal mortality)
Notes	The clinical trial was stopped prematurely because of a low malaria prevalence. The article presented the safety results among those women recruited and followed before the trial was stopped. All participants with a CD4 count < 350 cells/µl were treated with ART to prevent mother-to-child transmission of HIV.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The randomization was stratified by HIV status. Eligible women were randomized to one of the two arms according to a predefined randomization list pre-

Manyando 2014 *(Continued)*

		pared at Institute of Tropical Medicine, Antwerp. Method of randomization was not described.
Allocation concealment (selection bias)	Unclear risk	Participants were assigned sequential study numbers, which were matched with numbered envelopes containing the arm allocation that were opened by the study nurses only after recruitment of the study participant. No information is provided on concealment of allocation or access to the predefined randomization key.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was an open-label clinical trial. There was no blinding as each of the study drugs was openly administered.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was an open-label clinical trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not observed
Selective reporting (reporting bias)	Unclear risk	Maternal mortality was not reported.
Other bias	Unclear risk	Baseline characteristics were not reported and compared among the 52 HIV-positive women with CD4 > 200 cells/microL included in the clinical trial.

Menéndez 2008

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled trial
Participants	207 HIV-positive pregnant women in Southern Mozambique Inclusion criteria • Attending the Manhiça District Hospital antenatal care clinic (Mozambique) • Gestational age equal or below 28 weeks • Permanent residents in the study area Exclusion criteria • Allergies to sulfa drugs
Interventions	2 doses of SP for IPTp delivered through antenatal clinics vs placebo
Outcomes	The primary study outcome was low birth weight. Secondary outcomes were maternal peripheral parasitaemia at delivery, placental malaria, haemoglobin level at delivery, maternal anaemia, maternal viral load at delivery, prematurity rate, mean birth weight, and mother-to-child transmission of HIV. Of note, this trial also assessed safety outcomes for the overall sample of HIV-positive and uninfected women. We requested disaggregated data by HIV-status, but safety outcomes could not be retrieved for the subgroup of HIV-positive women.
Notes	All participants received an LLIN.

Menéndez 2008 *(Continued)*

All participants were given nevirapine prophylaxis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated sequential list contained the study numbers linked to treatment identification letters, randomly ordered in blocks of 10. After written informed consent was obtained, the lowest available study number was assigned.
Allocation concealment (selection bias)	Unclear risk	Allocation was stored in a computer-generated list, but there is no information about where this list was kept or who had access to it.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was a double-blind, placebo-controlled trial. Tablets of SP or placebo, identical in shape and colour, were stored in 10 bottles labelled only with a single treatment identification letter. Women were randomized to receive 3 tablets of SP (1500 mg sulphadoxine/75 mg pyrimetamine) or placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As nurses and doctors were blinded, and the principal outcome of the study was low birth weight, we judged the study to have a low risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The paper does not explain why a few children did not have data on weight, or whether baseline characteristics were balanced among those who were weighed and those who were not.
Selective reporting (reporting bias)	Low risk	Not observed
Other bias	Low risk	Not observed

Natureeba 2017

Study characteristics

Methods	Double-blind, randomized, placebo-controlled superiority trial
Participants	200 HIV-positive pregnant women living in Tororo, Uganda Inclusion criteria • HIV-1 infection, confirmed by 2 assays • Age ≥ 16 years • Living within 30 km of the study site • Gestation of 12 to 28 weeks confirmed by ultrasound Exclusion criteria • History of any adverse events associated with cotrimoxazole or dihydroartemisinin/piperaquine therapy • Active medical problem requiring inpatient evaluation • WHO HIV disease stage 4 conditions not stable under treatment • History of cardiac problems • Signs of labour

Natureeba 2017 *(Continued)*

	• Current intake of ritonavir, drugs associated with known risk of torsades de pointes, or Cyt P450 3A inhibitors medications
Interventions	Daily cotrimoxazole plus monthly dihydroartemisinin-piperaquine vs daily cotrimoxazole plus monthly placebo
Outcomes	The primary outcome was prevalence of placental malaria and incidence of malaria. Secondary outcomes included maternal peripheral parasitaemia during pregnancy and at delivery, maternal anaemia, cord blood parasitaemia, adverse birth outcomes, and adverse drug reactionss.
Notes	All participants received an LLIN. All participants received combination ART with efavirenz/tenofovir/lamivudine.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed in a 1:1 ratio using permuted variable-sized blocks of 4 and 6.
Allocation concealment (selection bias)	Low risk	Pharmacists not otherwise involved in the study were responsible for treatment allocation and preparation of study drugs.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study is a double-blind, placebo-controlled RCT. Participants assigned to receive daily CTXp alone were given placebo with the same appearance and number of tablets as active dihydroartemisinin/piperaquine.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigators assessing blood smears and placental histopathology were blinded to both treatment assignment and findings of prior assessments. Blinding of other staff involved in outcome assessment is unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study does not explain why not all (194/200, 97%) of enrolled women had placental tissue collected for histopathologic analysis (4 in the daily CTXp arm and 2 in the daily CTXp + monthly dihydroartemisinin/piperaquine arm).
Selective reporting (reporting bias)	Low risk	Not observed
Other bias	Unclear risk	Possible selection bias due to a difference in baseline characteristics between the groups: a higher proportion of primigravidae enrolled in the CTXp plus monthly dihydroartemisinin/piperaquine arm. It is not clear whether this difference was accounted for during data analysis. Adherence to treatment was not reported.

Abbreviations
ART: antiretroviral therapy; ATP: according to protocol; CD4: white blood cells with CD4 glycoprotein in their surface; CDC: Centers for Disease Control; CTXp: daily cotrimoxazole prophylaxis; HIV: human immunodeficiency virus; IPTp: intermittent preventive treatment of pregnancy; ITT: intention to treat; LLIN: long-lasting insecticidal net; mg: milligrams; µL: microlitre; PCR: polymerase chain reaction; PMTCT: prevention of mother-to-child transmission; RCT: randomized controlled trial; SAE: severe adverse event; SP: sulfadoxine-pyrimethamine; WHO: World Health Organization; vs: versus

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

Study	Reason for exclusion
Gill 2007	Secondary analysis of trial data (Hamer 2007)
Luntamo 2010	Incomplete information and lack of disaggregated data by HIV status for principal outcomes in the published articles. It was not possible to retrieve the information from study authors that would have allowed for the trial's inclusion in meta-analysis.
Parise 1998	Non-randomized trial

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

NCT00132535

Study name	Influence of HIV infection on the effectiveness of malaria prevention during pregnancy, with emphasis on the effect of chloroquine on HIV viral load among pregnant women in Uganda
Methods	Double-blind placebo-controlled RCT
Participants	2548 pregnant women (270 with HIV) in Uganda
Interventions	SP + chloroquine (chloroquine 300 mg weekly) or SP + placebo (IPTp twice during pregnancy)
Outcomes	The primary outcomes are maternal peripheral parasitaemia. placental parasitaemia, clinical malaria, maternal and infant haemoglobin, birth weight, congenital parasitaemia, and maternal HIV viral load at inclusion and before delivery.
Starting date	August 2003
Contact information	Lucy N Korukiiko, Uganda AIDS Commission
Notes	

NCT00164255

Study name	Efficacy of intermittent sulfadoxine-pyrimethamine and sulfadoxine-pyrimethamine + artesunate treatment in the prevention of malaria in pregnancy in an area with chloroquine-resistant *Plasmodium falciparum*
Methods	Open-label RCT
Participants	1614 pregnant women with and without HIV infection in Tanzania
Interventions	Sulfadoxine/pyrimethamine and sulfadoxine/pyrimethamine plus artesunate
Outcomes	The primary outcomes are placental parasitaemia and reported or noted adverse reactions. Secondary outcomes are parasitaemia at delivery (maternal peripheral, placental and cord), maternal illness, birth weight, gestational age, foetal and infant health, impact of maternal HIV infection on efficacy of malaria prevention during pregnancy.
Starting date	January 2003
Contact information	John MacArthur, Centers for Disease Control and Prevention

NCT00164255 *(Continued)*

Notes	

NCT03431168 (PREMISE)

Study name	The PREMISE trial: a novel regimen to prevent malaria and sexually transmitted infections in pregnant women with HIV
Methods	Double-blinded, phase II RCT
Participants	308 pregnant women with HIV in Cameroon
Interventions	Azithromycin/CTXp vs placebo/CTXp
Outcomes	The primary outcomes are *Plasmodium falciparum* peripheral parasitaemia and proportion of participants with composite STI outcome. Secondary outcomes include clinical malaria, placental malaria, maternal anaemia, low birth weight, and adverse birth outcomes.
Starting date	7 March 2018
Contact information	Jodie Dionne-Odom, University of Alabama at Birmingham
Notes	

PACTR201612001901313

Study name	Effectiveness of the combination of dihydroartemisinin and piperaquine for prevention of falciparum malaria during pregnancy in Tanzania
Methods	Blinded RCT
Participants	200 women with HIV infection in Tanzania
Interventions	Daily co-trimoxazole alone versus dihydroartemisinin/piperaquine added to daily cotrimoxazole
Outcomes	The primary outcome is active or recent placental malaria measured at delivery Secondary outcomes are incidence of malaria infection and clinical malaria during pregnancy, defined as fever or recent history of fever in the presence of malaria parasites; and prevalence of adverse newborn morbidity at birth, defined as a composite of either preterm delivery (< 37 weeks' gestation), low birth weight (< 2500 g), and, anaemia (haemoglobin<11 g/dL) during pregnancy or at delivery.
Starting date	7 November 2016
Contact information	Mwelecele Malcela, National Institute for Medical Researches
Notes	

Abbreviations: AIDS: acquired immunodeficiency syndrome; CTXp: daily cotrimoxazole prophylaxis; HIV: human immunodeficiency virus; IPTp: intermittent preventive treatment in pregnancy; RCT: randomized controlled trial; SP: sulfadoxine-pyrimethamine; STI: sexually transmitted infection; vs: versus

DATA AND ANALYSES

Comparison 1. Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care)

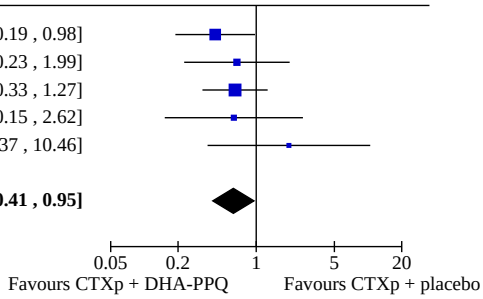
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Maternal peripheral parasitaemia at delivery (amplification techniques)	5	2406	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.41, 0.95]
1.2 Maternal peripheral parasitaemia at delivery (microscopy)	3	1614	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.17, 3.58]
1.3 Maternal anaemia at delivery (< 11 g/dL)	3	2417	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.90, 1.07]
1.4 Placental malaria (any test)	5	2690	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.42, 1.03]
1.5 Placental malaria (blood smear)	3	1337	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.31, 0.93]
1.6 Placental malaria (amplification techniques)	3	1171	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.09, 2.19]
1.7 Placental malaria (histopathologic analysis)	3	1570	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.50, 0.90]
1.8 Maternal peripheral parasitaemia during pregnancy (any test)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.9 Clinical malaria episodes during pregnancy	4		Rate Ratio (IV, Fixed, 95% CI)	0.67 [0.35, 1.32]
1.10 Mean haemoglobin at delivery (in g/dL)	4	2145	Mean Difference (IV, Random, 95% CI)	-0.06 [-0.28, 0.17]
1.11 Maternal severe anaemia at delivery (< 7 g/dL)	4	2621	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.73, 1.98]
1.12 Low birth weight (less than 2500 g)	5	2915	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.95, 1.41]
1.13 Mean birth weight (g)	4	2718	Mean Difference (IV, Fixed, 95% CI)	-46.90 [-85.96, -7.84]
1.14 Cord blood parasitaemia (blood smear)	5	2696	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.04, 1.64]
1.15 Cord blood parasitaemia (loop-mediated isothermal amplification)	1	190	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.16 Prematurity	5	2401	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.78, 1.47]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.17 Severe adverse events during pregnancy	4	2797	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.60, 0.97]
1.18 Foetal loss	5	2957	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.73, 1.46]
1.19 Congenital malformations	5	2904	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.51, 1.58]
1.20 Maternal mortality	4	2787	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.27, 2.65]
1.21 Neonatal mortality	4	2706	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.68, 2.14]

Analysis 1.1. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 1: Maternal peripheral parasitaemia at delivery (amplification techniques)

Study or Subgroup	CTXp + DHA-PPQ Events	CTXp + DHA-PPQ Total	CTXp + placebo Events	CTXp + placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	8	367	18	355	33.8%	0.43 [0.19 , 0.98]
Denoeud-Ndam 2014a	5	106	8	114	14.2%	0.67 [0.23 , 1.99]
González 2014	12	285	25	384	39.3%	0.65 [0.33 , 1.27]
González 2024	3	291	5	306	9.0%	0.63 [0.15 , 2.62]
Natureeba 2017	4	100	2	98	3.7%	1.96 [0.37 , 10.46]
Total		**1149**		**1257**	**100.0%**	**0.62 [0.41 , 0.95]**
Total events:	32		58			

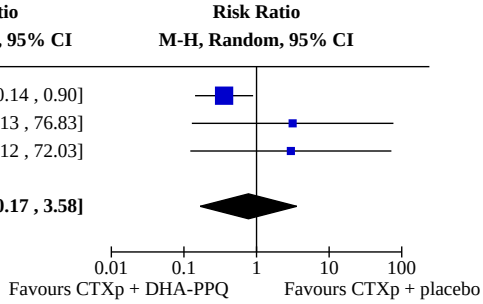
Test for overall effect: Z = 2.18 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 2.62, df = 4 (P = 0.62); I² = 0%



Analysis 1.2. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 2: Maternal peripheral parasitaemia at delivery (microscopy)

Study or Subgroup	CTXp + DHA-PPQ Events	CTXp + DHA-PPQ Total	CTXp + placebo Events	CTXp + placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Barsosio 2024	6	405	17	410	64.0%	0.36 [0.14 , 0.90]
González 2024	1	294	0	308	18.0%	3.14 [0.13 , 76.83]
Natureeba 2017	1	99	0	98	18.0%	2.97 [0.12 , 72.03]
Total (Wald{fn})		**798**		**816**	**100.0%**	**0.77 [0.17 , 3.58]**
Total events:	8		17			

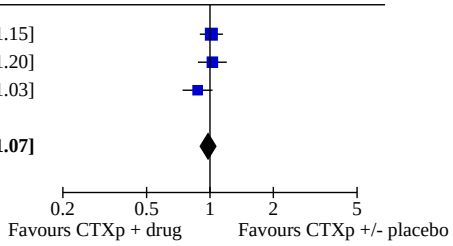
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.73; Chi² = 2.99, df = 2 (P = 0.22); I² = 33%



Analysis 1.3. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 3: Maternal anaemia at delivery (< 11 g/dL)

Study or Subgroup	CTXp + drug Events	Total	CTXp +/- placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024[a]	223	415	226	427	39.2%	1.02 [0.89 , 1.15]
González 2014	190	479	187	484	32.8%	1.03 [0.88 , 1.20]
González 2024	136	300	162	312	28.0%	0.87 [0.74 , 1.03]
Total		**1194**		**1223**	**100.0%**	**0.98 [0.90 , 1.07]**
Total events:	549		575			

Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 2.54, df = 2 (P = 0.28); I² = 21%



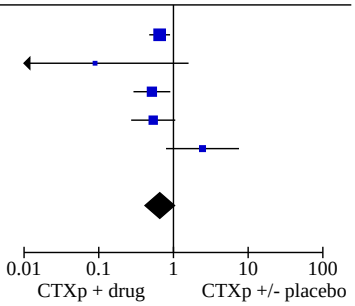
Footnotes

[a]Haemoglobin at delivery or otherwise in the third trimester if the measurement at delivery was unavailable

Analysis 1.4. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 4: Placental malaria (any test)

Study or Subgroup	CTXp + drug Events	Total	CTXp +/- placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Barsosio 2024	52	389	79	386	36.8%	0.65 [0.47 , 0.90]
Denoeud-Ndam 2014a	0	105	5	103	2.3%	0.09 [0.00 , 1.59]
González 2014	17	449	34	462	26.4%	0.51 [0.29 , 0.91]
González 2024	12	297	23	305	22.4%	0.54 [0.27 , 1.06]
Natureeba 2017	10	98	4	96	12.0%	2.45 [0.80 , 7.54]
Total (Wald{fn})		**1338**		**1352**	**100.0%**	**0.66 [0.42 , 1.03]**
Total events:	91		145			

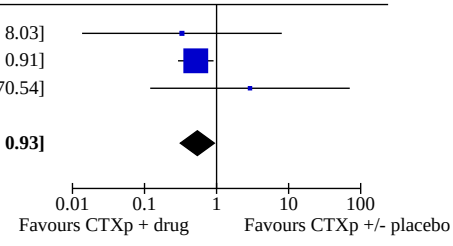
Test for overall effect: Z = 1.82 (P = 0.07)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.12; Chi² = 8.12, df = 4 (P = 0.09); I² = 51%



Analysis 1.5. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 5: Placental malaria (blood smear)

Study or Subgroup	CTXp + drug Events	Total	CTXp +/- placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	0	117	1	116	4.2%	0.33 [0.01 , 8.03]
González 2014	17	449	34	462	94.3%	0.51 [0.29 , 0.91]
Natureeba 2017	1	98	0	95	1.4%	2.91 [0.12 , 70.54]
Total		**664**		**673**	**100.0%**	**0.54 [0.31 , 0.93]**
Total events:	18		35			

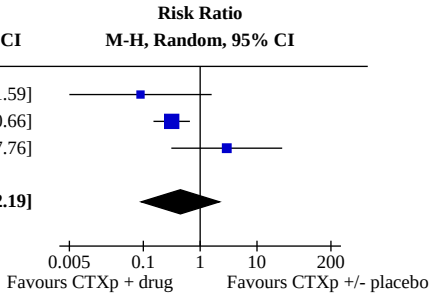
Test for overall effect: Z = 2.22 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.19, df = 2 (P = 0.55); I² = 0%



Analysis 1.6. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 6: Placental malaria (amplification techniques)

Study or Subgroup	CTXp + drug Events	Total	CTXp +/- placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Denoeud-Ndam 2014a	0	105	5	103	20.1%	0.09 [0.00 , 1.59]
González 2014	9	388	28	381	52.8%	0.32 [0.15 , 0.66]
Natureeba 2017	3	98	1	96	27.1%	2.94 [0.31 , 27.76]
Total (Wald{fn})		**591**		**580**	**100.0%**	**0.45 [0.09 , 2.19]**
Total events:	12		34			

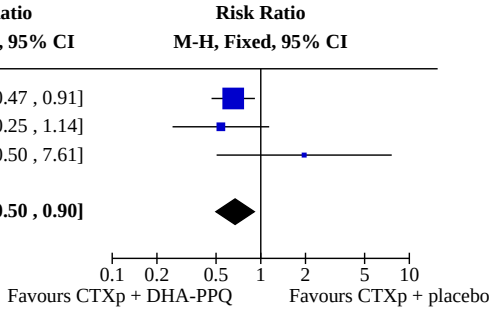
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 1.10; Chi² = 4.38, df = 2 (P = 0.11); I² = 54%



Analysis 1.7. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 7: Placental malaria (histopathologic analysis)

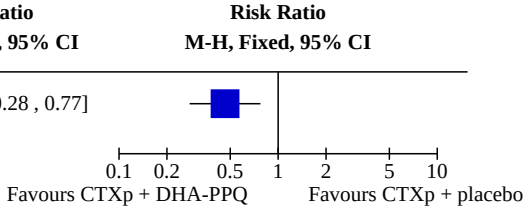
Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	48	389	73	386	77.1%	0.65 [0.47 , 0.91]
González 2024	10	297	19	304	19.7%	0.54 [0.25 , 1.14]
Natureeba 2017	6	98	3	96	3.2%	1.96 [0.50 , 7.61]
Total		**784**		**786**	**100.0%**	**0.67 [0.50 , 0.90]**
Total events:	64		95			

Test for overall effect: Z = 2.63 (P = 0.009)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 2.75, df = 2 (P = 0.25); I² = 27%



Analysis 1.8. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 8: Maternal peripheral parasitaemia during pregnancy (any test)

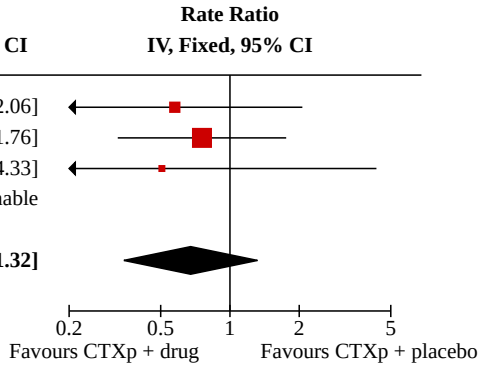
Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	20	443	44	452	0.46 [0.28 , 0.77]



Analysis 1.9. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 9: Clinical malaria episodes during pregnancy

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI
Barsosio 2024	-0.55208602	0.65133895	27.4%	0.58 [0.16 , 2.06]
González 2014	-0.28	0.43	62.9%	0.76 [0.33 , 1.76]
González 2024	-0.68124124	1.09544512	9.7%	0.51 [0.06 , 4.33]
Natureeba 2017	0	0		Not estimable
Total			**100.0%**	**0.67 [0.35 , 1.32]**

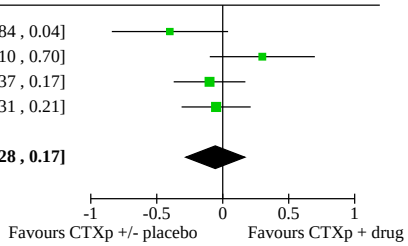
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.20, df = 2 (P = 0.91); I² = 0%



Analysis 1.10. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 10: Mean haemoglobin at delivery (in g/dL)

Study or Subgroup	CTXp + drug Mean	SD	Total	CTXp +/- placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Barsosio 2024	10.7	2.2	190	11.1	2.1	176	17.6%	-0.40 [-0.84 , 0.04]
Denoeud-Ndam 2014a	11.1	1.4	96	10.8	1.5	108	20.2%	0.30 [-0.10 , 0.70]
González 2014	11.2	2.1	479	11.3	2.2	484	30.6%	-0.10 [-0.37 , 0.17]
González 2024	10.74	1.7	300	10.79	1.6	312	31.6%	-0.05 [-0.31 , 0.21]
Total (Wald{fn})			**1065**			**1080**	**100.0%**	**-0.06 [-0.28 , 0.17]**

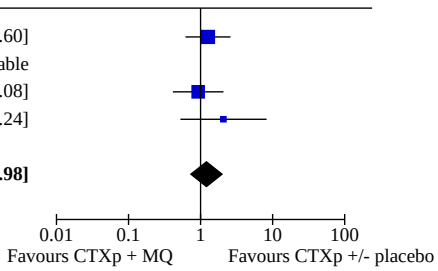
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.02; Chi² = 5.52, df = 3 (P = 0.14); I² = 46%



Analysis 1.11. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 11: Maternal severe anaemia at delivery (< 7 g/dL)

Study or Subgroup	CTXp +MQ Events	Total	CTXp +/- placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024[a]	16	415	13	427	46.3%	1.27 [0.62 , 2.60]
Denoeud-Ndam 2014a	0	96	0	108		Not estimable
González 2014	11	479	12	484	43.1%	0.93 [0.41 , 2.08]
González 2024	6	300	3	312	10.6%	2.08 [0.52 , 8.24]
Total		**1290**		**1331**	**100.0%**	**1.21 [0.73 , 1.98]**
Total events:	33		28			

Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.03, df = 2 (P = 0.60); I² = 0%



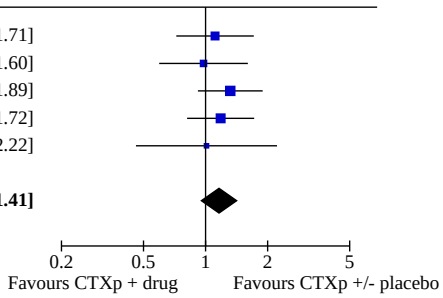
Footnotes

[a]Haemoglobin at delivery or otherwise in the third trimester if the measurement at delivery was unavailable

Analysis 1.12. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 12: Low birth weight (less than 2500 g)

Study or Subgroup	CTXp + drug Events	CTXp + drug Total	CTXp +/- placebo Events	CTXp +/- placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	39	422	36	433	22.1%	1.11 [0.72 , 1.71]
Denoeud-Ndam 2014a	24	119	26	126	15.7%	0.98 [0.60 , 1.60]
González 2014	61	489	46	486	28.7%	1.32 [0.92 , 1.89]
González 2024	50	315	44	328	26.8%	1.18 [0.81 , 1.72]
Natureeba 2017[a]	11	98	11	99	6.8%	1.01 [0.46 , 2.22]
Total		**1443**		**1472**	**100.0%**	**1.16 [0.95 , 1.41]**
Total events:	185		163			

Test for overall effect: Z = 1.50 (P = 0.13)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.11, df = 4 (P = 0.89); I² = 0%



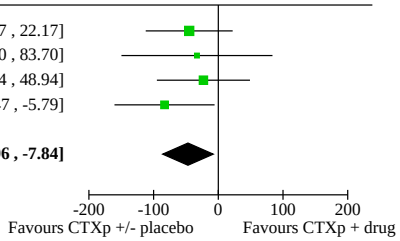
Footnotes

[a]Data are limited to those with a gestational age of ≥ 28 weeks

Analysis 1.13. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 13: Mean birth weight (g)

Study or Subgroup	CTXp + drug Mean	CTXp + drug SD	CTXp + drug Total	CTXp +/- placebo Mean	CTXp +/- placebo SD	CTXp +/- placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Barsosio 2024	3079	502	422	3124	500	433	33.8%	-45.00 [-112.17 , 22.17]
Denoeud-Ndam 2014a	2856	454	119	2889	478	126	11.2%	-33.00 [-149.70 , 83.70]
González 2014	3036.3	570.6	489	3059.3	575.5	486	29.5%	-23.00 [-94.94 , 48.94]
González 2024	2827.95	645.6	315	2911.08	277	328	25.5%	-83.13 [-160.47 , -5.79]
Total			**1345**			**1373**	**100.0%**	**-46.90 [-85.96 , -7.84]**

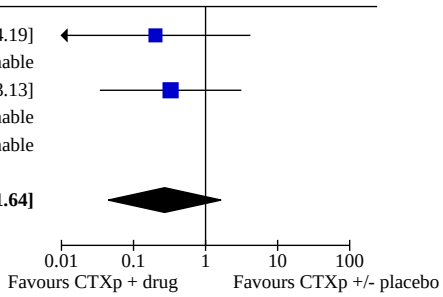
Test for overall effect: Z = 2.35 (P = 0.02)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.32, df = 3 (P = 0.72); I² = 0%



Analysis 1.14. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 14: Cord blood parasitaemia (blood smear)

Study or Subgroup	CTXp + drug Events	CTXp + drug Total	CTXp +/- placebo Events	CTXp +/- placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	0	371	2	374	45.1%	0.20 [0.01 , 4.19]
Denoeud-Ndam 2014a	0	117	0	116		Not estimable
González 2014	1	471	3	462	54.9%	0.33 [0.03 , 3.13]
González 2024	0	296	0	298		Not estimable
Natureeba 2017	0	97	0	94		Not estimable
Total		**1352**		**1344**	**100.0%**	**0.27 [0.04 , 1.64]**
Total events:	1		5			

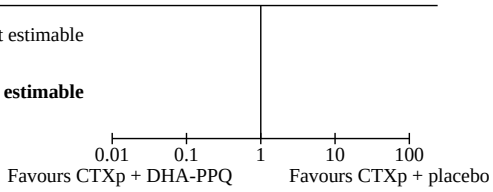
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%



Analysis 1.15. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 15: Cord blood parasitaemia (loop-mediated isothermal amplification)

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Natureeba 2017	0	96	0	94		Not estimable
Total		**96**		**94**		**Not estimable**
Total events:	0		0			

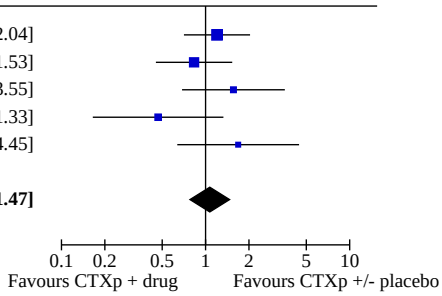
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 1.16. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 16: Prematurity

Study or Subgroup	CTXp + drug Events	Total	CTXp +/- placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	28	417	24	429	34.3%	1.20 [0.71 , 2.04]
Denoeud-Ndam 2014a	16	125	20	130	28.4%	0.83 [0.45 , 1.53]
González 2014	14	284	9	285	13.0%	1.56 [0.69 , 3.55]
González 2024	5	263	11	271	15.7%	0.47 [0.16 , 1.33]
Natureeba 2017	10	98	6	99	8.6%	1.68 [0.64 , 4.45]
Total		**1187**		**1214**	**100.0%**	**1.07 [0.78 , 1.47]**
Total events:	73		70			

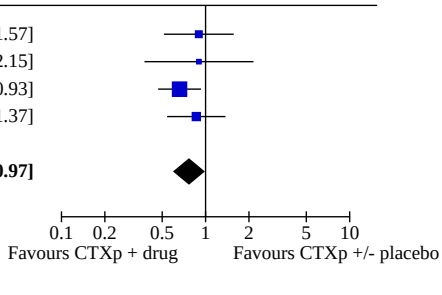
Test for overall effect: Z = 0.42 (P = 0.68)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 4.89, df = 4 (P = 0.30); I² = 18%



Analysis 1.17. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 17: Severe adverse events during pregnancy

Study or Subgroup	CTXp + drug Events	Total	CTXp +/- placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	22	446	25	455	17.4%	0.90 [0.51 , 1.57]
Denoeud-Ndam 2014a	9	146	10	146	7.0%	0.90 [0.38 , 2.15]
González 2014	48	523	74	532	51.7%	0.66 [0.47 , 0.93]
González 2024	29	273	34	276	23.8%	0.86 [0.54 , 1.37]
Total		**1388**		**1409**	**100.0%**	**0.77 [0.60 , 0.97]**
Total events:	108		143			

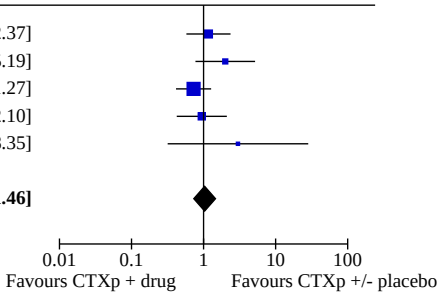
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.42, df = 3 (P = 0.70); I² = 0%



Analysis 1.18. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 18: Foetal loss

Study or Subgroup	CTXp + drug Events	Total	CTXp +/- placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	16	433	14	443	22.9%	1.17 [0.58 , 2.37]
Denoeud-Ndam 2014a	12	146	6	146	9.9%	2.00 [0.77 , 5.19]
González 2014	20	523	28	532	45.9%	0.73 [0.41 , 1.27]
González 2024	11	263	12	271	19.6%	0.94 [0.42 , 2.10]
Natureeba 2017	3	100	1	100	1.7%	3.00 [0.32 , 28.35]
Total		**1465**		**1492**	**100.0%**	**1.03 [0.73 , 1.46]**
Total events:	62		61			

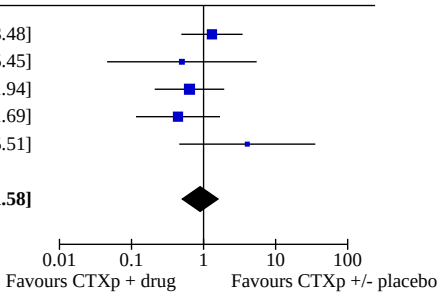
Test for overall effect: Z = 0.19 (P = 0.85)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 4.39, df = 4 (P = 0.36); I² = 9%



Analysis 1.19. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 19: Congenital malformations

Study or Subgroup	CTXp + drug Events	Total	CTXp +/- placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	9	428	7	435	28.0%	1.31 [0.49 , 3.48]
Denoeud-Ndam 2014a	1	146	2	146	8.1%	0.50 [0.05 , 5.45]
González 2014	5	505	8	515	32.0%	0.64 [0.21 , 1.94]
González 2024	3	263	7	271	27.9%	0.44 [0.12 , 1.69]
Natureeba 2017[a]	4	97	1	98	4.0%	4.04 [0.46 , 35.51]
Total		**1439**		**1465**	**100.0%**	**0.90 [0.51 , 1.58]**
Total events:	22		25			

Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 4.08, df = 4 (P = 0.40); I² = 2%



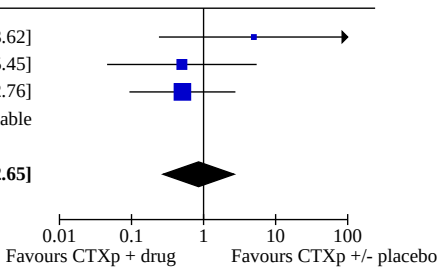
Footnotes

[a]Data are limited to those with a gestational age of ≥28 weeks.

Analysis 1.20. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 20: Maternal mortality

Study or Subgroup	CTXp + drug Events	Total	CTXp +/- placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	2	446	0	445	7.7%	4.99 [0.24 , 103.62]
Denoeud-Ndam 2014a	1	146	2	146	30.9%	0.50 [0.05 , 5.45]
González 2014	2	523	4	532	61.3%	0.51 [0.09 , 2.76]
González 2024	0	273	0	276		Not estimable
Total		**1388**		**1399**	**100.0%**	**0.85 [0.27 , 2.65]**
Total events:	5		6			

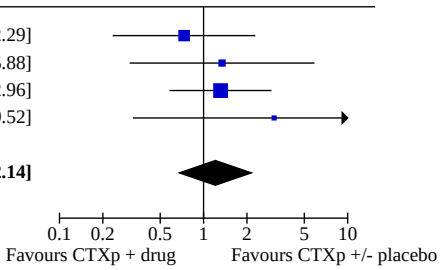
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.85, df = 2 (P = 0.40); I² = 0%



Analysis 1.21. Comparison 1: Daily cotrimoxazole (CTXp) with any other drug regimen (mefloquine (MQ) or dihydroartemisinin-piperaquine (DHA-PPQ)) versus CTXp with or without placebo (current standard of care), Outcome 21: Neonatal mortality

Study or Subgroup	CTXp + drug Events	Total	CTXp +/- placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	5	416	7	426	33.2%	0.73 [0.23 , 2.29]
Denoeud-Ndam 2014a	4	129	3	130	14.3%	1.34 [0.31 , 5.88]
González 2014	13	488	10	492	47.8%	1.31 [0.58 , 2.96]
González 2024	3	308	1	317	4.7%	3.09 [0.32 , 29.52]
Total		**1341**		**1365**	**100.0%**	**1.21 [0.68 , 2.14]**
Total events:	25		21			

Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.47, df = 3 (P = 0.69); I² = 0%



Comparison 2. Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp

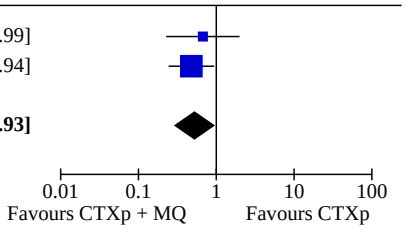
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Maternal peripheral parasitaemia at delivery (polymerase chain reaction)	2	989	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.30, 0.93]
2.2 Maternal anaemia at delivery (< 9.5 g/dL)	2	1197	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.73, 1.20]
2.3 Placental malaria (blood smear)	2	1144	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.29, 0.89]
2.4 Placental malaria (polymerase chain reaction)	2	977	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.14, 0.57]
2.5 Clinical malaria episodes during pregnancy	1		Rate Ratio (IV, Fixed, 95% CI)	Subtotals only
2.6 Mean haemoglobin at delivery (in g/dL)	2	1167	Mean Difference (IV, Random, 95% CI)	0.07 [-0.32, 0.46]
2.7 Maternal severe anaemia at delivery	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.8 Low birth weight (< 2500 g)	2	1220	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.60]
2.9 Mean birth weight (g)	2	1220	Mean Difference (IV, Fixed, 95% CI)	-25.75 [-86.99, 35.49]
2.10 Cord blood parasitaemia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.11 Prematurity	2	824	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.58, 1.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.12 Severe adverse events during pregnancy	2	1347	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.50, 0.95]
2.13 Foetal loss	2	1347	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.42, 2.98]
2.14 Congenital malformations	2	1312	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.22, 1.67]
2.15 Maternal mortality	2	1347	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.13, 2.01]
2.16 Neonatal mortality	2	1239	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.65, 2.69]
2.17 Adverse events: headache	2	1347	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.28, 2.10]
2.18 Adverse events: vomiting	2	1347	Risk Ratio (M-H, Random, 95% CI)	20.88 [1.40, 311.66]
2.19 Adverse events: dizziness	2	1347	Risk Ratio (M-H, Random, 95% CI)	16.34 [0.39, 684.99]
2.20 Adverse events: fatigue/weakness	2	1347	Risk Ratio (M-H, Random, 95% CI)	2.95 [0.26, 32.93]
2.21 Mother-to-child transmission of HIV	2	1019	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.13, 3.25]
2.22 Undetectable viral load	2	1220	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.81, 1.08]

Analysis 2.1. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 1: Maternal peripheral parasitaemia at delivery (polymerase chain reaction)

	MQ + CTXp		CTXp			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	5	106	8	114	23.5%	0.67 [0.23 , 1.99]	
González 2014	12	385	25	384	76.5%	0.48 [0.24 , 0.94]	
Total		**491**		**498**	**100.0%**	**0.52 [0.30 , 0.93]**	
Total events:	17		33				

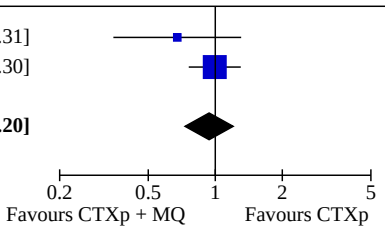
Test for overall effect: Z = 2.22 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.60); I² = 0%



Analysis 2.2. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 2: Maternal anaemia at delivery (< 9.5 g/dL)

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	12	96	20	108	17.7%	0.68 [0.35 , 1.31]
González 2014	87	495	88	498	82.3%	0.99 [0.76 , 1.30]
Total		**591**		**606**	**100.0%**	**0.94 [0.73 , 1.20]**
Total events:	99		108			

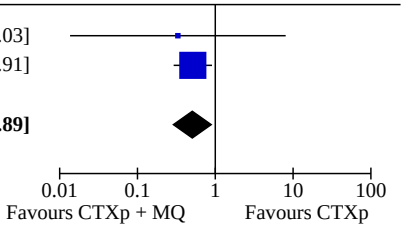
Test for overall effect: Z = 0.50 (P = 0.61)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.13, df = 1 (P = 0.29); I² = 12%



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

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	0	117	1	116	4.3%	0.33 [0.01 , 8.03]
González 2014	17	449	34	462	95.7%	0.51 [0.29 , 0.91]
Total		**566**		**578**	**100.0%**	**0.51 [0.29 , 0.89]**
Total events:	17		35			

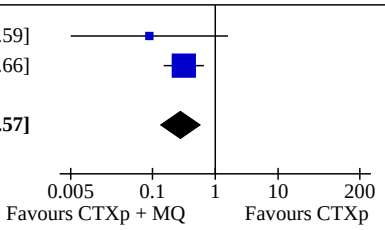
Test for overall effect: Z = 2.39 (P = 0.02)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%



Analysis 2.4. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 4: Placental malaria (polymerase chain reaction)

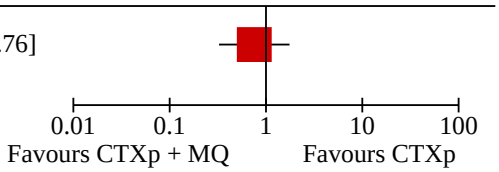
Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	0	105	5	103	16.4%	0.09 [0.00 , 1.59]
González 2014	9	388	28	381	83.6%	0.32 [0.15 , 0.66]
Total		**493**		**484**	**100.0%**	**0.28 [0.14 , 0.57]**
Total events:	9		33			

Test for overall effect: Z = 3.53 (P = 0.0004)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%



Analysis 2.5. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 5: Clinical malaria episodes during pregnancy

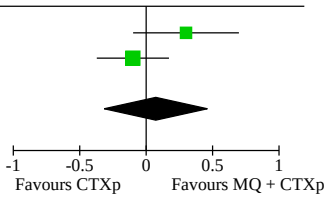
Study or Subgroup	log[Rate Ratio]	SE	Rate Ratio IV, Fixed, 95% CI
González 2014	-0.28	0.43	0.76 [0.33 , 1.76]



Analysis 2.6. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 6: Mean haemoglobin at delivery (in g/dL)

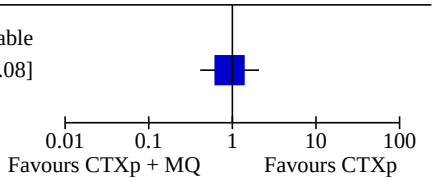
Study or Subgroup	CTXp + MQ Mean	SD	Total	CTXp Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Denoeud-Ndam 2014a	11.1	1.4	96	10.8	1.5	108	43.1%	0.30 [-0.10 , 0.70]
González 2014	11.2	2.1	479	11.3	2.2	484	56.9%	-0.10 [-0.37 , 0.17]
Total (Wald{fn})			**575**			**592**	**100.0%**	**0.07 [-0.32 , 0.46]**

Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.05; Chi² = 2.65, df = 1 (P = 0.10); I² = 62%



Analysis 2.7. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 7: Maternal severe anaemia at delivery

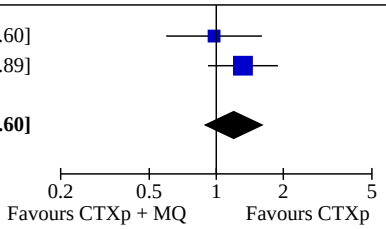
Study or Subgroup	MQ + CTXp Events	Total	CTXp Events	Total	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	0	96	0	108	Not estimable
González 2014	11	479	12	484	0.93 [0.41 , 2.08]



Analysis 2.8. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 8: Low birth weight (< 2500 g)

Study or Subgroup	MQ + CTXp Events	Total	CTXp Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	24	119	26	126	35.4%	0.98 [0.60 , 1.60]
González 2014	61	489	46	486	64.6%	1.32 [0.92 , 1.89]
Total		**608**		**612**	**100.0%**	**1.20 [0.89 , 1.60]**
Total events:	85		72			

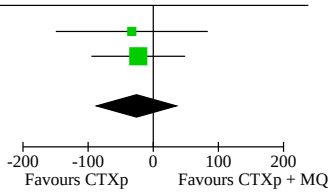
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² = 0%



Analysis 2.9. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 9: Mean birth weight (g)

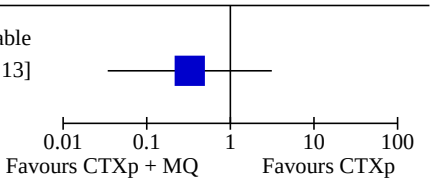
Study or Subgroup	CTXp + MQ Mean	SD	Total	CTXp Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Denoeud-Ndam 2014a	2856	454	119	2889	478	126	27.5%	-33.00 [-149.70 , 83.70]
González 2014	3036.3	570.6	489	3059.3	575.5	486	72.5%	-23.00 [-94.94 , 48.94]
Total			**608**			**612**	**100.0%**	**-25.75 [-86.99 , 35.49]**

Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%



Analysis 2.10. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 10: Cord blood parasitaemia

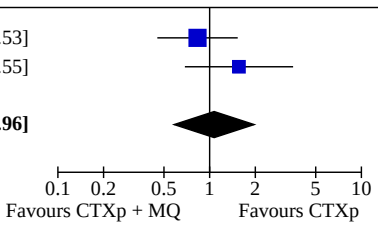
Study or Subgroup	MQ + CTXp Events	Total	CTXp Events	Total	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	0	117	0	116	Not estimable
González 2014	1	471	3	462	0.33 [0.03 , 3.13]



Analysis 2.11. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 11: Prematurity

Study or Subgroup	MQ + CTXp Events	Total	CTXp Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Denoeud-Ndam 2014a	16	125	20	130	59.9%	0.83 [0.45 , 1.53]
González 2014	14	284	9	285	40.1%	1.56 [0.69 , 3.55]
Total (Wald{fn})		**409**		**415**	**100.0%**	**1.07 [0.58 , 1.96]**
Total events:	30		29			

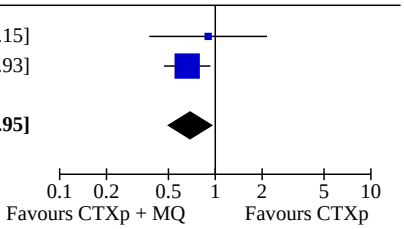
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.06; Chi² = 1.46, df = 1 (P = 0.23); I² = 32%



Analysis 2.12. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 12: Severe adverse events during pregnancy

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	9	146	10	146	12.0%	0.90 [0.38 , 2.15]
González 2014	48	523	74	532	88.0%	0.66 [0.47 , 0.93]
Total		**669**		**678**	**100.0%**	**0.69 [0.50 , 0.95]**
Total events:	57		84			

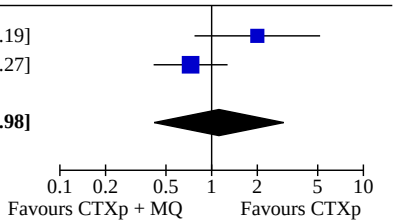
Test for overall effect: Z = 2.30 (P = 0.02)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² = 0%



Analysis 2.13. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 13: Foetal loss

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Random, 95% CI
Denoeud-Ndam 2014a	12	146	6	146	42.5%	2.00 [0.77 , 5.19]
González 2014	20	523	28	532	57.5%	0.73 [0.41 , 1.27]
Total (Wald{fn})		**669**		**678**	**100.0%**	**1.12 [0.42 , 2.98]**
Total events:	32		34			

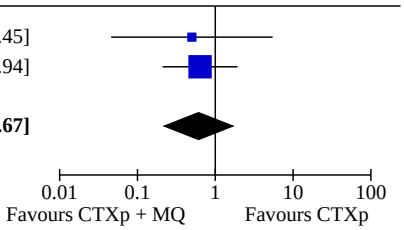
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.35; Chi² = 3.22, df = 1 (P = 0.07); I² = 69%



Analysis 2.14. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 14: Congenital malformations

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	1	146	2	146	20.2%	0.50 [0.05 , 5.45]
González 2014	5	505	8	515	79.8%	0.64 [0.21 , 1.94]
Total		**651**		**661**	**100.0%**	**0.61 [0.22 , 1.67]**
Total events:	6		10			

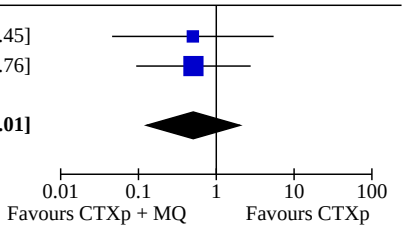
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%



Analysis 2.15. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 15: Maternal mortality

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	1	146	2	146	33.5%	0.50 [0.05 , 5.45]
González 2014	2	523	4	532	66.5%	0.51 [0.09 , 2.76]
Total		**669**		**678**	**100.0%**	**0.51 [0.13 , 2.01]**
Total events:	3		6			

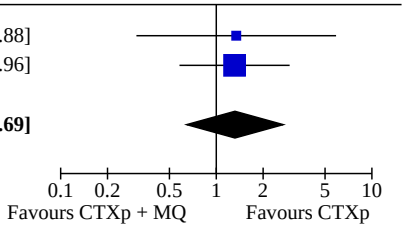
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%



Analysis 2.16. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 16: Neonatal mortality

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	4	129	3	130	23.1%	1.34 [0.31 , 5.88]
González 2014	13	488	10	492	76.9%	1.31 [0.58 , 2.96]
Total		**617**		**622**	**100.0%**	**1.32 [0.65 , 2.69]**
Total events:	17		13			

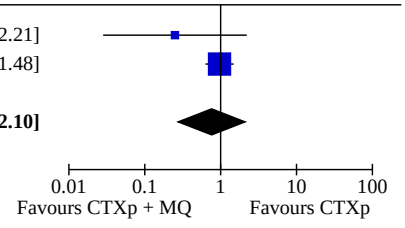
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%



Analysis 2.17. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 17: Adverse events: headache

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Random, 95% CI
Denoeud-Ndam 2014a	1	146	4	146	17.7%	0.25 [0.03 , 2.21]
González 2014	38	523	40	532	82.3%	0.97 [0.63 , 1.48]
Total (Wald{fn})		**669**		**678**	**100.0%**	**0.76 [0.28 , 2.10]**
Total events:	39		44			

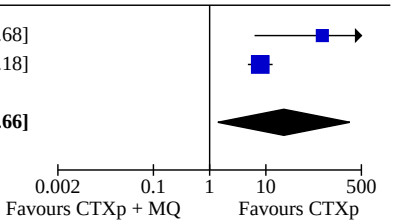
Test for overall effect: Z = 0.53 (P = 0.60)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.28; Chi² = 1.43, df = 1 (P = 0.23); I² = 30%



Analysis 2.18. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 18: Adverse events: vomiting

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Random, 95% CI
Denoeud-Ndam 2014a	50	146	0	146	38.0%	101.00 [6.29 , 1621.68]
González 2014	125	523	16	532	62.0%	7.95 [4.79 , 13.18]
Total (Wald{fn})		**669**		**678**	**100.0%**	**20.88 [1.40 , 311.66]**
Total events:	175		16			

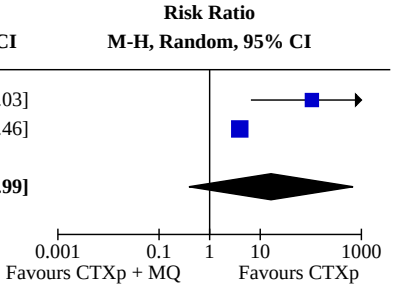
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 3.00; Chi² = 3.90, df = 1 (P = 0.05); I² = 74%



Analysis 2.19. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 19: Adverse events: dizziness

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Random, 95% CI
Denoeud-Ndam 2014a	52	146	0	146	43.3%	105.00 [6.54 , 1685.03]
González 2014	155	523	40	532	56.7%	3.94 [2.85 , 5.46]
Total (Wald{fn})		**669**		**678**	**100.0%**	**16.34 [0.39 , 684.99]**
Total events:	207		40			

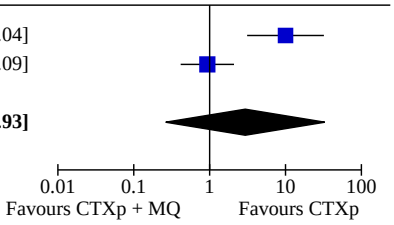
Test for overall effect: Z = 1.47 (P = 0.14)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 6.38; Chi² = 7.28, df = 1 (P = 0.007); I² = 86%



Analysis 2.20. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 20: Adverse events: fatigue/weakness

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Random, 95% CI
Denoeud-Ndam 2014a	30	146	3	146	48.5%	10.00 [3.12 , 32.04]
González 2014	11	523	12	532	51.5%	0.93 [0.42 , 2.09]
Total (Wald{fn})		**669**		**678**	**100.0%**	**2.95 [0.26 , 32.93]**
Total events:	41		15			

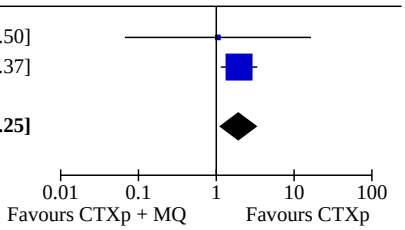
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 2.77; Chi² = 11.60, df = 1 (P = 0.0007); I² = 91%



Analysis 2.21. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 21: Mother-to-child transmission of HIV

Study or Subgroup	MQ + CTXp Events	MQ + CTXp Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	1	80	1	84	5.0%	1.05 [0.07 , 16.50]
González 2014	36	420	19	435	95.0%	1.96 [1.14 , 3.37]
Total		**500**		**519**	**100.0%**	**1.92 [1.13 , 3.25]**
Total events:	37		20			

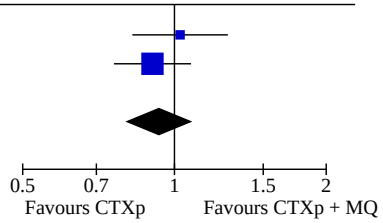
Test for overall effect: Z = 2.41 (P = 0.02)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%



Analysis 2.22. Comparison 2: Mefloquine (MQ) plus daily cotrimoxazole (CTXp) versus CTXp, Outcome 22: Undetectable viral load

Study or Subgroup	CTXp + MQ Events	CTXp + MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014a	52	75	50	74	22.0%	1.03 [0.83 , 1.28]
González 2014	161	534	179	537	78.0%	0.90 [0.76 , 1.08]
Total		**609**		**611**	**100.0%**	**0.93 [0.81 , 1.08]**
Total events:	213		229			

Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%



Comparison 3. Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp

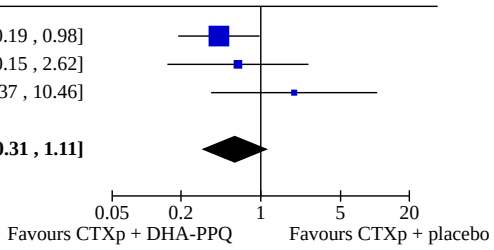
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Maternal peripheral parasitaemia at delivery (amplification techniques)	3	1517	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.31, 1.11]
3.2 Maternal peripheral parasitaemia at delivery (microscopy)	3	1614	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.17, 3.58]
3.3 Maternal anaemia at delivery (< 11g/dL)	2	1454	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.82, 1.10]
3.4 Placental malaria (any test)	3	1571	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.42, 1.49]
3.5 Placental malaria (histopathologic analysis)	3	1570	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.50, 0.90]
3.6 Maternal peripheral parasitaemia during pregnancy (any test)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.7 Clinical malaria episodes during pregnancy	3		Rate Ratio (IV, Fixed, 95% CI)	0.56 [0.19, 1.67]
3.8 Mean haemoglobin at delivery (g/dL)	2	978	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.51, 0.15]
3.9 Maternal severe anaemia at delivery (< 7g/dL)	2	1454	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.75, 2.67]
3.10 Low birth weight (< 2500 g)	3	1695	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.87, 1.48]
3.11 Mean birth weight (g)	2	1498	Mean Difference (IV, Fixed, 95% CI)	-61.39 [-112.11, -10.68]
3.12 Cord blood parasitaemia (microscopy)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.13 Cord blood parasitaemia (loop-mediated isothermal amplification)	1	190	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.14 Prematurity	3	1577	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.56, 1.94]
3.15 Severe adverse events during pregnancy	2	1450	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.61, 1.25]
3.16 Foetal loss	3	1610	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.68, 1.90]
3.17 Congenital malformations	3	1592	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.39, 3.06]
3.18 Maternal mortality	2	1440	Risk Ratio (M-H, Fixed, 95% CI)	4.99 [0.24, 103.62]
3.19 Neonatal mortality	2	1467	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.39, 2.72]
3.20 Adverse events: headache	2	1447	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.62, 4.10]
3.21 Adverse events: gastrointestinal disorders after first IPTp dose	2	1447	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.51, 3.98]
3.22 Adverse events: dizziness after first IPTp dose	2	1447	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.26, 5.96]
3.23 Mother-to-child transmission of HIV	2	1063	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.26, 9.19]
3.24 Undetectable HIV viral load at delivery	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Analysis 3.1. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 1: Maternal peripheral parasitaemia at delivery (amplification techniques)

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	8	367	18	355	72.6%	0.43 [0.19 , 0.98]
González 2024	3	291	5	306	19.3%	0.63 [0.15 , 2.62]
Natureeba 2017	4	100	2	98	8.0%	1.96 [0.37 , 10.46]
Total		**758**		**759**	**100.0%**	**0.59 [0.31 , 1.11]**
Total events:	15		25			

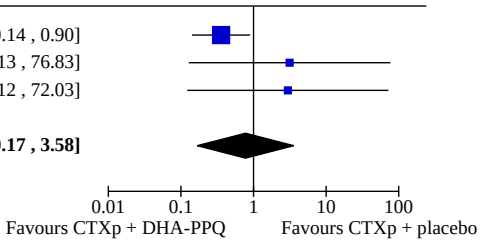
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 2.56, df = 2 (P = 0.28); I² = 22%



Analysis 3.2. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 2: Maternal peripheral parasitaemia at delivery (microscopy)

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Barsosio 2024	6	405	17	410	64.0%	0.36 [0.14 , 0.90]
González 2024	1	294	0	308	18.0%	3.14 [0.13 , 76.83]
Natureeba 2017	1	99	0	98	18.0%	2.97 [0.12 , 72.03]
Total (Wald{fn})		**798**		**816**	**100.0%**	**0.77 [0.17 , 3.58]**
Total events:	8		17			

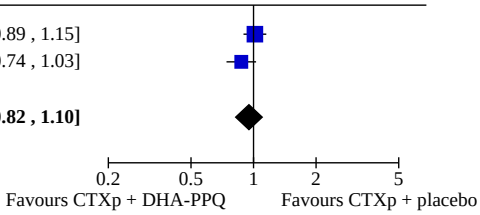
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.73; Chi² = 2.99, df = 2 (P = 0.22); I² = 33%



Analysis 3.3. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 3: Maternal anaemia at delivery (< 11g/dL)

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Barsosio 2024[a]	223	415	226	427	56.2%	1.02 [0.89 , 1.15]
González 2024	136	300	162	312	43.8%	0.87 [0.74 , 1.03]
Total (Wald{fn})		**715**		**739**	**100.0%**	**0.95 [0.82 , 1.10]**
Total events:	359		388			

Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.01; Chi² = 2.05, df = 1 (P = 0.15); I² = 51%



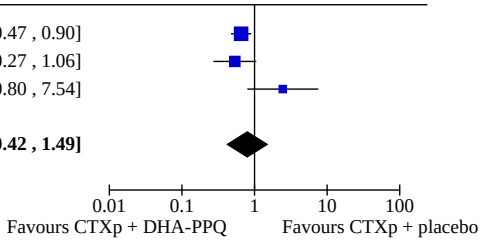
Footnotes

[a]Haemoglobin at delivery or otherwise in the third trimester if the measurement at delivery was unavailable

Analysis 3.4. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 4: Placental malaria (any test)

Study or Subgroup	CTXp + DHA-PPQ Events	CTXp + DHA-PPQ Total	CTXp + placebo Events	CTXp + placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Barsosio 2024	52	389	79	386	47.2%	0.65 [0.47 , 0.90]
González 2024	12	297	23	305	33.0%	0.54 [0.27 , 1.06]
Natureeba 2017	10	98	4	96	19.8%	2.45 [0.80 , 7.54]
Total (Wald{fn})		**784**		**787**	**100.0%**	**0.79 [0.42 , 1.49]**
Total events:	74		106			

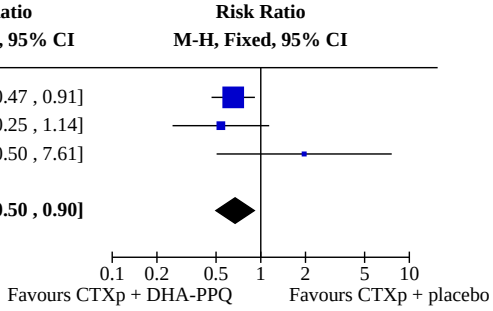
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.19; Chi² = 5.53, df = 2 (P = 0.06); I² = 64%



Analysis 3.5. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 5: Placental malaria (histopathologic analysis)

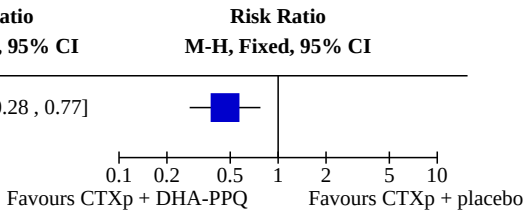
Study or Subgroup	CTXp + DHA-PPQ Events	CTXp + DHA-PPQ Total	CTXp + placebo Events	CTXp + placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	48	389	73	386	77.1%	0.65 [0.47 , 0.91]
González 2024	10	297	19	304	19.7%	0.54 [0.25 , 1.14]
Natureeba 2017	6	98	3	96	3.2%	1.96 [0.50 , 7.61]
Total		**784**		**786**	**100.0%**	**0.67 [0.50 , 0.90]**
Total events:	64		95			

Test for overall effect: Z = 2.63 (P = 0.009)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 2.75, df = 2 (P = 0.25); I² = 27%



Analysis 3.6. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 6: Maternal peripheral parasitaemia during pregnancy (any test)

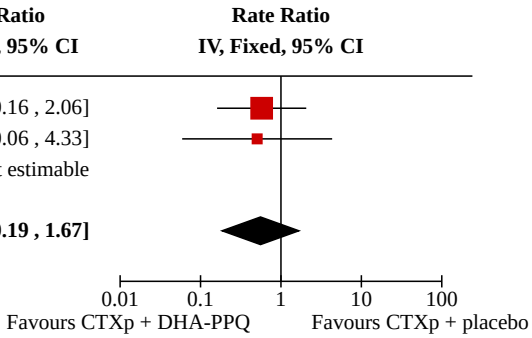
Study or Subgroup	CTXp + DHA-PPQ Events	CTXp + DHA-PPQ Total	CTXp + placebo Events	CTXp + placebo Total	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	20	443	44	452	0.46 [0.28 , 0.77]



Analysis 3.7. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 7: Clinical malaria episodes during pregnancy

Study or Subgroup	log[Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI
Barsosio 2024	-0.55208602	0.65133895	73.9%	0.58 [0.16 , 2.06]
González 2024	-0.68124124	1.09544512	26.1%	0.51 [0.06 , 4.33]
Natureeba 2017	0	0		Not estimable
Total			**100.0%**	**0.56 [0.19 , 1.67]**

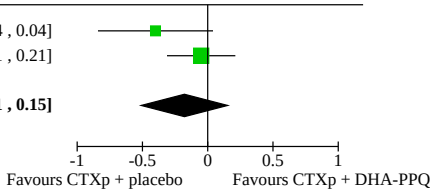
Test for overall effect: Z = 1.05 (P = 0.30)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%



Analysis 3.8. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 8: Mean haemoglobin at delivery (g/dL)

Study or Subgroup	CTXp + DHA-PPQ Mean	SD	Total	CTXp + Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Barsosio 2024	10.7	2.2	190	11.1	2.1	176	36.7%	-0.40 [-0.84 , 0.04]
González 2024	10.74	1.7	300	10.79	1.6	312	63.3%	-0.05 [-0.31 , 0.21]
Total (Wald{fn})			**490**			**488**	**100.0%**	**-0.18 [-0.51 , 0.15]**

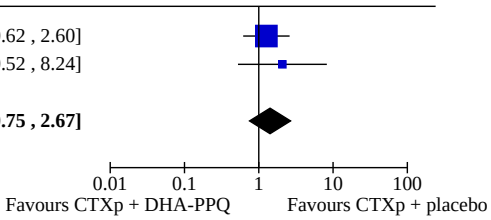
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.03; Chi² = 1.79, df = 1 (P = 0.18); I² = 44%



Analysis 3.9. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 9: Maternal severe anaemia at delivery (< 7g/dL)

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024[a]	16	415	13	427	81.3%	1.27 [0.62 , 2.60]
González 2024	6	300	3	312	18.7%	2.08 [0.52 , 8.24]
Total		**715**		**739**	**100.0%**	**1.42 [0.75 , 2.67]**
Total events:	22		16			

Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%



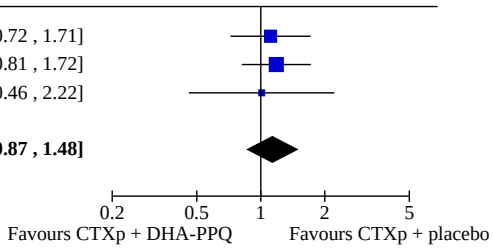
Footnotes

[a]Haemoglobin at delivery or otherwise in the third trimester if the measurement at delivery was unavailable

Analysis 3.10. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 10: Low birth weight (< 2500 g)

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	39	422	36	433	39.7%	1.11 [0.72 , 1.71]
González 2024	50	315	44	328	48.1%	1.18 [0.81 , 1.72]
Natureeba 2017[a]	11	98	11	99	12.2%	1.01 [0.46 , 2.22]
Total		**835**		**860**	**100.0%**	**1.13 [0.87 , 1.48]**
Total events:	100		91			

Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² = 0%



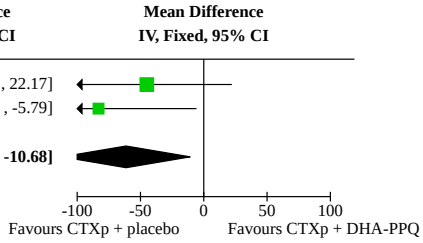
Footnotes

[a]Data are limited to those with a gestational age of ≥ 28 weeks

Analysis 3.11. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 11: Mean birth weight (g)

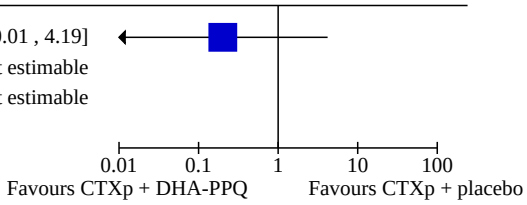
Study or Subgroup	CTXp + DHA-PPQ Mean	SD	Total	CTX + placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Barsosio 2024	3079	502	422	3124	500	433	57.0%	-45.00 [-112.17 , 22.17]
González 2024	2827.95	645.6	315	2911.08	277	328	43.0%	-83.13 [-160.47 , -5.79]
Total			**737**			**761**	**100.0%**	**-61.39 [-112.11 , -10.68]**

Test for overall effect: Z = 2.37 (P = 0.02)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%



Analysis 3.12. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 12: Cord blood parasitaemia (microscopy)

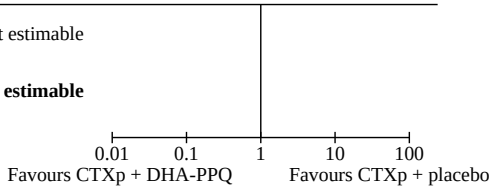
Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	0	371	2	374	0.20 [0.01 , 4.19]
González 2024	0	296	0	298	Not estimable
Natureeba 2017	0	97	0	94	Not estimable



Analysis 3.13. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 13: Cord blood parasitaemia (loop-mediated isothermal amplification)

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Natureeba 2017	0	96	0	94		Not estimable
Total		**96**		**94**		**Not estimable**
Total events:	0		0			

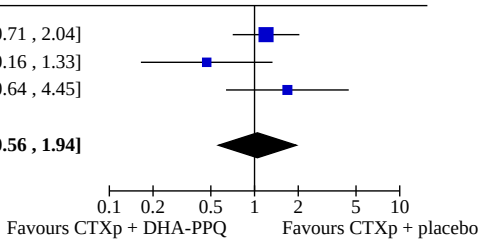
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 3.14. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 14: Prematurity

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Barsosio 2024	28	417	24	429	49.4%	1.20 [0.71 , 2.04]
González 2024	5	263	11	271	24.1%	0.47 [0.16 , 1.33]
Natureeba 2017	10	98	6	99	26.5%	1.68 [0.64 , 4.45]
Total (Wald{fn})		**778**		**799**	**100.0%**	**1.05 [0.56 , 1.94]**
Total events:	43		41			

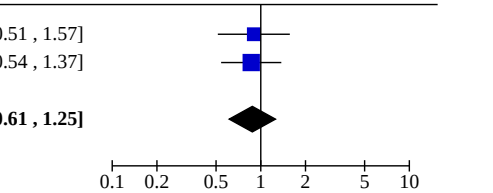
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.13; Chi² = 3.42, df = 2 (P = 0.18); I² = 42%



Analysis 3.15. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 15: Severe adverse events during pregnancy

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	22	446	25	455	42.3%	0.90 [0.51 , 1.57]
González 2024	29	273	34	276	57.7%	0.86 [0.54 , 1.37]
Total		**719**		**731**	**100.0%**	**0.88 [0.61 , 1.25]**
Total events:	51		59			

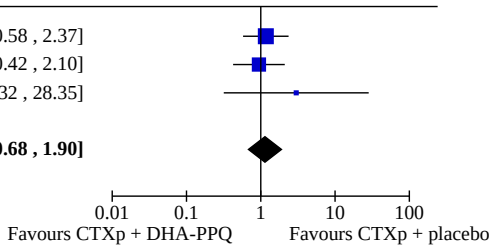
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%



Analysis 3.16. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 16: Foetal loss

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	16	433	14	443	51.9%	1.17 [0.58 , 2.37]
González 2024	11	263	12	271	44.3%	0.94 [0.42 , 2.10]
Natureeba 2017	3	100	1	100	3.8%	3.00 [0.32 , 28.35]
Total		**796**		**814**	**100.0%**	**1.14 [0.68 , 1.90]**
Total events:	30		27			

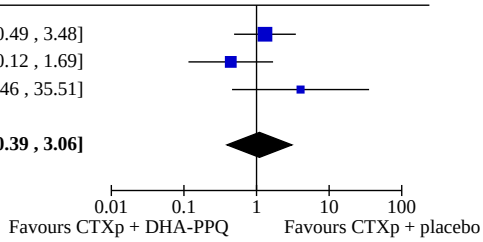
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.93, df = 2 (P = 0.63); I² = 0%



Analysis 3.17. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 17: Congenital malformations

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Barsosio 2024	9	428	7	435	47.8%	1.31 [0.49 , 3.48]
González 2024	3	263	7	271	34.6%	0.44 [0.12 , 1.69]
Natureeba 2017[a]	4	97	1	98	17.7%	4.04 [0.46 , 35.51]
Total (Wald{fn})		**788**		**804**	**100.0%**	**1.10 [0.39 , 3.06]**
Total events:	16		15			

Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.33; Chi² = 3.27, df = 2 (P = 0.19); I² = 39%



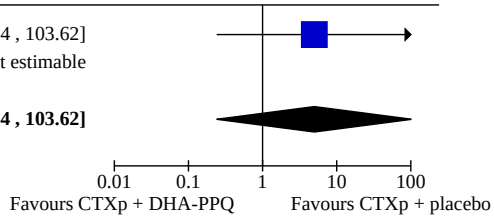
Footnotes

[a]Data are limited to those with a gestational age of ≥28 weeks.

Analysis 3.18. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 18: Maternal mortality

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	2	446	0	445	100.0%	4.99 [0.24 , 103.62]
González 2024	0	273	0	276		Not estimable
Total		**719**		**721**	**100.0%**	**4.99 [0.24 , 103.62]**
Total events:	2		0			

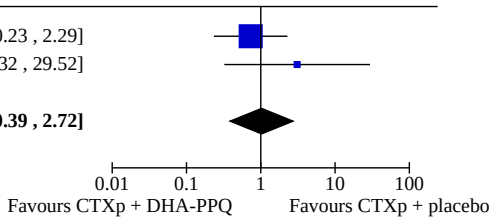
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 3.19. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 19: Neonatal mortality

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	5	416	7	426	87.5%	0.73 [0.23 , 2.29]
González 2024	3	308	1	317	12.5%	3.09 [0.32 , 29.52]
Total		**724**		**743**	**100.0%**	**1.03 [0.39 , 2.72]**
Total events:	8		8			

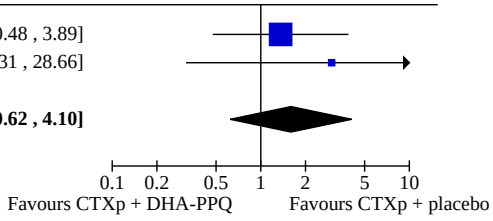
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.25, df = 1 (P = 0.26); I² = 20%



Analysis 3.20. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 20: Adverse events: headache

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	8	446	6	455	85.6%	1.36 [0.48 , 3.89]
González 2024	3	273	1	273	14.4%	3.00 [0.31 , 28.66]
Total		**719**		**728**	**100.0%**	**1.60 [0.62 , 4.10]**
Total events:	11		7			

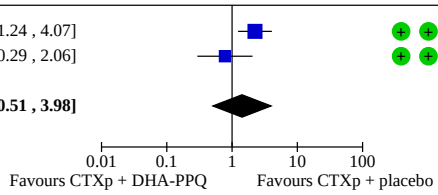
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%



Analysis 3.21. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 21: Adverse events: gastrointestinal disorders after first IPTp dose

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Barsosio 2024[a]	33	446	15	455	56.9%	2.24 [1.24 , 4.07]	+ + + + + + +
González 2024[b]	7	273	9	273	43.1%	0.78 [0.29 , 2.06]	+ + + + + + +
Total (Wald{fn})		**719**		**728**	**100.0%**	**1.42 [0.51 , 3.98]**	
Total events:	40		24				

Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.39; Chi² = 3.31, df = 1 (P = 0.07); I² = 70%



Footnotes

[a]Vomiting within 4 days of first drug administered during a treatment cycle.
[b]Any gastrointestinal disorder within 3 days of first drug administered during a treatment cycle.

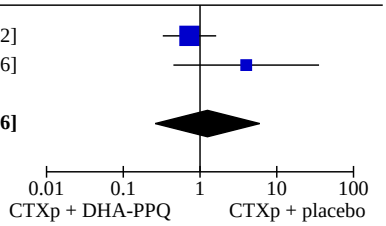
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.22. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 22: Adverse events: dizziness after first IPTp dose

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Barsosio 2024	10	446	14	455	68.3%	0.73 [0.33 , 1.62]
González 2024	4	273	1	273	31.7%	4.00 [0.45 , 35.56]
Total (Wald{fn})		**719**		**728**	**100.0%**	**1.25 [0.26 , 5.96]**
Total events:	14		15			

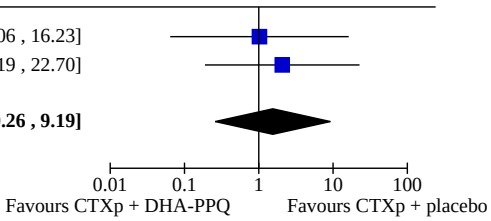
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.76; Chi² = 2.08, df = 1 (P = 0.15); I² = 52%



Analysis 3.23. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 23: Mother-to-child transmission of HIV

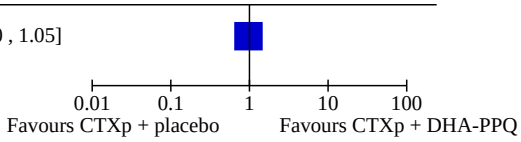
Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsosio 2024	1	239	1	244	50.2%	1.02 [0.06 , 16.23]
González 2024	2	285	1	295	49.8%	2.07 [0.19 , 22.70]
Total		**524**		**539**	**100.0%**	**1.54 [0.26 , 9.19]**
Total events:	3		2			

Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.70); I² = 0%



Analysis 3.24. Comparison 3: Dihydroartemisinin-piperaquine (DHA-PPQ) plus daily cotrimoxazole (CTXp) versus placebo plus CTXp, Outcome 24: Undetectable HIV viral load at delivery

Study or Subgroup	CTXp + DHA-PPQ Events	Total	CTXp + placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
González 2024	238	305	253	315	0.97 [0.90 , 1.05]



Comparison 4. Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP

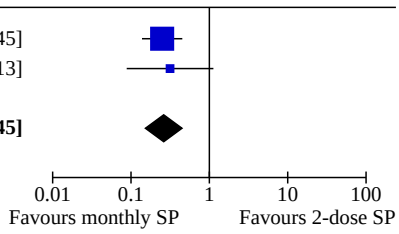
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Maternal peripheral parasitaemia at delivery (blood smear)	2	622	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.15, 0.45]
4.2 Maternal anaemia at delivery (haemoglobin < 11 g/dL)	2	604	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.82, 1.14]
4.3 Placental malaria (blood smear)	2	612	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.24, 0.75]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 Clinical malaria episodes during pregnancy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.5 Maternal haemoglobin at delivery (in g/dL)	2	604	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.07, 0.13]
4.6 Low birth weight (< 2500 g)	2	624	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.61, 1.24]
4.7 Mean birth weight (in kg)	2	624	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.08, 0.09]
4.8 Cord blood parasitaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.9 Prematurity	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.10 Severe adverse events during pregnancy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.11 Spontaneous abortion	1	456	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.12 Stillbirth	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.13 Maternal mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.14 Neonatal mortality	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 4.1. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 1: Maternal peripheral parasitaemia at delivery (blood smear)

Study or Subgroup	Monthly SP Events	Monthly SP Total	2-dose SP Events	2-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Filler 2006	12	135	42	118	82.1%	0.25 [0.14 , 0.45]
Hamer 2007	3	180	10	189	17.9%	0.32 [0.09 , 1.13]
Total		**315**		**307**	**100.0%**	**0.26 [0.15 , 0.45]**
Total events:	15		52			

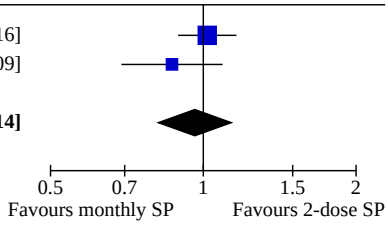
Test for overall effect: Z = 4.90 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.75); I² = 0%



Analysis 4.2. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 2: Maternal anaemia at delivery (haemoglobin < 11 g/dL)

Study or Subgroup	Monthly SP Events	Monthly SP Total	2-dose SP Events	2-dose SP Total	Weight	Risk Ratio M-H, Random, 95% CI
Filler 2006	106	135	91	118	64.7%	1.02 [0.89 , 1.16]
Hamer 2007	70	164	92	187	35.3%	0.87 [0.69 , 1.09]
Total (Wald{fn})		**299**		**305**	**100.0%**	**0.96 [0.82 , 1.14]**
Total events:	176		183			

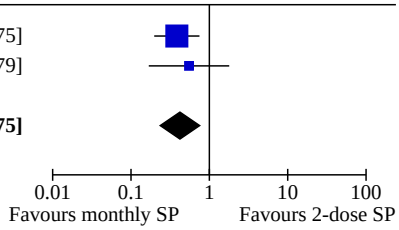
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² = 0.01; Chi² = 1.71, df = 1 (P = 0.19); I² = 41%



Analysis 4.3. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 3: Placental malaria (blood smear)

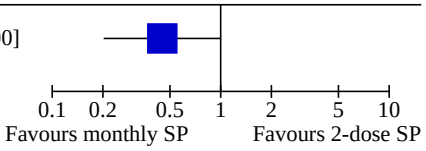
Study or Subgroup	Monthly SP Events	Monthly SP Total	2-dose SP Events	2-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Filler 2006	11	135	25	118	77.8%	0.38 [0.20 , 0.75]
Hamer 2007	4	171	8	188	22.2%	0.55 [0.17 , 1.79]
Total		**306**		**306**	**100.0%**	**0.42 [0.24 , 0.75]**
Total events:	15		33			

Test for overall effect: Z = 2.93 (P = 0.003)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.61); I² = 0%



Analysis 4.4. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 4: Clinical malaria episodes during pregnancy

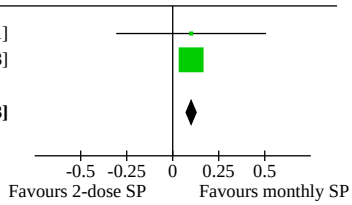
Study or Subgroup	Monthly SP Events	Monthly SP Total	2-dose SP Events	2-dose SP Total	Risk Ratio M-H, Fixed, 95% CI
Hamer 2007	8	187	19	200	0.45 [0.20 , 1.00]



Analysis 4.5. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 5: Maternal haemoglobin at delivery (in g/dL)

Study or Subgroup	Monthly SP Mean	SD	Total	2-dose SP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Filler 2006	9.8	1.41	135	9.7	1.83	118	0.4%	0.10 [-0.31 , 0.51]
Hamer 2007	11.4	0.13	164	11.3	0.13	187	99.6%	0.10 [0.07 , 0.13]
Total			**299**			**305**	**100.0%**	**0.10 [0.07 , 0.13]**

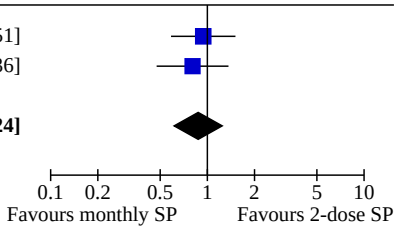
Test for overall effect: Z = 7.21 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%



Analysis 4.6. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 6: Low birth weight (< 2500 g)

Study or Subgroup	Monthly SP Events	Total	2-dose SP Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Filler 2006	28	135	26	118	50.7%	0.94 [0.59 , 1.51]
Hamer 2007	21	179	28	192	49.3%	0.80 [0.47 , 1.36]
Total		**314**		**310**	**100.0%**	**0.87 [0.61 , 1.24]**
Total events:	49		54			

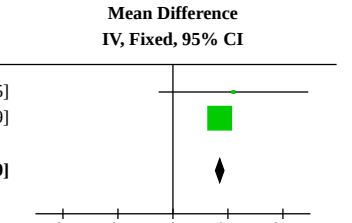
Test for overall effect: Z = 0.75 (P = 0.45)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%



Analysis 4.7. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 7: Mean birth weight (in kg)

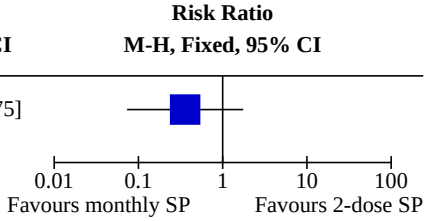
Study or Subgroup	Monthly SP Mean	SD	Total	2-dose SP Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Filler 2006	2.85	0.54	135	2.74	0.56	118	0.3%	0.11 [-0.03 , 0.25]
Hamer 2007	2.987	0.04077	179	2.902	0.03416	192	99.7%	0.08 [0.08 , 0.09]
Total			**314**			**310**	**100.0%**	**0.09 [0.08 , 0.09]**

Test for overall effect: Z = 21.74 (P < 0.00001)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%



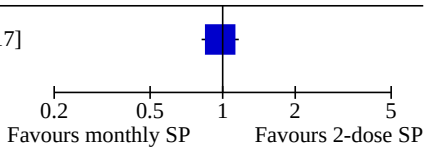
Analysis 4.8. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 8: Cord blood parasitaemia

Study or Subgroup	Monthly SP Events	Total	2-dose SP Events	Total	Risk Ratio M-H, Fixed, 95% CI
Hamer 2007	2	173	6	186	0.36 [0.07 , 1.75]



Analysis 4.9. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 9: Prematurity

Study or Subgroup	Monthly SP Events	Monthly SP Total	2-dose SP Events	2-dose SP Total	Risk Ratio M-H, Fixed, 95% CI
Hamer 2007[a]	101	181	112	196	0.98 [0.82 , 1.17]

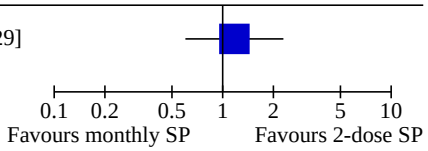


Footnotes

[a]Defined as delivery before gestation week 37

Analysis 4.10. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 10: Severe adverse events during pregnancy

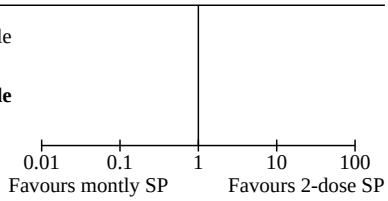
Study or Subgroup	Monthly SP Events	Monthly SP Total	2-dose SP Events	2-dose SP Total	Risk Ratio M-H, Fixed, 95% CI
Hamer 2007	17	224	15	232	1.17 [0.60 , 2.29]



Analysis 4.11. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 11: Spontaneous abortion

Study or Subgroup	Monthly SP Events	Monthly SP Total	2-dose SP Events	2-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hamer 2007[a]	0	224	0	232		Not estimable
Total		**224**		**232**		**Not estimable**
Total events:	0		0			

Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

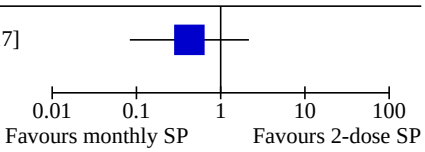


Footnotes

[a]Defined as dead delivery before 28 weeks gestation.

Analysis 4.12. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 12: Stillbirth

Study or Subgroup	Monthly SP Events	Monthly SP Total	2-dose SP Events	2-dose SP Total	Risk Ratio M-H, Fixed, 95% CI
Hamer 2007[a]	2	191	5	203	0.43 [0.08 , 2.17]

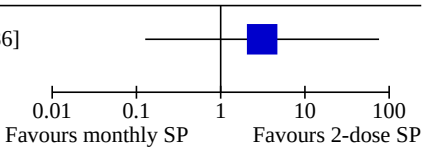


Footnotes

[a]Defined as dead delivery after 28 weeks gestation

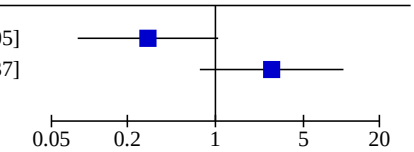
Analysis 4.13. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 13: Maternal mortality

Study or Subgroup	Monthly SP Events	Monthly SP Total	2-dose SP Events	2-dose SP Total	Risk Ratio M-H, Fixed, 95% CI
Hamer 2007	1	224	0	232	3.11 [0.13 , 75.86]



Analysis 4.14. Comparison 4: Monthly sulfadoxine-pyrimethamine (SP) versus two doses of SP, Outcome 14: Neonatal mortality

Study or Subgroup	Monthly SP Events	Monthly SP Total	2-dose SP Events	2-dose SP Total	Risk Ratio M-H, Random, 95% CI
Filler 2006[a]	3	135	9	118	0.29 [0.08 , 1.05]
Hamer 2007[b]	8	189	3	198	2.79 [0.75 , 10.37]



Footnotes

[a]Defined as death occuring within 30 days of birth

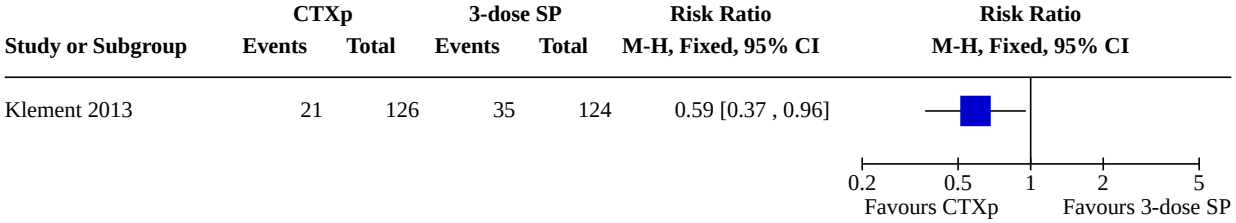
[b]Defined as death occurring between days 0 and 28 post-partum

Comparison 5. Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Maternal peripheral parasitaemia during pregnancy	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.2 Maternal anaemia during delivery	2	362	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.98, 2.53]
5.3 Placental malaria (histology)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4 Placental malaria (microscopy or polymerase chain reaction)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.5 Clinical malaria episodes during pregnancy	2	362	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.92, 2.07]
5.6 Maternal haemoglobin level at delivery (in g/dL)	1	250	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5.7 Low birth weight (< 2500 g)	3	392	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.68, 1.80]
5.8 Mean birth weight (in grams)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.9 Cord blood parasitaemia (rapid diagnostic test)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.10 Congenital malaria	1	231	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.43, 1.89]
5.11 Prematurity	3	391	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.54, 1.55]
5.12 SAEs during pregnancy	3	412	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.06, 3.15]
5.13 Spontaneous abortion	3	400	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.06, 2.65]
5.14 Stillbirth	3	400	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.31, 2.87]
5.15 Congenital malformations	2	277	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.06, 15.26]
5.16 Maternal mortality	2	362	Risk Ratio (M-H, Fixed, 95% CI)	2.95 [0.12, 71.79]
5.17 Neonatal mortality	3	392	Risk Ratio (M-H, Fixed, 95% CI)	3.79 [0.43, 33.43]
5.18 Infant mortality	1	231	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.89]
5.19 Adverse events: rash	1	250	Risk Ratio (M-H, Fixed, 95% CI)	2.95 [0.31, 28.00]
5.20 Mother-to-child transmission of HIV	2	310	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.34, 3.06]

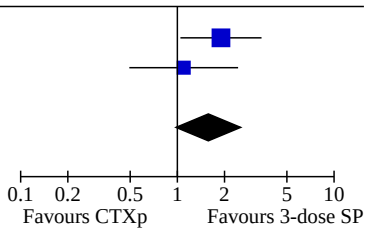
Analysis 5.1. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 1: Maternal peripheral parasitaemia during pregnancy



Analysis 5.2. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 2: Maternal anaemia during delivery

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013	27	126	14	124	59.8%	1.90 [1.05 , 3.44]
Manirakiza 2021[a]	11	59	9	53	40.2%	1.10 [0.49 , 2.44]
Total		**185**		**177**	**100.0%**	**1.58 [0.98 , 2.53]**
Total events:	38		23			

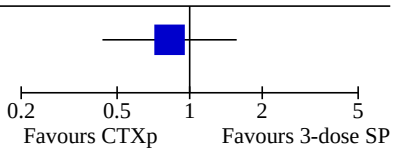
Test for overall effect: Z = 1.88 (P = 0.06)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.16, df = 1 (P = 0.28); I² = 14%



Footnotes
[a]Defined as Hb level < 10 g/dL

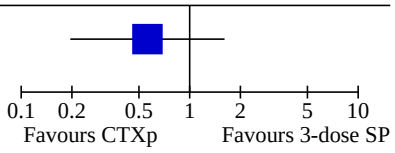
Analysis 5.3. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 3: Placental malaria (histology)

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Risk Ratio M-H, Fixed, 95% CI
Klement 2013	15	74	14	57	0.83 [0.43 , 1.57]



Analysis 5.4. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 4: Placental malaria (microscopy or polymerase chain reaction)

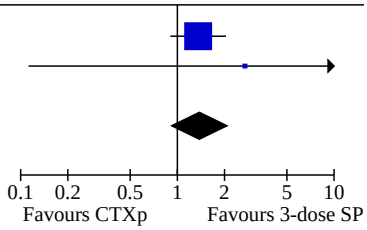
Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Risk Ratio M-H, Fixed, 95% CI
Manirakiza 2021	5	59	8	53	0.56 [0.20 , 1.61]



Analysis 5.5. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 5: Clinical malaria episodes during pregnancy

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013	40	126	29	124	98.2%	1.36 [0.90 , 2.04]
Manirakiza 2021	1	59	0	53	1.8%	2.70 [0.11 , 64.89]
Total		**185**		**177**	**100.0%**	**1.38 [0.92 , 2.07]**
Total events:	41		29			

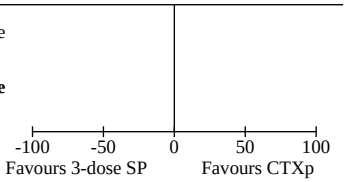
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%



Analysis 5.6. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 6: Maternal haemoglobin level at delivery (in g/dL)

Study or Subgroup	CTXp Mean	CTXp SD	CTXp Total	3-dose SP Mean	3-dose SP SD	3-dose SP Total	Weight	Mean Difference IV, Fixed, 95% CI
Klement 2013	10.1	0	126	10	0	124		Not estimable
Total			**126**			**124**		**Not estimable**

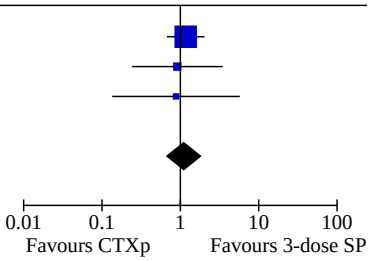
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.7. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 7: Low birth weight (< 2500 g)

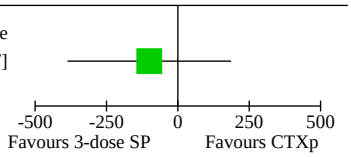
Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013	23	119	19	115	75.4%	1.17 [0.67 , 2.03]
Manirakiza 2021	4	58	4	53	16.3%	0.91 [0.24 , 3.47]
Manyando 2014	2	25	2	22	8.3%	0.88 [0.14 , 5.73]
Total		**202**		**190**	**100.0%**	**1.10 [0.68 , 1.80]**
Total events:	29		25			

Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.18, df = 2 (P = 0.92); I² = 0%



Analysis 5.8. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 8: Mean birth weight (in grams)

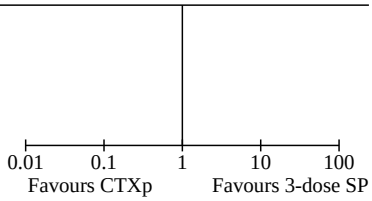
Study or Subgroup	CTXp Mean	CTXp SD	CTXp Total	3-dose SP Mean	3-dose SP SD	3-dose SP Total	Mean Difference IV, Fixed, 95% CI
Klement 2013	2900	0	119	2800	0	115	Not estimable
Manyando 2014	3100	500	25	3200	500	22	-100.00 [-386.47 , 186.47]



Analysis 5.9. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 9: Cord blood parasitaemia (rapid diagnostic test)

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Manirakiza 2021	0	53	0	47		Not estimable
Total		**53**		**47**		**Not estimable**
Total events:	0		0			

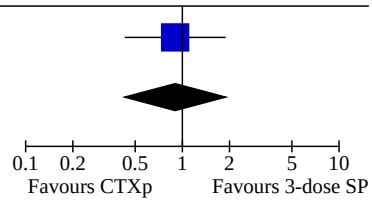
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.10. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 10: Congenital malaria

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013[a]	12	117	13	114	100.0%	0.90 [0.43 , 1.89]
Total		**117**		**114**	**100.0%**	**0.90 [0.43 , 1.89]**
Total events:	12		13			

Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



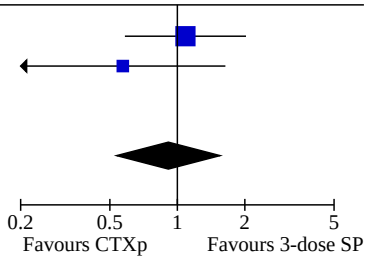
Footnotes

[a]Defined as symptoms attributable to malaria plus a positive TBS in the newborn within the first 7 days of life.

Analysis 5.11. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 11: Prematurity

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013[a]	18	117	16	113	66.1%	1.09 [0.58 , 2.02]
Manirakiza 2021[b]	5	58	8	53	33.9%	0.57 [0.20 , 1.64]
Manyando 2014[c]	0	26	0	24		Not estimable
Total		**201**		**190**	**100.0%**	**0.91 [0.54 , 1.55]**
Total events:	23		24			

Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.06, df = 1 (P = 0.30); I² = 6%



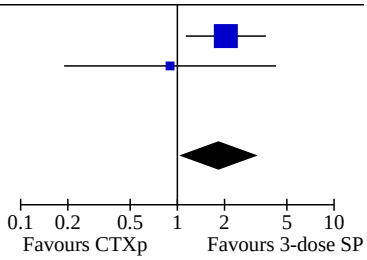
Footnotes

[a]Defined as ≤ 34 weeks
[b]Defined as < 37 weeks
[c]Defined as ≤ 37 weeks

Analysis 5.12. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 12: SAEs during pregnancy

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013	29	126	14	124	81.7%	2.04 [1.13 , 3.67]
Manirakiza 2021	3	59	3	53	18.3%	0.90 [0.19 , 4.26]
Manyando 2014	0	26	0	24		Not estimable
Total		**211**		**201**	**100.0%**	**1.83 [1.06 , 3.15]**
Total events:	32		17			

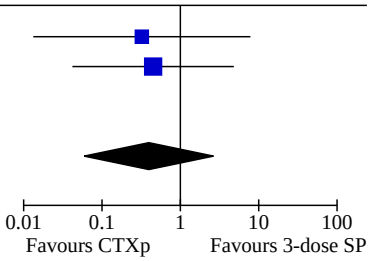
Test for overall effect: Z = 2.17 (P = 0.03)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.93, df = 1 (P = 0.33); I² = 0%



Analysis 5.13. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 13: Spontaneous abortion

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013	0	121	1	117	42.0%	0.32 [0.01 , 7.84]
Manirakiza 2021[a]	1	59	2	53	58.0%	0.45 [0.04 , 4.81]
Manyando 2014	0	26	0	24		Not estimable
Total		**206**		**194**	**100.0%**	**0.40 [0.06 , 2.65]**
Total events:	1		3			

Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%



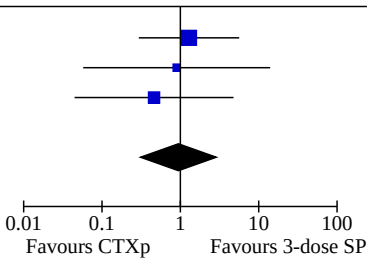
Footnotes

[a]Defined as foetal death < 28 weeks gestation

Analysis 5.14. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 14: Stillbirth

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013	4	121	3	117	49.3%	1.29 [0.29 , 5.64]
Manirakiza 2021[a]	1	59	1	53	17.0%	0.90 [0.06 , 14.01]
Manyando 2014	1	26	2	24	33.6%	0.46 [0.04 , 4.77]
Total		**206**		**194**	**100.0%**	**0.94 [0.31 , 2.87]**
Total events:	6		6			

Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.53, df = 2 (P = 0.77); I² = 0%



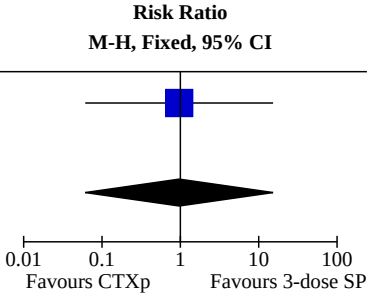
Footnotes

[a]Defined as foetal death ≥ 28 weeks gestation

Analysis 5.15. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 15: Congenital malformations

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013	1	117	1	113	100.0%	0.97 [0.06 , 15.26]
Manyando 2014	0	25	0	22		Not estimable
Total		**142**		**135**	**100.0%**	**0.97 [0.06 , 15.26]**
Total events:	1		1			

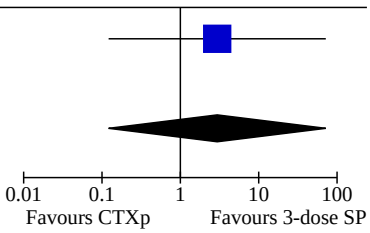
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.16. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 16: Maternal mortality

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013	1	126	0	124	100.0%	2.95 [0.12 , 71.79]
Manirakiza 2021[a]	0	59	0	53		Not estimable
Total		**185**		**177**	**100.0%**	**2.95 [0.12 , 71.79]**
Total events:	1		0			

Test for overall effect: Z = 0.67 (P = 0.51)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



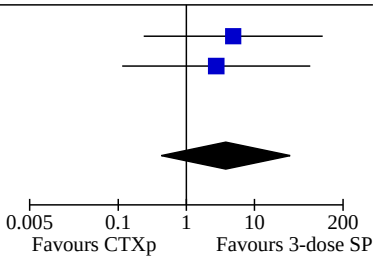
Footnotes

[a]Defined as maternal death occuring before/at delivery

Analysis 5.17. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 17: Neonatal mortality

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013[a]	2	117	0	114	49.2%	4.87 [0.24 , 100.40]
Manirakiza 2021[b]	1	58	0	53	50.8%	2.75 [0.11 , 65.98]
Manyando 2014[c]	0	26	0	24		Not estimable
Total		**201**		**191**	**100.0%**	**3.79 [0.43 , 33.43]**
Total events:	3		0			

Test for overall effect: Z = 1.20 (P = 0.23)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0%



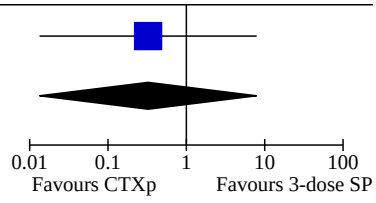
Footnotes

[a]Defined as death occuring in first month of life
[b]Defined as death occuring "after birth". The 1 death in the CMX arm occured 1 day after birth.
[c]Defined as death occurring between days 0 and 28 post-partum

Analysis 5.18. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 18: Infant mortality

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013[a]	0	117	1	114	100.0%	0.32 [0.01 , 7.89]
Total		**117**		**114**	**100.0%**	**0.32 [0.01 , 7.89]**
Total events:	0		1			

Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



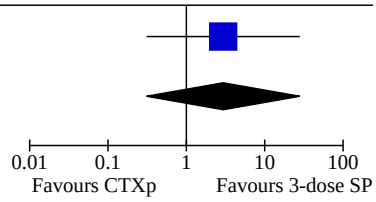
Footnotes

[a]Defined as death between months 1 and 3 post-partum

Analysis 5.19. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 19: Adverse events: rash

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013	3	126	1	124	100.0%	2.95 [0.31 , 28.00]
Total		**126**		**124**	**100.0%**	**2.95 [0.31 , 28.00]**
Total events:	3		1			

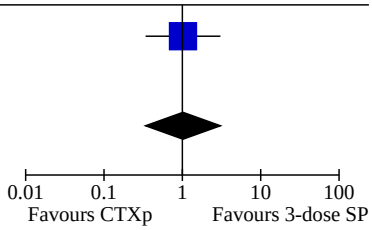
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 5.20. Comparison 5: Daily cotrimoxazole (CTXp) versus three doses of sulfadoxine-pyrimethamine (SP), Outcome 20: Mother-to-child transmission of HIV

Study or Subgroup	CTXp Events	CTXp Total	3-dose SP Events	3-dose SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klement 2013	6	107	6	109	100.0%	1.02 [0.34 , 3.06]
Manirakiza 2021[a]	0	50	0	44		Not estimable
Total		**157**		**153**	**100.0%**	**1.02 [0.34 , 3.06]**
Total events:	6		6			

Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Footnotes

[a]Defined as HIV PCR-positive at birth

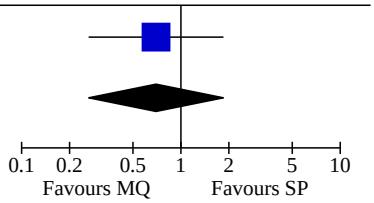
Comparison 6. Mefloquine (MQ) versus sulfadoxine-pyrimethamine (SP)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Maternal peripheral parasitemia at delivery (blood smear)	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.26, 1.85]
6.2 Placental malaria (blood smear)	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.12, 4.04]
6.3 Low birth weight (< 2500 g)	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.28]
6.4 Prematurity	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.07, 1.67]
6.5 Adverse events: nausea	1	131	Risk Ratio (M-H, Fixed, 95% CI)	8.37 [1.08, 65.08]
6.6 Adverse events: headache	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.02, 1.18]
6.7 Adverse events: vomiting	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.41]
6.8 Adverse events: dizziness	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.08, 2.08]
6.9 Adverse events: gastric pain	1	131	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.07, 16.38]

Analysis 6.1. Comparison 6: Mefloquine (MQ) versus sulfadoxine-pyrimethamine (SP), Outcome 1: Maternal peripheral parasitemia at delivery (blood smear)

Study or Subgroup	MQ Events	MQ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2018	6	64	9	67	100.0%	0.70 [0.26 , 1.85]
Total		**64**		**67**	**100.0%**	**0.70 [0.26 , 1.85]**
Total events:	6		9			

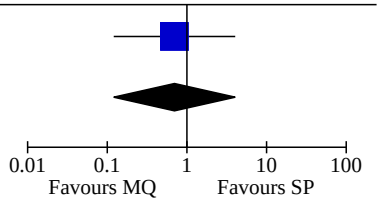
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 6.2. Comparison 6: Mefloquine (MQ) versus sulfadoxine-pyrimethamine (SP), Outcome 2: Placental malaria (blood smear)

Study or Subgroup	MQ Events	MQ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2018	2	64	3	67	100.0%	0.70 [0.12 , 4.04]
Total		**64**		**67**	**100.0%**	**0.70 [0.12 , 4.04]**
Total events:	2		3			

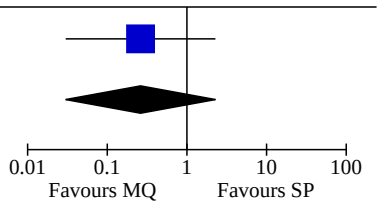
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 6.3. Comparison 6: Mefloquine (MQ) versus sulfadoxine-pyrimethamine (SP), Outcome 3: Low birth weight (< 2500 g)

Study or Subgroup	MQ Events	MQ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2018	1	64	4	67	100.0%	0.26 [0.03 , 2.28]
Total		**64**		**67**	**100.0%**	**0.26 [0.03 , 2.28]**
Total events:	1		4			

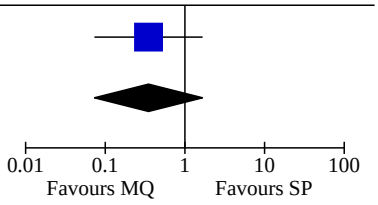
Test for overall effect: Z = 1.21 (P = 0.22)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 6.4. Comparison 6: Mefloquine (MQ) versus sulfadoxine-pyrimethamine (SP), Outcome 4: Prematurity

Study or Subgroup	MQ Events	MQ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2018[a]	2	64	6	67	100.0%	0.35 [0.07 , 1.67]
Total		**64**		**67**	**100.0%**	**0.35 [0.07 , 1.67]**
Total events:	2		6			

Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



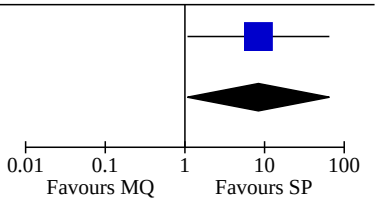
Footnotes

[a]Defined as delivery before gestation week 37

Analysis 6.5. Comparison 6: Mefloquine (MQ) versus sulfadoxine-pyrimethamine (SP), Outcome 5: Adverse events: nausea

Study or Subgroup	MQ Events	MQ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2018	8	64	1	67	100.0%	8.37 [1.08 , 65.08]
Total		**64**		**67**	**100.0%**	**8.37 [1.08 , 65.08]**
Total events:	8		1			

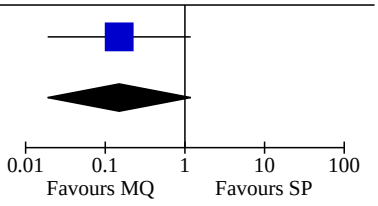
Test for overall effect: Z = 2.03 (P = 0.04)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 6.6. Comparison 6: Mefloquine (MQ) versus sulfadoxine-pyrimethamine (SP), Outcome 6: Adverse events: headache

Study or Subgroup	MQ Events	MQ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2018	1	64	7	67	100.0%	0.15 [0.02 , 1.18]
Total		**64**		**67**	**100.0%**	**0.15 [0.02 , 1.18]**
Total events:	1		7			

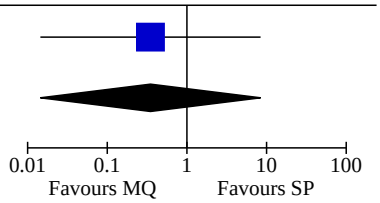
Test for overall effect: Z = 1.80 (P = 0.07)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 6.7. Comparison 6: Mefloquine (MQ) versus sulfadoxine-pyrimethamine (SP), Outcome 7: Adverse events: vomiting

Study or Subgroup	MQ Events	MQ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2018	0	64	1	67	100.0%	0.35 [0.01 , 8.41]
Total		**64**		**67**	**100.0%**	**0.35 [0.01 , 8.41]**
Total events:	0		1			

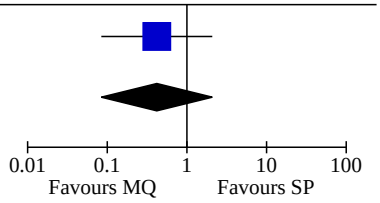
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 6.8. Comparison 6: Mefloquine (MQ) versus sulfadoxine-pyrimethamine (SP), Outcome 8: Adverse events: dizziness

Study or Subgroup	MQ Events	MQ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2018	2	64	5	67	100.0%	0.42 [0.08 , 2.08]
Total		**64**		**67**	**100.0%**	**0.42 [0.08 , 2.08]**
Total events:	2		5			

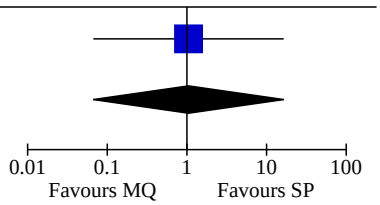
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 6.9. Comparison 6: Mefloquine (MQ) versus sulfadoxine-pyrimethamine (SP), Outcome 9: Adverse events: gastric pain

Study or Subgroup	MQ Events	MQ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2018	1	64	1	67	100.0%	1.05 [0.07 , 16.38]
Total		**64**		**67**	**100.0%**	**1.05 [0.07 , 16.38]**
Total events:	1		1			

Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Comparison 7. Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP)

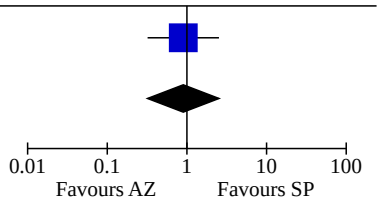
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Maternal peripheral parasitaemia at delivery (blood smear)	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.32, 2.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Maternal anaemia at delivery	1	123	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.53, 2.52]
7.3 Placental malaria (blood smear)	1	123	Risk Ratio (M-H, Fixed, 95% CI)	3.15 [0.34, 29.45]
7.4 Clinical malaria episodes during pregnancy	1	123	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.84, 2.47]
7.5 Low birth weight (< 2.5 kg)	1	123	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [0.55, 8.02]
7.6 Mean birth weight (in kg)	1	123	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.17, 0.05]
7.7 Prematurity	1	123	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.27, 4.01]
7.8 SAEs during pregnancy	1	123	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.9 Spontaneous abortion	1	123	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.10 Stillbirth	1	123	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.11 Congenital malformations	1	123	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.12 Maternal mortality	1	123	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.13 Neonatal mortality	1	123	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.14 Adverse events: headache	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.41]
7.15 Adverse events: nausea	1	123	Risk Ratio (M-H, Fixed, 95% CI)	7.35 [0.93, 57.97]
7.16 Adverse events: vomiting	1	123	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [0.20, 22.56]
7.17 Adverse events: dizziness	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.08, 2.08]
7.18 Adverse events: abdominal pain	1	123	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.07, 16.41]

Analysis 7.1. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 1: Maternal peripheral parasitaemia at delivery (blood smear)

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	6	60	7	63	100.0%	0.90 [0.32 , 2.52]
Total		**60**		**63**	**100.0%**	**0.90 [0.32 , 2.52]**
Total events:	6		7			

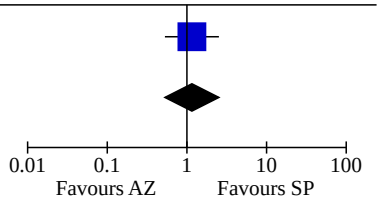
Test for overall effect: Z = 0.20 (P = 0.84)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.2. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 2: Maternal anaemia at delivery

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019[a]	11	60	10	63	100.0%	1.16 [0.53 , 2.52]
Total		**60**		**63**	**100.0%**	**1.16 [0.53 , 2.52]**
Total events:	11		10			

Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



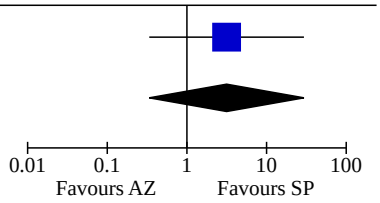
Footnotes

[a]Anaemia was defined as a PCV (packed cell volume) <30%.

Analysis 7.3. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 3: Placental malaria (blood smear)

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	3	60	1	63	100.0%	3.15 [0.34 , 29.45]
Total		**60**		**63**	**100.0%**	**3.15 [0.34 , 29.45]**
Total events:	3		1			

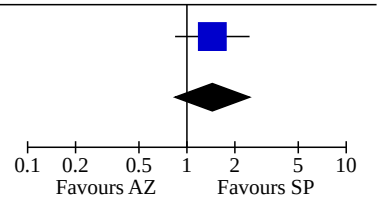
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.4. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 4: Clinical malaria episodes during pregnancy

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	22	60	16	63	100.0%	1.44 [0.84 , 2.47]
Total		**60**		**63**	**100.0%**	**1.44 [0.84 , 2.47]**
Total events:	22		16			

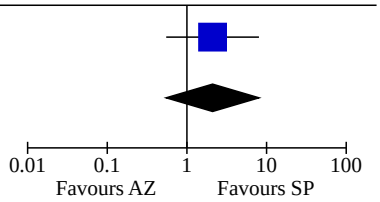
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.5. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 5: Low birth weight (< 2.5 kg)

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	6	60	3	63	100.0%	2.10 [0.55 , 8.02]
Total		**60**		**63**	**100.0%**	**2.10 [0.55 , 8.02]**
Total events:	6		3			

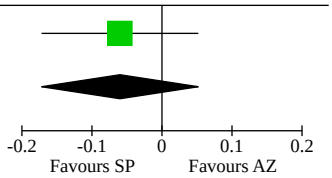
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.6. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 6: Mean birth weight (in kg)

Study or Subgroup	AZ Mean	AZ SD	AZ Total	SP Mean	SP SD	SP Total	Weight	Mean Difference IV, Fixed, 95% CI
Akinyotu 2019	2.84	0.34	60	2.9	0.29	63	100.0%	-0.06 [-0.17 , 0.05]
Total			**60**			**63**	**100.0%**	**-0.06 [-0.17 , 0.05]**

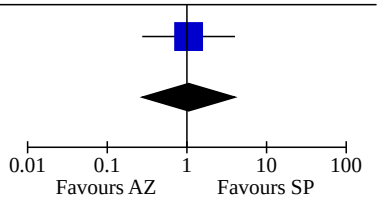
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.7. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 7: Prematurity

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	4	60	4	63	100.0%	1.05 [0.27 , 4.01]
Total		**60**		**63**	**100.0%**	**1.05 [0.27 , 4.01]**
Total events:	4		4			

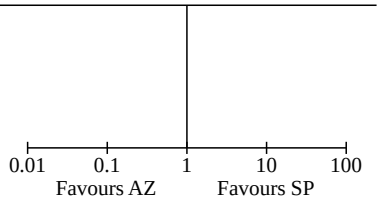
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.8. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 8: SAEs during pregnancy

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	0	60	0	63		Not estimable
Total		**60**		**63**		**Not estimable**
Total events:	0		0			

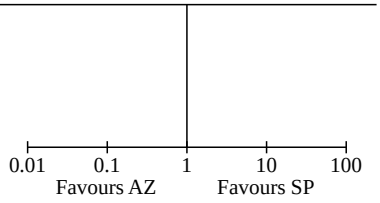
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.9. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 9: Spontaneous abortion

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	0	60	0	63		Not estimable
Total		**60**		**63**		**Not estimable**
Total events:	0		0			

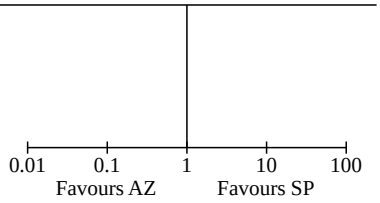
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.10. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 10: Stillbirth

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	0	60	0	63		Not estimable
Total		**60**		**63**		**Not estimable**
Total events:	0		0			

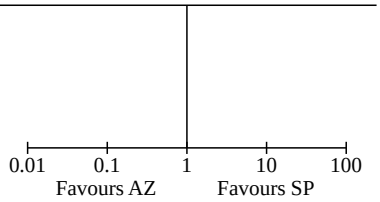
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.11. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 11: Congenital malformations

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	0	60	0	63		Not estimable
Total		**60**		**63**		**Not estimable**
Total events:	0		0			

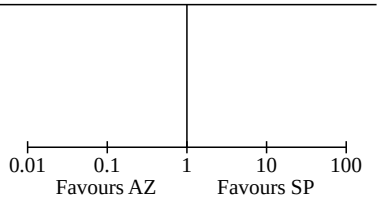
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.12. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 12: Maternal mortality

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	0	60	0	63		Not estimable
Total		**60**		**63**		**Not estimable**
Total events:	0		0			

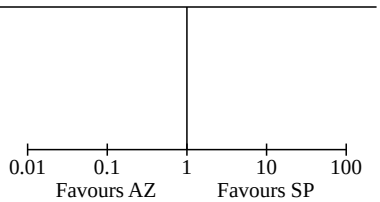
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.13. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 13: Neonatal mortality

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	0	60	0	63		Not estimable
Total		**60**		**63**		**Not estimable**
Total events:	0		0			

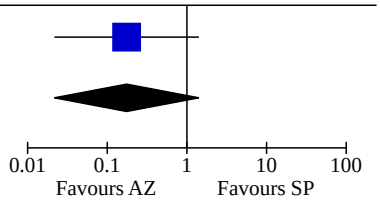
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.14. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 14: Adverse events: headache

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	1	60	6	63	100.0%	0.17 [0.02 , 1.41]
Total		**60**		**63**	**100.0%**	**0.18 [0.02 , 1.41]**
Total events:	1		6			

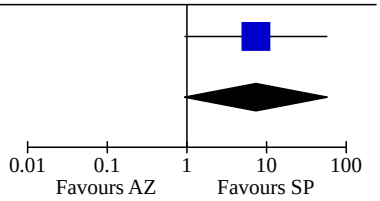
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.15. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 15: Adverse events: nausea

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	7	60	1	63	100.0%	7.35 [0.93 , 57.97]
Total		**60**		**63**	**100.0%**	**7.35 [0.93 , 57.97]**
Total events:	7		1			

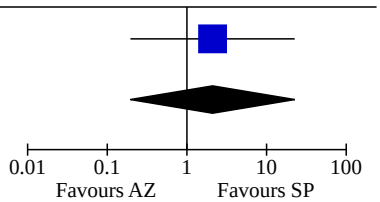
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.16. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 16: Adverse events: vomiting

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	2	60	1	63	100.0%	2.10 [0.20 , 22.56]
Total		**60**		**63**	**100.0%**	**2.10 [0.20 , 22.56]**
Total events:	2		1			

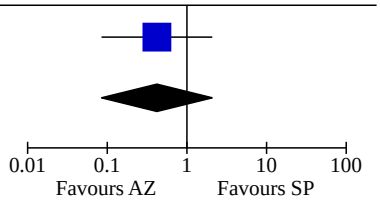
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.17. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 17: Adverse events: dizziness

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	2	60	5	63	100.0%	0.42 [0.08 , 2.08]
Total		**60**		**63**	**100.0%**	**0.42 [0.08 , 2.08]**
Total events:	2		5			

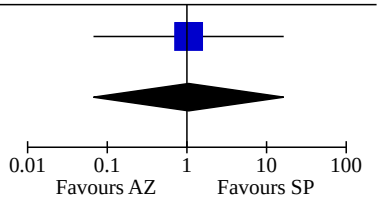
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 7.18. Comparison 7: Azithromycin (AZ) versus sulfadoxine-pyrimethamine (SP), Outcome 18: Adverse events: abdominal pain

Study or Subgroup	AZ Events	AZ Total	SP Events	SP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2019	1	60	1	63	100.0%	1.05 [0.07 , 16.41]
Total		**60**		**63**	**100.0%**	**1.05 [0.07 , 16.41]**
Total events:	1		1			

Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Comparison 8. Mefloquine (MQ) versus daily cotrimoxazole (CTXp)

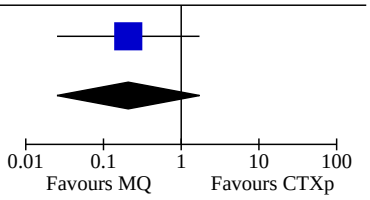
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Maternal peripheral parasitaemia at delivery (polymerase chain reaction)	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.03, 1.72]
8.2 Maternal anaemia at delivery	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.26, 3.16]
8.3 Placental malaria (polymerase chain reaction)	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.13, 4.15]
8.4 Placental malaria (blood smear)	1	108	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.01, 8.30]
8.5 Maternal haemoglobin level at delivery (in g/dL)	1	100	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.67, 0.47]
8.6 Low birth weight (< 2500 g)	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.56, 4.13]
8.7 Mean birth weight (in grams)	1	120	Mean Difference (IV, Fixed, 95% CI)	-102.00 [-255.52, 51.52]
8.8 Cord blood parasitaemia	1	140	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.9 Prematurity	1	125	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.33, 3.56]
8.10 SAEs during pregnancy	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.28, 4.07]
8.11 Spontaneous abortion	1	139	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.07, 16.84]
8.12 Stillbirth	1	139	Risk Ratio (M-H, Fixed, 95% CI)	4.30 [0.49, 37.49]
8.13 Congenital malformations	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.05, 5.79]
8.14 Maternal mortality	1	139	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
8.15 Early neonatal mortality (< 7 days)	1	129	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.07, 16.39]
8.16 Infant mortality (≥ 7 days up to 6 weeks of age)	1	129	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [0.19, 22.54]
8.17 Adverse events: headache	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.39]
8.18 Adverse events: vomiting	1	139	Risk Ratio (M-H, Fixed, 95% CI)	13.43 [3.31, 54.54]
8.19 Adverse events: dizziness	1	139	Risk Ratio (M-H, Fixed, 95% CI)	52.60 [3.26, 848.24]
8.20 Adverse events: fatigue/weakness	1	139	Risk Ratio (M-H, Fixed, 95% CI)	6.99 [1.64, 29.81]

Analysis 8.1. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 1: Maternal peripheral parasitaemia at delivery (polymerase chain reaction)

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	1	48	5	50	100.0%	0.21 [0.03 , 1.72]
Total		**48**		**50**	**100.0%**	**0.21 [0.03 , 1.72]**
Total events:	1		5			

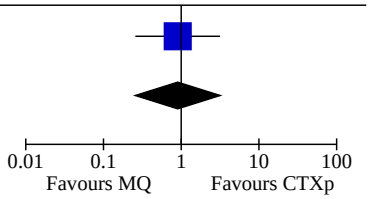
Test for overall effect: Z = 1.46 (P = 0.15)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.2. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 2: Maternal anaemia at delivery

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b[a]	4	47	5	53	100.0%	0.90 [0.26 , 3.16]
Total		**47**		**53**	**100.0%**	**0.90 [0.26 , 3.16]**
Total events:	4		5			

Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



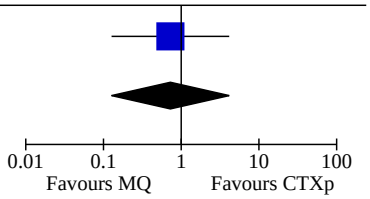
Footnotes

[a]Defined as hemoglobin level < 9.5 g/dL.

Analysis 8.3. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 3: Placental malaria (polymerase chain reaction)

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	2	45	3	49	100.0%	0.73 [0.13 , 4.15]
Total		**45**		**49**	**100.0%**	**0.73 [0.13 , 4.15]**
Total events:	2		3			

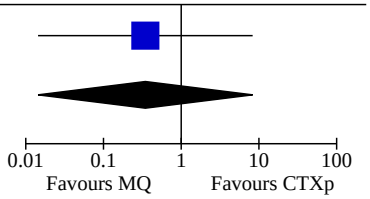
Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.4. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 4: Placental malaria (blood smear)

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	0	53	1	55	100.0%	0.35 [0.01 , 8.30]
Total		**53**		**55**	**100.0%**	**0.35 [0.01 , 8.30]**
Total events:	0		1			

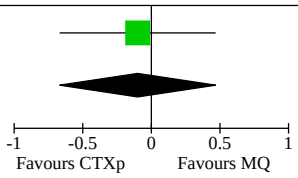
Test for overall effect: Z = 0.65 (P = 0.51)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.5. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 5: Maternal haemoglobin level at delivery (in g/dL)

Study or Subgroup	MQ Mean	MQ SD	MQ Total	CTXp Mean	CTXp SD	CTXp Total	Weight	Mean Difference IV, Fixed, 95% CI
Denoeud-Ndam 2014b	11.2	1.4	47	11.3	1.5	53	100.0%	-0.10 [-0.67 , 0.47]
Total			**47**			**53**	**100.0%**	**-0.10 [-0.67 , 0.47]**

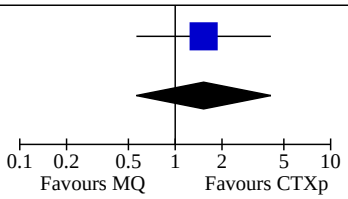
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.6. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 6: Low birth weight (< 2500 g)

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	8	56	6	64	100.0%	1.52 [0.56 , 4.13]
Total		**56**		**64**	**100.0%**	**1.52 [0.56 , 4.13]**
Total events:	8		6			

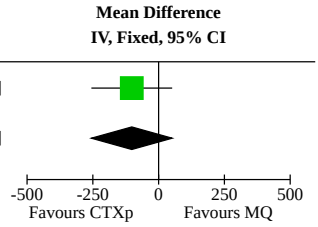
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.7. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 7: Mean birth weight (in grams)

Study or Subgroup	MQ Mean	MQ SD	MQ Total	CTXp Mean	CTXp SD	CTXp Total	Weight	Mean Difference IV, Fixed, 95% CI
Denoeud-Ndam 2014b	2902	421	56	3004	436	64	100.0%	-102.00 [-255.52 , 51.52]
Total			**56**			**64**	**100.0%**	**-102.00 [-255.52 , 51.52]**

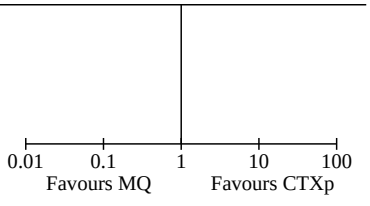
Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.8. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 8: Cord blood parasitaemia

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	0	72	0	68		Not estimable
Total		**72**		**68**		**Not estimable**
Total events:	0		0			

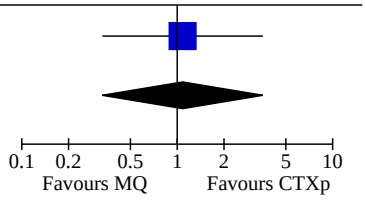
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.9. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 9: Prematurity

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b[a]	5	60	5	65	100.0%	1.08 [0.33 , 3.56]
Total		**60**		**65**	**100.0%**	**1.08 [0.33 , 3.56]**
Total events:	5		5			

Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

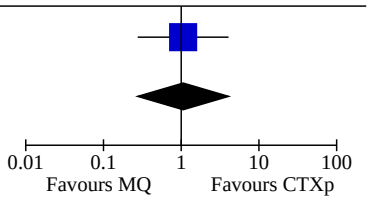


Footnotes
[a]Defined as delivery before gestation week 37

Analysis 8.10. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 10: SAEs during pregnancy

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	4	68	4	72	100.0%	1.06 [0.28 , 4.07]
Total		**68**		**72**	**100.0%**	**1.06 [0.28 , 4.07]**
Total events:	4		4			

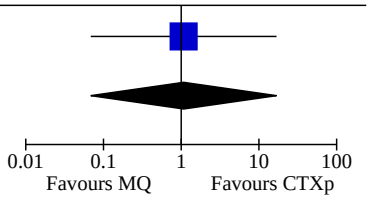
Test for overall effect: Z = 0.08 (P = 0.93)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.11. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 11: Spontaneous abortion

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b[a]	1	67	1	72	100.0%	1.07 [0.07 , 16.84]
Total		**67**		**72**	**100.0%**	**1.07 [0.07 , 16.84]**
Total events:	1		1			

Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

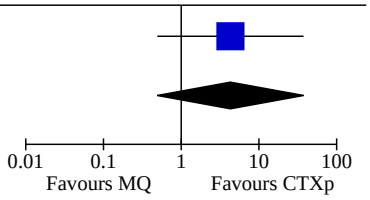


Footnotes
[a]Defined as death <28 weeks gestation.

Analysis 8.12. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 12: Stillbirth

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	4	67	1	72	100.0%	4.30 [0.49 , 37.49]
Total		**67**		**72**	**100.0%**	**4.30 [0.49 , 37.49]**
Total events:	4		1			

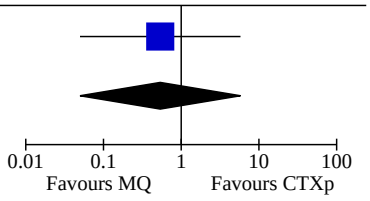
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.13. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 13: Congenital malformations

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b[a]	1	67	2	72	100.0%	0.54 [0.05 , 5.79]
Total		**67**		**72**	**100.0%**	**0.54 [0.05 , 5.79]**
Total events:	1		2			

Test for overall effect: Z = 0.51 (P = 0.61)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



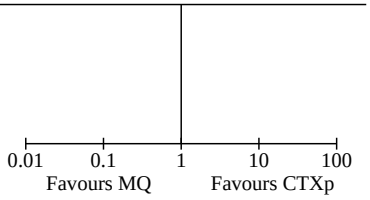
Footnotes

[a]Reported congenital anomalies: encephalocele and ventral hernia, clubfoot, umbilical hernia, and hydrocephaly.

Analysis 8.14. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 14: Maternal mortality

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	0	67	0	72		Not estimable
Total		**67**		**72**		**Not estimable**
Total events:	0		0			

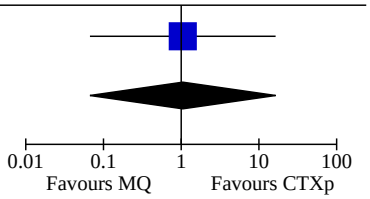
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.15. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 15: Early neonatal mortality (< 7 days)

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	1	63	1	66	100.0%	1.05 [0.07 , 16.39]
Total		**63**		**66**	**100.0%**	**1.05 [0.07 , 16.39]**
Total events:	1		1			

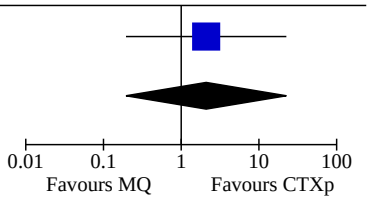
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.16. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 16: Infant mortality (≥ 7 days up to 6 weeks of age)

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	2	63	1	66	100.0%	2.10 [0.19 , 22.54]
Total		**63**		**66**	**100.0%**	**2.10 [0.19 , 22.54]**
Total events:	2		1			

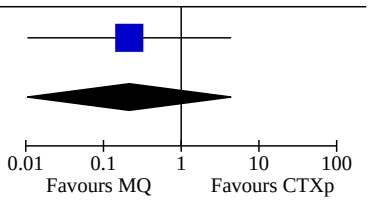
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.17. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 17: Adverse events: headache

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	0	67	2	72	100.0%	0.21 [0.01 , 4.39]
Total		**67**		**72**	**100.0%**	**0.21 [0.01 , 4.39]**
Total events:	0		2			

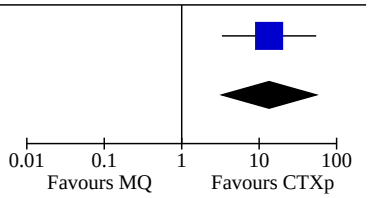
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.18. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 18: Adverse events: vomiting

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	25	67	2	72	100.0%	13.43 [3.31 , 54.54]
Total		**67**		**72**	**100.0%**	**13.43 [3.31 , 54.54]**
Total events:	25		2			

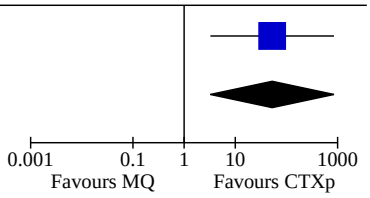
Test for overall effect: Z = 3.63 (P = 0.0003)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.19. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 19: Adverse events: dizziness

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	24	67	0	72	100.0%	52.60 [3.26 , 848.24]
Total		**67**		**72**	**100.0%**	**52.60 [3.26 , 848.24]**
Total events:	24		0			

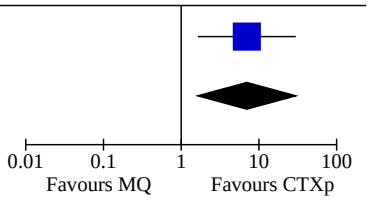
Test for overall effect: Z = 2.79 (P = 0.005)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 8.20. Comparison 8: Mefloquine (MQ) versus daily cotrimoxazole (CTXp), Outcome 20: Adverse events: fatigue/weakness

Study or Subgroup	MQ Events	MQ Total	CTXp Events	CTXp Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Denoeud-Ndam 2014b	13	67	2	72	100.0%	6.99 [1.64 , 29.81]
Total		**67**		**72**	**100.0%**	**6.99 [1.64 , 29.81]**
Total events:	13		2			

Test for overall effect: Z = 2.63 (P = 0.009)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Comparison 9. Sulfadoxine-pyrimethamine (SP) versus placebo

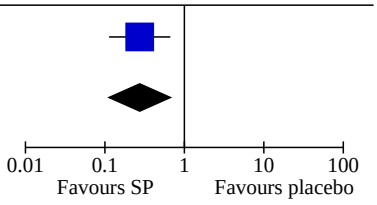
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Maternal peripheral parasitaemia at delivery (blood smear)	1	199	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.11, 0.67]
9.2 Maternal anaemia at delivery (packed cell volume <33%)	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.72, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3 Maternal anaemia at delivery (< 120 g/L)	1	135	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.88, 1.03]
9.4 Placental malaria: acute infection (histology)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.5 Placental malaria: chronic infection (histology)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.6 Mean haemoglobin at delivery (in g/L)	1	135	Mean Difference (IV, Fixed, 95% CI)	3.38 [-1.40, 8.15]
9.7 Low birth weight (< 2500 g)	1	208	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.63, 2.17]
9.8 Mean birth weight (in grams)	1	208	Mean Difference (IV, Fixed, 95% CI)	-43.71 [-253.05, 165.63]
9.9 Prematurity	1	208	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.20, 2.06]
9.10 Mother-to-child transmission of HIV	1	153	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.38, 2.06]
9.11 Maternal viral load at delivery (≥ 10 000 copies/mL)	1	81	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.48, 3.00]

Analysis 9.1. Comparison 9: Sulfadoxine-pyrimethamine (SP) versus placebo, Outcome 1: Maternal peripheral parasitaemia at delivery (blood smear)

	SP		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Menéndez 2008	6	112	17	87	100.0%	0.27 [0.11 , 0.67]	
Total		**112**		**87**	**100.0%**	**0.27 [0.11 , 0.67]**	
Total events:	6		17				

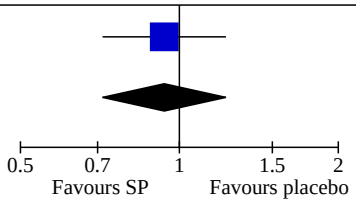
Test for overall effect: Z = 2.86 (P = 0.004)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.2. Comparison 9: Sulfadoxine-pyrimethamine (SP) versus placebo, Outcome 2: Maternal anaemia at delivery (packed cell volume <33%)

Study or Subgroup	SP Events	SP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Menéndez 2008	56	112	47	88	100.0%	0.94 [0.72 , 1.23]
Total		**112**		**88**	**100.0%**	**0.94 [0.72 , 1.23]**
Total events:	56		47			

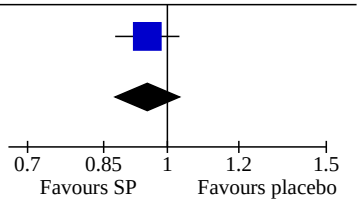
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.3. Comparison 9: Sulfadoxine-pyrimethamine (SP) versus placebo, Outcome 3: Maternal anaemia at delivery (< 120 g/L)

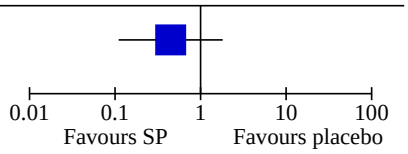
Study or Subgroup	SP Events	SP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Menéndez 2008	68	74	59	61	100.0%	0.95 [0.88 , 1.03]
Total		**74**		**61**	**100.0%**	**0.95 [0.88 , 1.03]**
Total events:	68		59			

Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



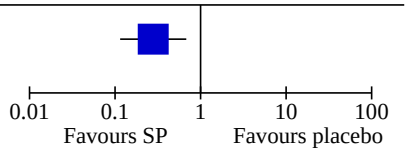
Analysis 9.4. Comparison 9: Sulfadoxine-pyrimethamine (SP) versus placebo, Outcome 4: Placental malaria: acute infection (histology)

Study or Subgroup	SP Events	SP Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Menéndez 2008	3	102	5	76	0.45 [0.11 , 1.81]



Analysis 9.5. Comparison 9: Sulfadoxine-pyrimethamine (SP) versus placebo, Outcome 5: Placental malaria: chronic infection (histology)

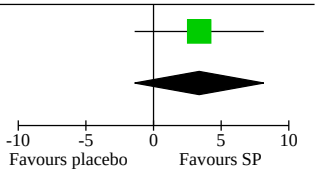
Study or Subgroup	SP Events	SP Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Akinyotu 2018	6	102	16	76	0.28 [0.11 , 0.68]



Analysis 9.6. Comparison 9: Sulfadoxine-pyrimethamine (SP) versus placebo, Outcome 6: Mean haemoglobin at delivery (in g/L)

Study or Subgroup	SP Mean	SP SD	SP Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Menéndez 2008	102.3919	15.22778	74	99.01639	13.05436	61	100.0%	3.38 [-1.40 , 8.15]
Total			**74**			**61**	**100.0%**	**3.38 [-1.40 , 8.15]**

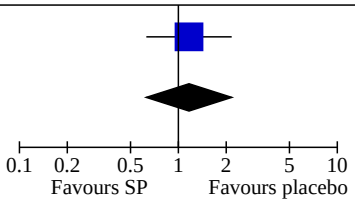
Test for overall effect: Z = 1.39 (P = 0.17)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.7. Comparison 9: Sulfadoxine-pyrimethamine (SP) versus placebo, Outcome 7: Low birth weight (< 2500 g)

Study or Subgroup	SP Events	SP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Menéndez 2008	21	117	14	91	100.0%	1.17 [0.63 , 2.17]
Total		**117**		**91**	**100.0%**	**1.17 [0.63 , 2.17]**
Total events:	21		14			

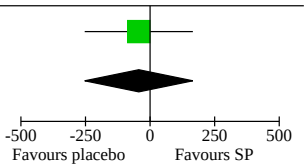
Test for overall effect: Z = 0.49 (P = 0.63)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.8. Comparison 9: Sulfadoxine-pyrimethamine (SP) versus placebo, Outcome 8: Mean birth weight (in grams)

Study or Subgroup	SP Mean	SP SD	SP Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Menéndez 2008	2838.699	700.1927	117	2882.409	810.4521	91	100.0%	-43.71 [-253.05 , 165.63]
Total			**117**			**91**	**100.0%**	**-43.71 [-253.05 , 165.63]**

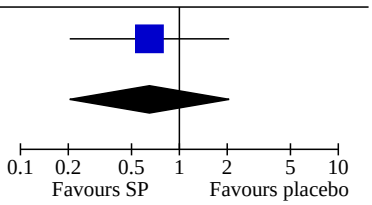
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.9. Comparison 9: Sulfadoxine-pyrimethamine (SP) versus placebo, Outcome 9: Prematurity

Study or Subgroup	SP Events	SP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Menéndez 2008[a]	5	117	6	91	100.0%	0.65 [0.20 , 2.06]
Total		**117**		**91**	**100.0%**	**0.65 [0.20 , 2.06]**
Total events:	5		6			

Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable

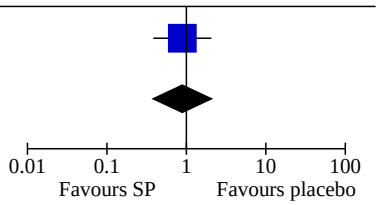


Footnotes
[a]Defined as delivery before gestation week 37.

Analysis 9.10. Comparison 9: Sulfadoxine-pyrimethamine (SP) versus placebo, Outcome 10: Mother-to-child transmission of HIV

Study or Subgroup	SP Events	SP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Menéndez 2008	10	85	9	68	100.0%	0.89 [0.38 , 2.06]
Total		**85**		**68**	**100.0%**	**0.89 [0.38 , 2.06]**
Total events:	10		9			

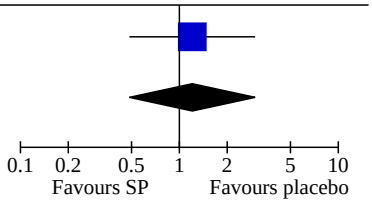
Test for overall effect: Z = 0.27 (P = 0.78)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Analysis 9.11. Comparison 9: Sulfadoxine-pyrimethamine (SP) versus placebo, Outcome 11: Maternal viral load at delivery (≥ 10 000 copies/mL)

Study or Subgroup	SP Events	SP Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Menéndez 2008[a]	10	47	6	34	100.0%	1.21 [0.48 , 3.00]
Total		**47**		**34**	**100.0%**	**1.21 [0.48 , 3.00]**
Total events:	10		6			

Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable
Heterogeneity: Not applicable



Footnotes
[a]Data from paper by Naniche et al. (2008)

APPENDICES

Appendix 1. Search terms and strategies

PubMed (MEDLINE)

1	malaria*[Title/Abstract]
2	malaria[MeSH Major Topic]
3	(plasmodium falciparum[Title/Abstract]) OR (plasmodium[MeSH Terms])
4	(((plasmodium falciparum[Title/Abstract]) OR (plasmodium[MeSH Terms])) OR (malaria[MeSH Major Topic])) OR (malaria*[Title/Abstract])
5	HIV[Title/Abstract] OR hiv-1*[Title/Abstract] OR hiv-2*[Title/Abstract] OR hiv1[Title/Abstract] OR hiv2[Title/Abstract]
6	"hiv infect*"[Title/Abstract] OR "human immunodeficiency virus"[Title/Abstract] OR "human immunedeficiency virus"[Title/Abstract]
7	"acquired immunodeficiency syndrome*"[Title/Abstract] OR "acquired immunedeficiency syndrome*"[Title/Abstract]
8	(HIV[MeSH Major Topic]) OR (HIV infections[MeSH Major Topic])
9	((((HIV[MeSH Major Topic]) OR (HIV infections[MeSH Major Topic])) OR ("acquired immunodeficiency syndrome*"[Title/Abstract] OR "acquired immunedeficiency syndrome*"[Title/Abstract])) OR ("hiv infect*"[Title/Abstract] OR "human immunodeficiency virus"[Title/Abstract] OR "human immunedeficiency virus"[Title/Abstract])) OR (HIV[Title/Abstract] OR hiv-1*[Title/Abstract] OR hiv-2*[Title/Abstract] OR hiv1[Title/Abstract] OR hiv2[Title/Abstract])
10	(((((HIV[MeSH Major Topic]) OR (HIV infections[MeSH Major Topic])) OR ("acquired immunodeficiency syndrome*"[Title/Abstract] OR "acquired immunedeficiency syndrome*"[Title/Abstract])) OR ("hiv infect*"[Title/Abstract] OR "human immunodeficiency virus"[Title/Abstract] OR "human immunedeficiency virus"[Title/Abstract])) OR (HIV[Title/Abstract] OR hiv-1*[Title/Abstract] OR hiv-2*[Title/Abstract] OR hiv1[Title/Abstract] OR hiv2[Title/Abstract])) AND ((((plasmodium falciparum[Title/Abstract]) OR (plasmodium[MeSH Terms])) OR (malaria[MeSH Major Topic])) OR (malaria*[Title/Abstract]))
11	intermittent[Title/Abstract] AND (prevent*[Title/Abstract] OR prophyla*[Title/Abstract] OR chemoprophyla*[Title/Abstract] OR presumptive[Title/Abstract])
12	IPT[Title/Abstract]
13	(IPT[Title/Abstract]) OR (intermittent[Title/Abstract] AND (prevent*[Title/Abstract] OR prophyla*[Title/Abstract] OR chemoprophyla*[Title/Abstract] OR presumptive[Title/Abstract]))
14	((IPT[Title/Abstract]) OR (intermittent[Title/Abstract] AND (prevent*[Title/Abstract] OR prophyla*[Title/Abstract] OR chemoprophyla*[Title/Abstract] OR presumptive[Title/Abstract]))) AND ((((((HIV[MeSH Major Topic]) OR (HIV infections[MeSH Major Topic])) OR ("acquired immunodeficiency syndrome*"[Title/Abstract] OR "acquired immunedeficiency syndrome*"[Title/Abstract])) OR ("hiv infect*"[Title/Abstract] OR "human immunodeficiency virus"[Title/Abstract] OR "human immunedeficiency virus"[Title/Abstract])) OR (HIV[Title/Abstract] OR hiv-1*[Title/Abstract] OR hiv-2*[Title/Abstract] OR hiv1[Title/Abstract] OR hiv2[Title/Abstract])) AND ((((plasmodium falciparum[Title/Abstract]) OR (plasmodium[MeSH Terms])) OR (malaria[MeSH Major Topic])) OR (malaria*[Title/Abstract])))
15	((IPT[Title/Abstract]) OR (intermittent[Title/Abstract] AND (prevent*[Title/Abstract] OR prophyla*[Title/Abstract] OR chemoprophyla*[Title/Abstract] OR presumptive[Title/Abstract]))) AND ((((((HIV[MeSH Major Topic]) OR (HIV infections[MeSH Major Topic])) OR ("acquired immunodeficiency syndrome*"[Title/Abstract] OR "acquired immunedeficiency syndrome*"[Title/Abstract])) OR ("hiv infect*"[Title/Abstract] OR "human immunodeficiency virus"[Title/Abstract] OR "human

(Continued)

	immunedeficiency virus"[Title/Abstract])) OR (HIV[Title/Abstract] OR hiv-1*[Title/Abstract] OR hiv-2*[Title/Abstract] OR hiv1[Title/Abstract] OR hiv2[Title/Abstract])) AND ((((plasmodium falciparum[Title/Abstract]) OR (plasmodium[MeSH Terms])) OR (malaria[MeSH Major Topic])) OR (malaria*[Title/Abstract]))))
16	((pregnancy[MeSH Terms]) OR (pregnant women[MeSH Terms])) OR (pregnan*[Title/Abstract] OR gestat*[Title/Abstract])
17	(((IPT[Title/Abstract]) OR (intermittent[Title/Abstract] AND (prevent*[Title/Abstract] OR prophyla*[Title/Abstract] OR chemoprophyla*[Title/Abstract] OR presumptive[Title/Abstract]))) AND ((((((HIV[MeSH Major Topic]) OR (HIV infections[MeSH Major Topic])) OR ("acquired immunodeficiency syndrome*"[Title/Abstract] OR "acquired immunedeficiency syndrome*"[Title/Abstract])) OR ("hiv infect*"[Title/Abstract] OR "human immunodeficiency virus"[Title/Abstract] OR "human immunedeficiency virus"[Title/Abstract])) OR (HIV[Title/Abstract] OR hiv-1*[Title/Abstract] OR hiv-2*[Title/Abstract] OR hiv1[Title/Abstract] OR hiv2[Title/Abstract])) AND ((((plasmodium falciparum[Title/Abstract]) OR (plasmodium[MeSH Terms])) OR (malaria[MeSH Major Topic])) OR (malaria*[Title/Abstract])))) AND (((pregnancy[MeSH Terms]) OR (pregnant women[MeSH Terms])) OR (pregnan*[Title/Abstract] OR gestat*[Title/Abstract]))

Embase (OVID) 1947 - present, updated daily

1 exp malaria/ or malaria.mp.

2 plasmodium.mp. or Plasmodium/

3 1 or 2

4 IPT*.mp.

5 ((intermittent or preventive or presumptive) adj2 (therapy or treatment)).mp.

6 (prophyla* or chemoprophyla*).mp.

7 4 or 5 or 6

8 3 and 7

9 pregnancy.mp. or exp pregnancy/

10 pregnant woman/ or pregnant.mp.

11 gestational.mp.

12 9 or 10 or 11

13 8 and 12

14 HIV*.mp.

15 Human immunodeficiency virus/

16 AIDS.mp. or acquired immune deficiency syndrome/

17 Human immunodeficiency virus/ or human immunodeficiency virus.mp.

18 HIV infection.mp. or Human immunodeficiency virus infection/

19 14 or 15 or 16 or 17 or 18

20 13 and 19

Cochrane Central Register of Controlled Trials (CENTRAL), Issue 1 of 12, January 2024

#1 malaria or plasmodium

#2 MeSH descriptor: [Malaria] explode all trees

#3 MeSH descriptor: [Plasmodium] explode all trees

#4 #1 or #2 or #3

#5 IPT* or "intermittent preventive"

#6 preventive or presumptive or prophyla* or chemoprophyla*

#7 #5 or #6

#8 #4 and #7

#9 MeSH descriptor: [Pregnancy] explode all trees

#10 MeSH descriptor: [Pregnant Women] explode all trees

#11 pregnan* or gestation*

#12 #9 or #10 or #11

#13 #8 and #12

LILACS (Latin American and Caribbean Health Science Information)

Search on: (malaria or plasmodium) AND (prevent$ or prophyla$ or IPT$ or intermittent) [Words] and pregna$ or gestat$ [Words] and HIV $ or AIDS or immunodeficiency [Words]

MiP (Malaria in Pregnancy) Library

Search (Current: IPT* AND (HIV* or AIDS or immunodeficien*)

Clinicaltrials.gov

pregnancy and HIV | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Interventional Studies | Malaria | Studies with Female Participants

Also searched for Pregnant

WHO ICTRP (World Health Organization International Clinical Trials Registry Platform)

malaria and pregnan* and HIV and (intermittent or IPT)

ISRCTN registry (International Standard Randomized Controlled Trial Number registry)

malaria and pregnant and HIV and IPT

WHAT'S NEW

Date	Event	Description
26 September 2024	New search has been performed	Revised protocol by new author team uploaded to PROSPERO in January 2021. The literature search was updated to 31 January 2024.
25 September 2024	New citation required and conclusions have changed	Fourteen trials, published in 13 articles, met the inclusion criteria. Twelve of them are new since the last published review version.

HISTORY

Protocol first published: Issue 3, 2007
Review first published: Issue 10, 2011

Date	Event	Description
18 July 2012	Amended	The GRADE assessments were adjusted in the summary of findings tables and the conclusions were modified in accordance with this.
5 October 2010	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

CPD and RG designed the study. CPD and KEY wrote the first version of the revised protocol. CPD, CMC, KEY, VB, and RG revised the final version of the protocol, which was approved by the CIDG Editors and uploaded to PROSPERO (CRD42021233901).

All authors, except authors of publications that could be included in the review, assessed trial eligibility and risk of bias, and extracted data. Any review author who participated in any of the trials included in the review did not participate in the data extraction or risk of bias assessment of their own articles. CPD and MJW performed the analyses. CPD, MJW, and RG wrote the first version of the review. All authors interpreted the results, contributed to, and approved the final version of the review prior to publication.

DECLARATIONS OF INTEREST

CPD is author of a trial included in this review (González 2024), but was not involved in assessing the eligibility, risk of bias assessment, or analyses of this study. She has no known conflicts of interest.

CMC has no known conflicts of interest.

KEY has no known conflicts of interest.

VB is author of a trial that is included in this review (Manirakiza 2021), but was not involved in assessing the eligibility, risk of bias assessment, or analyses of this study. VB was Chair of the Data and Safety Monitoring Board of another trial included in this review (González 2024). She has no known conflicts of interest.

MJW has no known conflicts of interest.

RG is an author on two trials that are included in this review (González 2014; González 2024), but was not involved in assessing the eligibility, in risk of bias assessment, or analyses of these studies. She has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Spanish Ministry of Science and Innovation, Spain

  The Barcelona Institute for Global Health (ISGlobal) is supported by the Spanish Ministry of Science and Innovation through the “Centro de Excelencia Severo Ochoa 2019-2023” Program [CEX2018-000806-S] and it is a member of CERCA, Generalitat de Catalunya.
- Generalitat de Catalunya, Spain

  ISGlobal is a member of the CERCA (Centres de Recerca de CAtalunya) Programme.
- Liverpool School of Tropical Medicine, UK

External sources

- Foreign, Commonwealth, and Development Office (FCDO), UK

  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We wrote a revised protocol for this update and uploaded it to PROSPERO (CRD42021233901). The differences between protocol and review listed in this section are in reference to the revised protocol on PROSPERO (CRD42021233901).

Types of participants

After screening the potential studies for inclusion in the review, we decided to revise our inclusion criteria to read that we would accept studies from areas of 'stable' rather than 'moderate-to-high' malaria transmission. IPTp has traditionally been recommended in countries with moderate to high malaria transmission (also named “stable” transmission areas, characterized by a steady prevalence pattern, with little variation from one year to another) and not in low transmission settings. That is the reason why in many IPTp studies the malaria transmission intensity is mentioned. Since June 2022, WHO chemoprevention recommendations (including IPTp) no longer specify transmission intensity thresholds to provide greater flexibility to national malaria programmes to adapt control strategies to suit their settings. We edited the wording of the review to reflect this updated recommendation.

Types of outcomes

We changed our outcome 'small for gestational age' from a primary to a secondary outcome.

We added 'severe anaemia' as a secondary outcome.

We edited the "severe adverse events" subcategory of outcomes and included "serious adverse events" as outcome. These were analysed as reported in the included studies.

We revised and modified the order of the primary and secondary outcomes in the Methods section to organize them in a more intuitive and understandable way.

When a study evaluated our outcomes in ways other than we had specified in our Methods, we presented that data. We performed the analyses using the data extracted from the included studies. We presented some outcomes as dichotomous (e.g. low birth weight, undetectable viral load), even if as had planned to present them as continuous. Similarly, we reported the outcomes of interest as defined and assessed in the original studies.

Subgroup and sensitivity analyses

We did not conduct subgroup analyses based on gravidity, CD4 counts, or malaria transmission for the primary outcomes due to small sample size and unavailability of disaggregated data.

We did not conduct subgroup analyses based on use of LLINs as these were used in the trials or data on LLINs were not available.

We did not conduct sensitivity analysis since not all trials reported in detail the proportion of missing data and the reasons for all exclusions in the evaluation of each individual outcome. It was not possible to conduct sensitivity analysis consistently across all comparisons.

GRADE and summary of findings tables

We added a section on assessing the certainty of the evidence and creating summary of findings tables for the comparisons and outcomes that we considered to be the most important for those making decisions about malaria prevention for HIV-positive pregnant women.

We had not specified in the protocol which comparisons and outcomes we would include in summary of findings tables. We chose our meta-analysis of studies evaluating the current standard of care (daily cotrimoxazole) compared to IPTp (mefloquine or dihydroartemisinin/piperaquine) as our main comparison for our first summary of findings table, omitting drug-related adverse events and HIV mother-to-child transmission, as we considered these to be drug-specific. In a second summary of findings table, we chose to present results for dihydroartemisinin/piperaquine plus daily cotrimoxazole versus daily cotrimoxazle alone as we wanted to focus on the drug that we judged to be the most promising candidate for IPTp in this population. Following Cochrane handbook, we did not include more than eight outcomes in SoF 2, so we omitted two outcomes that were presented in SoF 1 (severe adverse events and cord blood parasitaemia), but these results are available in the main text of the review, as are the results of the mefloquine studies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antimalarials [administration & dosage] [adverse effects] [therapeutic use]; Artemisinins [administration & dosage] [therapeutic use]; *Drug Combinations; HIV Infections [complications]; HIV Seropositivity [complications]; *Malaria [prevention & control]; Mefloquine [administration & dosage] [adverse effects] [therapeutic use]; Piperazines; Pregnancy Complications, Infectious [drug therapy]; Pregnancy Complications, Parasitic [prevention & control]; *Pyrimethamine [administration & dosage] [therapeutic use]; Quinolines; Randomized Controlled Trials as Topic; *Sulfadoxine [administration & dosage] [therapeutic use]; *Trimethoprim, Sulfamethoxazole Drug Combination [administration & dosage] [therapeutic use]

MeSH check words

Female; Humans; Pregnancy