

Drugs for preventing malaria in pregnant women (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	3
METHODS	3
RESULTS	4
DISCUSSION	7
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	9
CHARACTERISTICS OF STUDIES	11
DATA AND ANALYSES	22
Analysis 1.1. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 1 Death.	25
Analysis 1.2. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 2 Caesarean section.	25
Analysis 1.3. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 3 Complicated labour.	26
Analysis 1.4. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 4 Anaemia (any).	26
Analysis 1.5. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 5 Haematocrit.	27
Analysis 1.6. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 6 Need for blood transfusion.	27
Analysis 1.7. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 7 Antenatal parasitaemia.	28
Analysis 1.8. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 8 At least one malaria infection.	28
Analysis 1.9. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 9 Placental malaria.	29
Analysis 1.10. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 10 Fever episodes.	29
Analysis 2.1. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 1 Perinatal death.	30
Analysis 2.2. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 2 Stillbirth.	30
Analysis 2.3. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 3 Neonatal death.	31
Analysis 2.4. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 4 Infant death.	31
Analysis 2.5. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 5 Preterm birth.	32
Analysis 2.6. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 6 Mean birthweight.	32
Analysis 2.7. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 7 Low birthweight.	33
Analysis 2.8. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 8 High birthweight.	33
Analysis 3.1. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 1 Death.	34

Analysis 3.2. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 2 Caesarean section (prophylaxis only).	34
Analysis 3.3. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 3 Severe antenatal anaemia.	35
Analysis 3.4. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 4 Anaemia (any).	36
Analysis 3.5. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 5 Mean haematocrit.	36
Analysis 3.6. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 6 Mean haemoglobin.	37
Analysis 3.7. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 7 Antenatal parasitaemia.	38
Analysis 3.8. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 8 Women infected at least once (prophylaxis only).	39
Analysis 3.9. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 9 Treatment for suspected malaria (prophylaxis only).	39
Analysis 3.10. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 10 Placental malaria.	40
Analysis 4.1. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 1 Perinatal death.	41
Analysis 4.2. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 2 Stillbirth.	42
Analysis 4.3. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 3 Neonatal death.	43
Analysis 4.4. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 4 Infant death.	44
Analysis 4.5. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 5 Preterm birth.	44
Analysis 4.6. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 6 Mean birthweight.	45
Analysis 4.7. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 7 Low birthweight.	46
Analysis 4.8. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 8 High birthweight.	47
Analysis 4.9. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 9 Newborn malaria infection.	47
Analysis 5.1. Comparison 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes, Outcome 1 Severe anaemia.	48
Analysis 5.2. Comparison 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes, Outcome 2 Haemoglobin.	48
Analysis 5.3. Comparison 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes, Outcome 3 Fever episodes.	49
Analysis 5.4. Comparison 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes, Outcome 4 Antenatal parasitaemia.	49
Analysis 5.5. Comparison 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes, Outcome 5 Placental malaria.	50
Analysis 6.1. Comparison 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes, Outcome 1 Neonatal death.	50
Analysis 6.2. Comparison 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes, Outcome 2 Preterm birth.	51
Analysis 6.3. Comparison 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes, Outcome 3 Mean birthweight.	51

Analysis 6.4. Comparison 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes, Outcome 4 Low birthweight.	52
APPENDICES	52
WHAT'S NEW	56
HISTORY	56
CONTRIBUTIONS OF AUTHORS	56
DECLARATIONS OF INTEREST	57
SOURCES OF SUPPORT	57
INDEX TERMS	57

[Intervention Review]

Drugs for preventing malaria in pregnant women

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ABSTRACT

Background

Malaria contributes to maternal illness and anaemia in pregnancy, especially in first-time mothers, and can harm the mother and the baby. Drugs given routinely to prevent or mitigate the effects of malaria during pregnancy are often recommended.

Objectives

To assess drugs given to prevent malaria infection and its consequences in pregnant women living in malarial areas. This includes prophylaxis and intermittent preventive treatment (IPT).

Search strategy

We searched the Cochrane Infectious Diseases Group Specialized Register (March 2006), CENTRAL (*The Cochrane Library* 2006, Issue 1), MEDLINE (1966 to March 2006), EMBASE (1974 to March 2006), LILACS (1982 to March 2006), and reference lists. We also contacted researchers working in the field.

Selection criteria

Randomized and quasi-randomized controlled trials comparing antimalarial drugs given regularly with no antimalarial drugs for preventing malaria in pregnant women living in malaria-endemic areas.

Data collection and analysis

Both authors extracted data and assessed methodological quality. Dichotomous variables were combined using relative risks (RR) and mean differences (MD) for mean values, both with 95% confidence intervals (CI).

Main results

Sixteen trials (12,638 participants) met the inclusion criteria; two used adequate methods to conceal allocation. Antimalarials reduced antenatal parasitaemia when given to all pregnant women (RR 0.53, 95% CI 0.33 to 0.86; 328 participants, 2 trials), placental malaria (RR 0.34, 95% CI 0.26 to 0.45; 1236 participants, 3 trials), but no effect was detected with perinatal deaths (2890 participants, 4 trials). In women in their first or second pregnancy, antimalarial drugs reduced severe antenatal anaemia (RR 0.62, 95% CI 0.50 to 0.78; 2809 participants, 1 prophylaxis and 2 IPT trials), antenatal parasitaemia (RR 0.27, 95% CI 0.17 to 0.44, random-effects model; 2906 participants, 6 trials), and perinatal deaths (RR 0.73, 95% CI 0.53 to 0.99; 1986 participants, 2 prophylaxis and 1 IPT trial;

mean birthweight was higher (MD 126.70 g, 95% CI 88.64 to 164.75 g; 2648 participants, 8 trials), and low birthweight less frequent (RR 0.57, 95% CI 0.46 to 0.72; 2350 participants, 6 trials).

Proguanil performed better than chloroquine in one trial of women of all parities in relation to maternal fever episodes. Sulfadoxine-pyrimethamine performed better than chloroquine in two trials of low-parity women.

Authors' conclusions

Chemoprophylaxis or IPT reduces antenatal parasite prevalence and placental malaria when given to women in all parity groups. They also have positive effects on birthweight and possibly on perinatal death in low-parity women.

PLAIN LANGUAGE SUMMARY

Drugs for pregnant women to prevent malaria-related illness for them and their babies

Malaria is a parasitic disease spread by mosquitoes. It affects millions of people worldwide and causes illness and mortality. Uncomplicated malaria has symptoms such as fever, headache, muscle pain, and vomiting, and children commonly present with rapid breathing or cough. Severe malaria causes unconsciousness and death. Women living in malarial areas and who are pregnant for the first or second time are more likely to become infected with malaria. This brings severe anaemia causing weakness and tiredness for the mother, and slows the growth of the baby. The review of trials assessed whether giving drugs on a regular basis to prevent malaria would have advantages in terms of health gains for the mother and baby, as this has to be balanced against drug adverse effects, and against risks of the malaria parasite developing resistance to these drugs. The review found seven trials looking at drugs given to all pregnant women where there was no benefit identified for either mother or baby. The review also found six trials involving 2495 pregnant women having their first or second babies. Drugs, like chloroquine, pyrimethamine, proguanil, and mefloquine, given routinely to women in their first or second pregnancy, reduced the number of women with severe anaemia in pregnancy. They were also associated with higher birthweight in the baby and probably fewer perinatal deaths. It was not possible to assess any potential impact on drug resistance.

BACKGROUND

Women who live in areas with endemic malaria and who are pregnant for the first or second time are more likely to be infected with *Plasmodium falciparum* malaria than non-pregnant women of a similar age (Brabin 1983). This infection contributes to antenatal anaemia (Brabin 1990; Duffy 2001) and slows fetal growth (Kramer 1987), which may harm the mother and baby.

Drugs have been widely used to prevent infection or its consequences. From the 1980s, prophylaxis to prevent, suppress, or eradicate malaria parasites with a variety of drugs has been tested. From the 1990s, a modification of this called intermittent preventive treatment (IPT) has been used, where women are treated for malaria presumptively at fixed times during the pregnancy, usually drugs with a long half life, such as sulfadoxine-pyrimethamine. There remains debate as to whether the mechanism of IPT actually differs a lot from prophylaxis (White 2005), but the regimens are very different. IPT requires just two or three doses during

pregnancy, compared to prophylaxis regimens that may be daily (eg with proguanil) or weekly (eg with chloroquine). Prophylaxis and IPT are in addition to good care during pregnancy, which includes prompt treatment of women when they present clinically with fever or anaemia. Surprisingly, this latter area is remarkably under-researched (Orton 2005).

The research and policy question addressed in this review is whether giving drugs on a regular basis (prophylaxis or IPT) to prevent malaria has additional advantages in terms of health outcomes over prompt, appropriate treatment. The advantages with women taking regular, routine antimalarial drugs are that the drug will treat or suppress parasites in the blood and reduce the chances of illness or anaemia developing. In turn, this may ultimately benefit the fetus and impact on birthweight and long-term survival. The disadvantages of routine use of antimalarial drugs are that many drugs have adverse effects and that widespread use may contribute to the malaria parasite developing resistance to these drugs; and it

requires health systems to help ensure their implementation. The question is first addressed in terms of all pregnant women, and then secondly in women of low parity, where the effects of malaria are more marked.

One of the main problems in evaluating the effects of routine antimalarial drugs on the mother and the infant is identifying meaningful outcomes in terms of the direct impact on mother or baby. This review has identified two pragmatic outcome measures:

- Severe antenatal anaemia: there is a strong association between anaemia and poor maternal outcomes, so preventing severe anaemia is likely to be of benefit.
- Perinatal death: preventing death of the fetus and in the first week of life is one of the main reasons for giving malaria prophylaxis.

OBJECTIVES

To assess drugs given to prevent malaria infection and its consequences in pregnant women living in malarial areas. This includes prophylaxis and intermittent preventive treatment (IPT).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

Pregnant women living in endemic malaria areas.

Types of interventions

Interventions

Antimalarial drug prophylaxis (eg chloroquine given weekly) or IPT (typically sulfadoxine-pyrimethamine given two to three times during pregnancy).

Controls

- No regular or routine antimalarial drugs given; women receive malaria treatments for fever, anaemia, or clinical malaria, according to local protocols.
- Comparator regimens of prophylaxis or IPT.

Types of outcome measures

Mother

- Death.
- Antenatal hospital admission.
- Obstetric complications:
 - Caesarean section.
 - Complicated labour.
- Anaemia:
 - Severe anaemia*, defined as haemoglobin level less than 8 g/L; or haematocrit equivalent.
 - Anaemia (any).
 - Mean haematocrit.
 - Mean haemoglobin.
 - Need for a blood transfusion.
- Malaria infection:
 - Antenatal parasitaemia.
 - Incidence (number of women infected at least once; number treated for suspected malaria).
 - Placental malaria.
 - Fever.
- Adverse events leading to discontinuation of the drug or hospitalization.

Fetus

- Death:
 - Perinatal death* (death of the baby after 22nd week of pregnancy and first seven days after birth).
 - Stillbirth.
 - Neonatal death.
 - Infant death.
 - Preterm birth.
- Birthweight:
 - Mean birthweight.
 - Low birthweight.
 - High birthweight.
- Malaria infection.

*Primary outcome measures for the review.

Search methods for identification of studies

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

Databases

We searched the following databases using the search terms and strategy described in [Appendix 1](#): Cochrane Infectious Diseases Group Specialized Register (March 2006); Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2006, Issue 1); MEDLINE (1966 to March 2006); EMBASE (1974 to March 2006); and LILACS (1982 to March 2006).

Researchers

We contacted researchers working in the field for unpublished data, confidential reports, and raw data of published trials.

Reference lists

We also checked the citations of literature reviews ([Kramer 1987](#); [Brabin 1990](#)), and of all trials identified by the above methods, and asked the referees to check the search strategy.

Data collection and analysis

Selection of studies

Over the last 10 years, PG has periodically assessed titles and abstracts of articles identified by the literature search. Potentially relevant studies (describing the use of antimalarial drugs in pregnancy) were retrieved and examined. If they were potentially a trial, both authors applied the inclusion criteria and then compared their decisions; differences were resolved by discussion. Trials that appeared relevant but did not meet the inclusion criteria are listed in the '[Characteristics of excluded studies](#)'.

Data extraction and management

Both authors extracted data in most updates; in the 2006 update, PG extracted data and MG cross checked the papers for accuracy. Data were entered into [Review Manager 5](#).

Assessment of risk of bias in included studies

We independently assessed the trials' methodological quality (risk of bias). We judged the method used to generate the allocation sequence to be adequate if it was described and the resulting sequences were unpredictable, unclear if it was stated that the trial is randomized but the method was not described, and inadequate

if the sequences could be related to prognosis. We considered the method used to conceal allocation to be adequate if the participants and investigators enrolling participants could not foresee assignment, unclear if the trial was described as randomized but the method was not described, and inadequate if the participants and investigators enrolling participants could foresee the upcoming assignment. Blinding was classified as double (use a placebo or a double dummy technique such that neither the participant or care provider/assessor know which treatment is given), single (the participant or care provider/assessor is aware of the treatment given), or open (all parties are aware of treatment). In our assessment of losses to follow up, we assessed the loss between the initial cohort and those women included in the final analysis of outcomes. Where information appeared to have been collected but was not fully reported, we approached the trial authors for further details.

Data synthesis

We used [Review Manager 5](#) for the analysis. We separated trials into those evaluating the intervention in all parity groups (generally the older trials) and those evaluating prophylaxis in low-parity women (parity one and two). Trials were grouped by those that evaluated prophylaxis and those evaluating IPT. We used risk ratios (RR) for dichotomous variables and mean differences (MD) for mean values. In the absence of heterogeneity we used a fixed-effect model with 95% confidence intervals (CI), and where we detected heterogeneity, we used a random-effects model for the meta-analysis. Weighted averages were calculated where required. In trials where standard deviations for birthweight were not available, we used an estimate of 500 g.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Sixteen trials met the inclusion criteria (*see* '[Characteristics of included studies](#)'); one trial had two arms ([Parise 1998i](#); [Parise 1998ii](#)), making 17 separate comparisons. One large trial with 4220 participants from Malawi was intended to be randomized ([Steketee 1996](#)), but this did not appear to happen in practice; this and the other excluded studies are detailed in the '[Characteristics of excluded studies](#)'.

Trial location

One trial was carried out in an area with unstable malaria in Thailand ([Nosten 1994](#)). All other trials were carried out in

highly endemic areas in countries in Africa: Burkina Faso (Cot 1992); Cameroon (Cot 1995); The Gambia (Greenwood 1989; Menendez 1994); Kenya (Parise 1998i; Parise 1998ii; Shulman 1999); Malawi (Schultz 1994); Mali (Kayentao 2005); Mozambique (Challis 2004); Nigeria (Morley 1964; Fleming 1985; Nahlen 1989); Tanzania (Mutabingwa 1991); and Uganda (Hamilton 1972; Ndyomugenyi 2000). Drug resistance varied over time and was incompletely reported in the papers.

Participants

The review includes 12,638 women (Appendix 2). All women regardless of number of previous pregnancies were included in seven trials (Morley 1964; Hamilton 1972; Greenwood 1989; Nahlen 1989; Mutabingwa 1991; Cot 1992; Nosten 1994); however, two of these trials selected women in their first pregnancy for follow up or reporting (Greenwood 1989; Mutabingwa 1991). Women in their first pregnancy were exclusively recruited in six trials (Fleming 1985; Menendez 1994; Cot 1995; Shulman 1999; Ndyomugenyi 2000; Challis 2004), and women in their first or second pregnancy were recruited in three trials (Parise 1998i; Parise 1998ii; Schultz 1994; Kayentao 2005).

Interventions

Ten prophylaxis trials used a placebo or no antimalarial drug as the control (Appendix 3). Different intervention drugs were used: chloroquine (Hamilton 1972; Cot 1992; Cot 1995; Ndyomugenyi 2000); pyrimethamine (Morley 1964; Nahlen 1989); proguanil (Fleming 1985); pyrimethamine-dapsone (Greenwood 1989; Menendez 1994); and mefloquine (Nosten 1994). One trial compared chloroquine prophylaxis with proguanil (Mutabingwa 1991).

Three trials evaluated IPT with sulfadoxine-pyrimethamine against placebo (Parise 1998; Shulman 1999; Challis 2004), and two evaluated IPT against chloroquine prophylaxis (Schultz 1994; Kayentao 2005).

Three trial reports describe access to treatment in the event of a malarial illness (Morley 1964; Nosten 1994; Shulman 1999), while the other trials did not describe the services available to the trial participants.

Oral iron and folic acid supplements were used in seven trials in various combinations.

Risk of bias in included studies

As shown in Appendix 4, three trials used an adequate method to generate the allocation sequence (Fleming 1985; Shulman 1999; Ndyomugenyi 2000), seven used an inadequate method (alternate allocation or allocation by day of attendance at clinic), and the method was unclear in six trials. Only two trials concealed allocation (Nosten 1994; Shulman 1999), while 10 trials did not

conceal allocation or used inadequate methods to do this, and the methods used were unclear in four trials. For blinding, three trials reported both that health staff and women were blinded from their intervention group (Nosten 1994; Shulman 1999; Challis 2004). One trial was described as double blind (Ndyomugenyi 2000) and another blinded the patients but was not clear about health staff (Fleming 1985); the other trials did not use blinding.

The percentage of randomized participants included in the analyses varied from 24% to 100% for maternal outcomes, and 62% to 100% for fetal outcomes (Appendix 5).

The two trials from The Gambia trials were randomized by cluster (Greenwood 1989; Menendez 1994), but the analysis did not take the cluster-design effects into consideration. However, pregnancy is a relatively infrequent event and the compounds (which were the units of randomization) generally have only a small number of houses. We therefore used the data as they were presented in the paper and ignored any possible design effects.

Effects of interventions

We examined trials allocating women to prophylaxis or IPT versus a control (placebo or no routine drug), first in trials that recruited and reported women of all parity groups, and then those recruiting and reporting women of low parity. We then examined head-to-head comparisons.

I. Any antimalarial drug versus no drug

I.1. Women of all parity groups

Six trials tested the overall benefit to women of routine drugs given during pregnancy: five were carried out in Africa (Morley 1964; Hamilton 1972; Greenwood 1989; Nahlen 1989; Cot 1992); and one was carried out in an area with unstable malaria in Thailand (Nosten 1994).

I.1.1. Mother

Death

One trial, Greenwood 1989, recorded maternal death and did not demonstrate a difference (1049 participants, Analysis 1.1).

Obstetric complications

There was no significant difference in the number of Caesarean sections in Hamilton 1972 (1137 participants, Analysis 1.2) or complicated labours in Nosten 1994 (301 participants, Analysis 1.3).

Anaemia

No statistically significant difference between the two groups was reported for women with any anaemia (Nosten 1994, 311 participants, Analysis 1.4), mean values of haematocrit (Greenwood 1989, 276 participants, Analysis 1.5), or the need for a blood transfusion (Nosten 1994, 339 participants, Analysis 1.6).

Malaria infection

Fewer women in the group that received antimalarial drugs had antenatal parasitaemia (RR 0.53, 95% CI 0.33 to 0.86; 328 participants, 2 trials, Analysis 1.7), at least one malaria infection (RR 0.14, 95% CI 0.06 to 0.34; 337 participants, 1 trial, Analysis 1.8), placental malaria (RR 0.34, 95% CI 0.26 to 0.45; 1236 participants, 3 trials, Analysis 1.9), and episodes of fever (RR 0.42, 95% CI 0.27 to 0.66; 227 participants, 1 trial, Analysis 1.10).

1.1.2. Fetal

Death

There was no statistically significant difference in the number of perinatal deaths in the meta-analysis of the four trials that reported this (2890 participants, 4 trials, Analysis 2.1), with no significant heterogeneity. Nosten 1994 had a trend of more perinatal deaths in the prophylaxis group that bordered on significance (RR 3.51, 95% CI 1.00 to 12.32; 311 participants). The analyses for still-birth (1493 participants, 2 trials, Analysis 2.2), neonatal death (419 participants, 1 trial, Analysis 2.3), and infant death (288 participants, 2 trials, Analysis 2.4) were underpowered and infrequently reported, with no significant differences demonstrated.

Preterm birth

Nosten 1994 reported on the number of preterm births, and no significant difference was demonstrated (199 participants, Analysis 2.5).

Birthweight

Four trials reported mean birthweight (2671 participants, Analysis 2.6). There was no significant difference in number with low birthweight (1438 participants, Analysis 2.7) or high birthweight (287 participants, Analysis 2.8), although there was significant heterogeneity between the trials ($P = 0.010$).

1.2. Women having their first or second baby

Seven trials reported on women in their first or second pregnancy (Fleming 1985; Greenwood 1989; Menendez 1994; Cot 1995;

Shulman 1999; Ndyomugenyi 2000; Challis 2004). In the analyses, we have stratified trials by whether women were given prophylaxis or IPT.

1.2.1. Mother

Death

The two trials that reported this outcome measure both used prophylaxis (Greenwood 1989; Ndyomugenyi 2000). They had too few participants to detect an effect on maternal death (772 participants, 2 trials, Analysis 3.1).

Obstetric complications

Two small trials that used prophylaxis measured the number of women having a Caesarean section (Fleming 1985; Cot 1995) and the meta-analysis showed no significant difference (294 participants, Analysis 3.2).

Anaemia

The group of women who received antimalarial drugs had fewer instances of severe antenatal anaemia (RR 0.62, 95% CI 0.50 to 0.78; 2809 participants, 1 prophylaxis trial, 2 IPT trials, Analysis 3.3) and any anaemia (RR 0.67, 95% CI 0.47 to 0.95; 566 participants, 1 prophylaxis trial, Analysis 3.4). This was also the case for mean haematocrit (MD 2.63, 95% CI 1.36 to 3.90; 118 participants, 2 prophylaxis trials, Analysis 3.5) and mean haemoglobin (MD 0.40, 95% CI 0.23 to 0.56; 1677 participants, 1 prophylaxis trial and 1 IPT trial, Analysis 3.6).

Malaria infection

Routine drug administration was associated with fewer women with parasites in the antenatal period (RR 0.27, 95% CI 0.17 to 0.44, random-effects model; 2906 participants, 3 prophylaxis trials and 3 IPT trials, Analysis 3.7); there was heterogeneity between the trials, but the direction of effect was consistent. The antimalarial drugs also had an effect on reducing the incidence of women having at least one malaria infection (RR 0.12, 95% CI 0.02 to 0.93; 83 participants, 1 prophylaxis trial, Analysis 2.8), the need for treatment for suspected malaria (RR 0.41, 95% CI 0.18 to 0.91; 133 participants, 1 prophylaxis trial, Analysis 3.9), and the number of women with placental malaria in the three prophylaxis trials (RR 0.71, 95% CI 0.60 to 0.85; 573 participants) and the two IPT trials (RR 0.35, 95% CI 0.27 to 0.47; 1232 participants; Analysis 3.10).

1.2.2. Fetus

Death

A meta-analysis of two prophylaxis trials and one IPT trial found that the use of antimalarial drugs is associated with fewer perinatal deaths (RR 0.73, 95% CI 0.53 to 0.99; 1986 participants, 2 prophylaxis and 1 IPT trial, [Analysis 4.1](#)). A sensitivity analysis of the one adequately concealed trial showed that the effect on perinatal deaths was smaller than in the other two trials (RR 0.78, 95% CI 0.52 to 1.17; 1237 participants, [Shulman 1999](#), [Analysis 4.1](#)). For stillbirth, no impact was detected (3454 participants, [Analysis 4.2](#)). In the three trials reporting neonatal deaths, the trend was towards protection, but again this was not statistically significant (2505 participants, [Analysis 4.3](#)). There was also no significant difference in the number of infant deaths in one small trial (349 participants, [Analysis 4.4](#)).

Preterm births

One prophylaxis trial reported no statistically significant difference in the number of preterm births (1051 participants, [Analysis 4.5](#)).

Birthweight

Babies born to women using antimalarial drugs had a higher mean birthweight (MD 126.70 g, 95% CI 88.64 to 164.75; 2648 participants, 8 trials, [Analysis 4.6](#) and were less likely to have a low birthweight (RR 0.57, 95% CI 0.46 to 0.72; 2350 participants, 6 trials, [Analysis 4.7](#)). One small trial reported on high birthweight, but there was no significant difference between the groups (121 participants, [Analysis 4.8](#)).

Malaria infection

Two trials reported on newborn malaria infection; one suggesting an effect and the other not showing a significant difference (639 participants, [Analysis 4.9](#)).

2. Head-to-head comparisons

2.1. Proguanil versus chloroquine

One trial carried out in Tanzania in women of all parities examined this comparison ([Mutabingwa 1991](#)). Compared with chloroquine, proguanil was associated with fewer fever episodes (RR 0.69, 95% CI 0.59 to 0.81; 223 participants, [Analysis 5.3](#)) and fewer women with antenatal parasitaemia (RR 0.80, 95% CI 0.71 to 0.91; 223 participants, [Analysis 5.4](#)), but there was no difference for haemoglobin (200 participants, [Analysis 5.2](#)). The difference in mean birthweight tended towards favouring proguanil, but this was not significant (197 participants, [Analysis 6.3](#)).

2.2. Sulfadoxine-pyrimethamine versus chloroquine

Two trials examined this comparison; both were conducted in Africa in low-parity women ([Schultz 1994](#); [Kayentao 2005](#)). There was no significant difference between the two interventions for the number of women with severe anaemia (717 participants, 1 trial, [Analysis 5.1](#)), but fewer women in the sulfadoxine-pyrimethamine group had antenatal parasitaemia (RR 0.71, 95% CI 0.56 to 0.91; 848 participants, 2 trials, [Analysis 5.4](#)) and placental malaria (RR 0.75, 95% CI 0.60 to 0.95; 831 participants, 2 trials [Analysis 5.5](#)). There was no significant difference for the number of neonatal deaths (696 participants, 1 trial, [Analysis 6.1](#)), preterm births (828 participants, 2 trials, [Analysis 6.2](#)), or mean birthweight (719 participants, 1 trial, [Analysis 6.3](#)); however, low birthweight was less common with sulfadoxine-pyrimethamine (RR 0.77, 95% CI 0.61 to 0.97; 828 participants, 2 trials, [Analysis 6.4](#)).

DISCUSSION

Prophylaxis with a variety of antimalarial drugs or IPT with sulfadoxine-pyrimethamine in women having their first or second baby is associated with fewer women having severe anaemia and fewer perinatal deaths. The size of the effect for severe anaemia is considerable, while the size of the effect with perinatal mortality is more modest. There was no obvious effect when prophylaxis or IPT was given to all women regardless of the number of previous pregnancies. Malaria parasitaemia in the blood or the placenta is also less common with prophylaxis or IPT.

For infants, the review shows emerging evidence of an effect on perinatal death in low-parity women. This also corresponds with the effect seen on birthweight, with fewer low birthweight infants in these women. Women with more than two previous pregnancies may accrue small benefits from prophylaxis, but there are insufficient data to demonstrate or refute this.

In [Fleming 1985](#), some women in the intervention group also received iron or folic acid, or both, and in these women growth (height) also increased during pregnancy. The nutritional supplementation (not the prophylaxis) appeared to assist maternal growth in pregnancy and reduce the risk of Caesarean section.

We anticipated that there may be differences in effect between women living in areas where malaria is endemic and those living in epidemic areas. We know that host immunity means that malaria illness in semi-immune women is less severe than in women who have no host immunity. Thus it is reasonable to expect there to be differences in effects of preventive measures for malaria in pregnancy between women living in areas where malaria is highly endemic and women have acquired some host resistance compared with women living in areas where malaria is less common or occurs in epidemics and a malaria infection is likely to be associated

with a more severe illness. We were unable to stratify the analysis to explore for these differences because there were too few trials.

Trials on this question are not easy to conduct, particularly when mortality outcomes are sought, and a meta-analysis has something to offer by combining results from the different trials. Apart from the trial from The Gambia (Greenwood 1989), the recording of pregnancy outcome data in the trials was largely dependent on delivery in hospital. The large number of women lost or excluded from the final analyses could potentially mean the more disadvantaged groups were excluded from the results.

Much of the research emphasis has been on drugs for prevention, rather than prompt and appropriate treatment of illness episodes, including anaemia. Pregnant women need access to services that can provide treatment for illness episodes and anaemia. It may be that prophylaxis is an appropriate approach where such services are not available because the health system is insufficient to provide clinical care for illness episodes. An additional advantage of IPT could be in terms of adherence.

AUTHORS' CONCLUSIONS

Implications for practice

Routine antimalarial drugs have been shown to reduce antenatal parasitaemia and fever in pregnant women living in areas with endemic malaria. For women in their first or second pregnancy, this intervention reduces the instances of severe antenatal anaemia, antenatal parasitaemia, and perinatal deaths, and it has a positive effect on birthweight.

Even if quite modest, these effects may well be worth pursuing. The sulfadoxine-pyrimethamine regimen is feasible and practical to implement. There are public health consequences to giving drugs regularly to women during pregnancy in terms of increasing the risk of drug resistance developing.

There remains a question over what policies to adopt when sulfadoxine-pyrimethamine resistance rises. As impregnated mosquito nets have been shown to be effective in pregnancy (Gamble 2006), then IPT may be used in combination with them. Nets, if used

in combination with IPT or prophylaxis, may assist in preventing drug resistant strains of the parasite from spreading.

Implications for research

The confidence intervals for the meta-analysis for perinatal death in women in their first or second pregnancy just reaches statistical significance, but the point estimate indicates that the potential impact of this intervention on death could be high. Until the appropriate research is done, we cannot be sure how effective the intervention is in reducing perinatal deaths.

Large simple trials implemented through routine health services measuring mortality outcomes are widely used in areas outside malaria. Such a trial could compare prophylaxis or IPT with prompt regular treatment of morbidity in the mother (usually fever or anaemia). The outcomes should examine the effects on pregnancy outcome and death in the neonate and infant. Establishing whether there is an impact of routine prophylaxis or IPT is likely to re-emerge as an issue if sulfadoxine-pyrimethamine becomes ineffective through drug resistance, and policy makers are then faced with the potential of changing to effective drugs.

Iron deficiency is an important cause of anaemia in areas with malaria, so researchers contemplating a trial should consider a factorial design to examine also the impact of routine iron supplementation in malaria areas.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Challis 2004

Methods	Randomized controlled trial ^a
Participants	Low parity Number: 600 Inclusion criteria: nulliparous and primiparous women under 21 years Exclusion criteria: none stated
Interventions	1. Sulfadoxine-pyrimethamine (3 tablets): at enrolment and in third trimester 2. Placebo
Outcomes	1. Parasitaemia at second visit 2. Placenta malaria 3. Birthweight
Notes	Location: Mozambique Malaria transmission: 20% prevalence Drug resistance: chloroquine resistance present HIV prevalence: 10%

Cot 1992

Methods	Quasi-randomized controlled trial ^a
Participants	All women Number: 1464 Inclusion criteria: every pregnant woman attending urban maternal and child health centre Exclusion criteria: none stated
Interventions	1. Chloroquine: weekly 2. Nothing
Outcomes	1. Antenatal parasitaemia 2. Birthweight
Notes	Location: Burkina Faso Malaria transmission: hyperendemic, with seasonal transmission Drug resistance: chloroquine resistance may be present 19% parasitaemia in study population

Cot 1995

Methods	Quasi-randomized controlled trial ^a
Participants	Low parity Number: 266 Inclusion criteria: primigravidae antenatal clinic attendees Exclusion criteria: none stated
Interventions	1. Chloroquine: 300 mg per week until delivery 2. Nothing
Outcomes	1. Antenatal parasitaemia 2. Placental malaria 3. Birthweight
Notes	Location: Cameroon Malaria transmission: hyperendemic area with high transmission all year round Drug resistance: moderate chloroquine resistance

Fleming 1985

Methods	Randomized controlled trial ^a
Participants	Number: 200 Inclusion criteria: primigravidae under 16 years attending antenatal clinic; Hausa tribe Exclusion criteria: severe anaemia
Interventions	1. Proguanil daily 2. Placebo Other: all received single dose chloroquine on entry; folic acid and iron supplements included in randomized design
Outcomes	1. Antenatal parasitaemia and haemoglobin 2. Birthweight
Notes	Location: Nigeria Malaria transmission: unstable area with seasonal transmission Drug resistance: none

Greenwood 1989

Methods	Cluster-randomized controlled trial ^a
Participants	All women Number: 1049 Inclusion criteria: all women in study villages who became pregnant; some sub-studies only followed up primigravidae Exclusion criteria: none stated

Greenwood 1989 (Continued)

Interventions	1. Pyrimethamine and dapsone: weekly 2. Placebo Given by village people employed by the project
Outcomes	1. Antenatal parasitaemia 2. Birthweight 3. Packed cell volume 4. Maternal death 5. Perinatal death 6. Infant death
Notes	Location: The Gambia Malaria transmission: seasonal Drug resistance: none reported

Hamilton 1972

Methods	Quasi-randomized controlled trial ^a
Participants	All women Number: 1846 Inclusion criteria: attending antenatal clinic hospital with complications, or at high risk of complications; urban area. Exclusion criteria: none stated
Interventions	1. Chloroquine: weekly 2. Nothing Other: all women received iron
Outcomes	1. Antenatal parasitaemia and haemoglobin 2. Caesarean section 3. Birthweight
Notes	Location: Uganda Malaria transmission: low malaria endemicity (women < 5 % parasitaemia) Drug resistance: none

Kayentao 2005

Methods	Randomized controlled trial ^a
Participants	Low parity Number: 1163 Inclusion criteria: first or second pregnancy antenatal clinic attendees Exclusion criteria: > 15 km away; severely ill; sulfa sensitivity
Interventions	1. Chloroquine: treatment (25 mg/kg for 3 days; twice during pregnancy) then 300 mg per week 2. Sulfadoxine-pyrimethamine: twice during pregnancy

Kayentao 2005 (Continued)

	Other: all received iron and folic acid
Outcomes	1. Malaria blood slides 2. Haemoglobin at 34 weeks 3. Placental malaria 4. Birthweight 5. Neonatal death
Notes	Location: Mali Malaria transmission: year round, highest in rainy season Drug resistance: chloroquine in vivo resistance in < 5 years is moderate (85%) and sulfadoxine-pyrimethamine high efficacy

Menendez 1994

Methods	Cluster-randomized controlled trial ^a
Participants	Low parity Number: 230 Inclusion criteria: primigravidae resident in study area Exclusion criteria: none stated
Interventions	1. Pyrimethamine and dapsone: weekly 2. Placebo Given by village people employed by the project
Outcomes	1. Placental malaria 2. Birthweight
Notes	Location: The Gambia Malaria transmission: seasonal Drug resistance: none reported

Morley 1964

Methods	Quasi-randomized controlled trial ^a
Participants	All women Number: 429 Inclusion criteria: all pregnant women registered at dispensary Exclusion criteria: none stated
Interventions	1. Pyrimethamine: monthly 2. Placebo
Outcomes	1. Antenatal weight gain 2. Fever episodes 3. Parasitaemia

Morley 1964 (Continued)

	4. Placental infection 5. Birthweight 6. Perinatal mortality
Notes	Location: Nigeria Malaria transmission: holoendemic area Drug resistance: none

Mutabingwa 1991

Methods	Quasi-randomized controlled trial ^a
Participants	All women Number: 423 Inclusion criteria: all parities, willing to take prophylaxis and participate in the study Exclusion criteria: none stated
Interventions	1. Proguanil: daily 2. Chloroquine: weekly Other: all given 3 tablets of sulfadoxine-pyrimethamine at recruitment; and all given folic acid and iron
Outcomes	1. Antenatal parasitaemia 2. Antenatal illness 3. Birthweight
Notes	Location: Tanzania Malaria transmission: hyper/holoendemic malaria, seasonal transmission Drug resistance: chloroquine resistance present

Nahlen 1989

Methods	Randomized controlled trial ^a
Participants	All women Number: 71 Inclusion criteria: antenatal and attending hospital and health centre; < 34 weeks gestation; no recent chloroquine taken; parasitaemic > 500 parasites/ μ L blood Exclusion criteria: none stated
Interventions	1. Pyrimethamine (25 mg): weekly 2. Nothing Other: treated with two doses of chloroquine at recruitment; folic acid and iron given to all women
Outcomes	1. Antenatal parasitaemia
Notes	Location: Nigeria Malaria transmission: endemic area Drug resistance: possible pyrimethamine resistance present

Ndyomugenyi 2000

Methods	Randomized controlled trial ^a
Participants	Low parity Number: 860 Inclusion criteria: primigravidae Exclusion criteria: severe anaemia (< 8 g)
Interventions	1. Chloroquine 2. Chloroquine + iron + folate 3. Iron + folate
Outcomes	1. Haemoglobin 2. Birthweight
Notes	Location: Uganda Malaria transmission: hyperendemic area Drug resistance: unknown

Nosten 1994

Methods	Randomized controlled trial ^a
Participants	All parities Number: 339 Inclusion criteria: antenatal attendees > 20 weeks of gestation Exclusion criteria: none stated
Interventions	1. Mefloquine: weekly 2. Nothing Other: treated antenatally if parasitaemic; given folic acid and iron if anaemic
Outcomes	1. Antenatal episodes of parasitaemia 2. Anaemia 3. Preterm birth 4. Birthweight 5. Perinatal death
Notes	Location: Thailand Malaria transmission: unstable malarious area (mesoendemic) Drug resistance: multiple drug resistance present

Parise 1998i

Methods	Quasi-randomized controlled trial ^a
Participants	Low parity Number: 2077 Inclusion criteria: antenatal clinic attendees; first or second pregnancy

Parise 1998i (Continued)

	Exclusion criteria: none stated
Interventions	1. Sulfadoxine-pyrimethamine: treatment dose, repeated in late pregnancy 2. No intermittent preventive treatment, sulfadoxine-pyrimethamine given with recent history of fever or parasitaemia
Outcomes	1. Maternal anaemia 2. Mean haemoglobin 3. Placental infection 4. Birthweight 5. Preterm birth 6. Stillbirth 7. Neonatal death
Notes	Location: Kenya Malaria transmission: hyperendemic area Drug resistance: chloroquine HIV seroprevalence : 26.9% of study population

Parise 1998ii

Methods	As for Parise 1998i
Participants	As for Parise 1998i
Interventions	1. Sulfadoxine-pyrimethamine: monthly 2. No intermittent preventive treatment, sulfadoxine-pyrimethamine given with recent history of fever or parasitaemia
Outcomes	As for Parise 1998i
Notes	As for Parise 1998i

Schultz 1994

Methods	Quasi-randomized controlled trial ^a
Participants	Low parity Number: 357 Inclusion criteria: all parity 1 or 2; 16 to 32 weeks gestation Exclusion criteria: none stated
Interventions	1. Chloroquine: 25 mg/kg treatment followed by 300 mg weekly to delivery 2. 1.5 g pyrimethamine + sulfadoxine initially followed by chloroquine 300 mg weekly to delivery 3. 1.5 g pyrimethamine plus sulfadoxine initially and repeated in the third trimester
Outcomes	1. Parasitaemia at delivery 2. Placental malaria 3. Mean birthweight 4. Low birthweight

Schultz 1994 (Continued)

	5. Preterm
Notes	Location: Malawi Malaria transmission: hyperendemic Drug resistance: chloroquine-resistant malaria present

Shulman 1999

Methods	Randomized controlled trial ^a
Participants	Low parity Number: 1264 Inclusion criteria: primigravidae attending antenatal clinics at a health centre (1) or hospital (1); singleton pregnancy; 16 to 30 weeks gestation Exclusion criteria: severely anaemic and sick patients excluded
Interventions	1. Sulfadoxine-pyrimethamine: recruited at 16 to 19 weeks (2 doses); 20 to 26 weeks (2 doses); 27 to 30 weeks (1 dose) 2. Placebo Other: ferrous sulphate; impregnated bed nets in use in the area
Outcomes	1 Antenatal: parasitaemia and haemoglobin at 34 weeks 2. Stillbirth 3. Neonatal death 4. Maternal death 5. Morbidity
Notes	Location: Kenya Malaria transmission: hyperendemic and mesoendemic areas Drug resistance: present

^aSee [Appendix 4](#) and [Appendix 5](#) for details on methods for generation of allocation sequence, allocation concealment, and blinding.

Characteristics of excluded studies [ordered by study ID]

Dolan 1993	Trial of impregnated mosquito nets
Helitzer 1994	4 clinics trying different methods to achieve adherence; not randomized
Martin 1982	Reported as randomized 100 women, but analysis is by whether women complied, and those that did not comply (37 participants) analysed as a separate group

(Continued)

McDermott 1988	Started as a randomized controlled trial, but discontinued when reports elsewhere noted an association between amodiaquine and agranulocytosis; trial then became an observational study with the 2 arms of the trial combined
McGready 2001	Trial of repellent
Pertet 1994	Possible randomized controlled trial; wrote to the authors in 1998; no response
Shulman 1998	Study of impregnated mosquito nets
Steketee 1996	Study conducted in Malawi in 1989 and published in a series of papers in 1996. The trial is a comparative trial of three different chloroquine (CQ) regimens and mefloquine (MQ). In each of the 4 centres where women were enrolled, 1 of the 3 CQ regimens was compared to a MQ regimen by alternation (days of the week). Of the 4220 women enrolled in the trial, 3077 were in the CQ group (total received CQ) and 1032 in the MQ group. This trial was excluded because we were not convinced that the allocation was unbiased. The method reported should lead to a 1 : 1 ratio of women given mefloquine : chloroquine. However, there were 4 times as many women in the chloroquine group. That there was a bias in allocation was supported by statistically and clinically significant differences (mean weight, literacy, socioeconomic status, haematocrit, and malaria infection ($P = 0.06$)) between the 2 groups (all CQ versus MQ). Inquiries to obtain additional information (since 1993) have been politely answered but no data have been forthcoming despite assurances that it is available. Also, no data of outcomes analysed by treatment group have yet been presented, apart from an incidence of low birthweight of 15% reported in the chloroquine group ('Mangochi Malaria Research Project'; see Sketekee 1996). However, the number of babies that this number was based on was not provided. Despite being the largest antimalarial chemoprophylaxis trial during pregnancy that we are aware of, because of the limitations listed above, we have excluded this trial

Characteristics of ongoing studies [ordered by study ID]

Mnyika 2000

Trial name or title	Randomized trial of alternative malaria chemoprophylaxis strategies among pregnant women in Kigoma, Tanzania
Methods	-
Participants	728 women
Interventions	1. Proguanil prophylaxis 2. Chloroquine prophylaxis 3. Chemotherapy when ill
Outcomes	Not available
Starting date	Not available
Contact information	Not available

Mnyika 2000 (Continued)

Notes	Baseline data published; no data published to date
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DATA AND ANALYSES

Comparison 1. Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Caesarean section	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Complicated labour	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Anaemia (any)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Haematocrit	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Need for blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Antenatal parasitaemia	2	328	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.33, 0.86]
8 At least one malaria infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Placental malaria	3	1236	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.26, 0.45]
10 Fever episodes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	4	2890	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.73, 1.43]
2 Stillbirth	2	1493	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.80, 2.84]
3 Neonatal death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Infant death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Preterm birth	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Mean birthweight	4	2671	Mean Difference (IV, Fixed, 95% CI)	19.10 [-19.08, 57.27]
7 Low birthweight	2	1438	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.83, 1.34]
8 High birthweight	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2	772	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.32, 2.98]
1.1 Prophylaxis	2	772	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.32, 2.98]
2 Caesarean section (prophylaxis only)	2	294	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.35, 2.59]
3 Severe antenatal anaemia	4	2809	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.50, 0.78]
3.1 Prophylaxis	1	566	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.41, 2.03]

3.2 Intermittent preventive treatment	3	2243	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.48, 0.76]
4 Anaemia (any)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Prophylaxis	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Mean haematocrit	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Prophylaxis	2	118	Mean Difference (IV, Fixed, 95% CI)	2.63 [1.36, 3.90]
6 Mean haemoglobin	3	1677	Mean Difference (IV, Fixed, 95% CI)	0.40 [0.23, 0.56]
6.1 Prophylaxis	1	566	Mean Difference (IV, Fixed, 95% CI)	0.40 [0.14, 0.66]
6.2 Intermittent preventive treatment	2	1111	Mean Difference (IV, Fixed, 95% CI)	0.40 [0.19, 0.61]
7 Antenatal parasitaemia	7	2906	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.17, 0.44]
7.1 Prophylaxis	3	334	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.05, 1.18]
7.2 Intermittent preventive treatment	4	2572	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.17, 0.45]
8 Women infected at least once (prophylaxis only)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Treatment for suspected malaria (prophylaxis only)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Placental malaria	6	1805	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.38, 0.72]
10.1 Prophylaxis	3	573	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.60, 0.85]
10.2 Intermittent preventive treatment	3	1232	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.27, 0.47]

Comparison 4. Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perinatal death	3	1986	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.53, 0.99]
1.1 Prophylaxis	2	749	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.41, 1.06]
1.2 Intermittent preventive treatment	1	1237	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.52, 1.17]
2 Stillbirth	6	3454	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.62, 1.21]
2.1 Prophylaxis	3	882	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.45, 1.24]
2.2 Intermittent preventive treatment	3	2572	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.62, 1.50]
3 Neonatal death	4	2505	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.44, 1.05]
3.1 Prophylaxis	1	349	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.39, 1.88]
3.2 Intermittent preventive treatment	3	2156	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.37, 1.05]
4 Infant death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Prophylaxis	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Preterm birth	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Intermittent preventive treatment	2	1051	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.64, 1.29]
6 Mean birthweight	9	2648	Mean Difference (IV, Fixed, 95% CI)	126.70 [88.64, 164.75]

6.1 Prophylaxis	6	1249	Mean Difference (IV, Fixed, 95% CI)	130.60 [81.01, 180.20]
6.2 Intermittent preventive treatment	3	1399	Mean Difference (IV, Fixed, 95% CI)	121.11 [61.76, 180.45]
7 Low birthweight	7	2350	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.46, 0.72]
7.1 Prophylaxis	4	951	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.40, 0.79]
7.2 Intermittent preventive treatment	3	1399	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.43, 0.78]
8 High birthweight	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Newborn malaria infection	2	639	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.16]
9.1 Prophylaxis	1	337	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.78, 1.31]
9.2 Intermittent preventive treatment	1	302	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 0.82]

Comparison 5. Any antimalarial regimen versus weekly chloroquine: maternal outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe anaemia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Sulfadoxine-pyrimethamine	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Haemoglobin	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Proguanil	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Fever episodes	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Proguanil	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Antenatal parasitaemia	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Proguanil	1	223	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.71, 0.91]
4.2 Sulfadoxine-pyrimethamine	2	848	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.56, 0.91]
5 Placental malaria	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Sulfadoxine-pyrimethamine	2	831	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.60, 0.95]

Comparison 6. Any antimalarial regimen versus weekly chloroquine: fetal outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neonatal death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Sulfadoxine-pyrimethamine	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 Preterm birth	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Sulfadoxine-pyrimethamine	2	828	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.52, 1.49]
3 Mean birthweight	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Proguanil	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

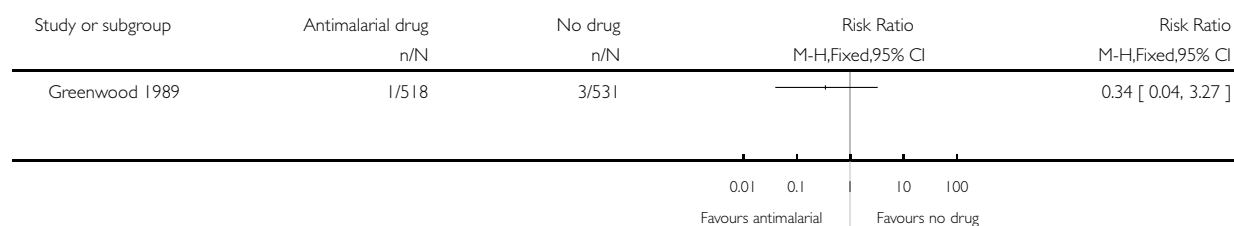
3.2 Sulfadoxine-pyrimethamine	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
4 Low birthweight	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Proguanil	1	134	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.54, 3.00]
4.2 Sulfadoxine-pyrimethamine	2	828	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.61, 0.97]

Analysis 1.1. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 1 Death.

Review: Drugs for preventing malaria in pregnant women

Comparison: 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes

Outcome: 1 Death

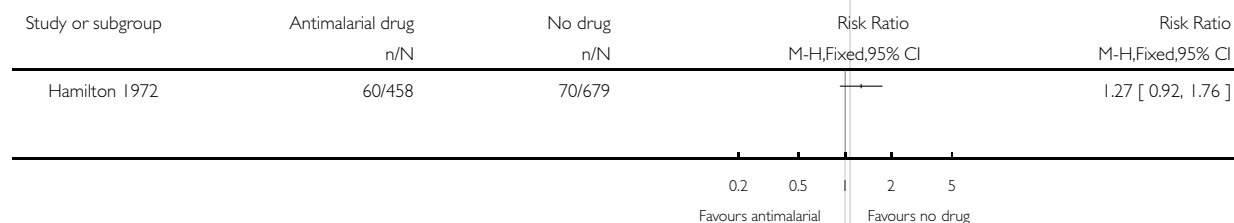


Analysis 1.2. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 2 Caesarean section.

Review: Drugs for preventing malaria in pregnant women

Comparison: 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes

Outcome: 2 Caesarean section

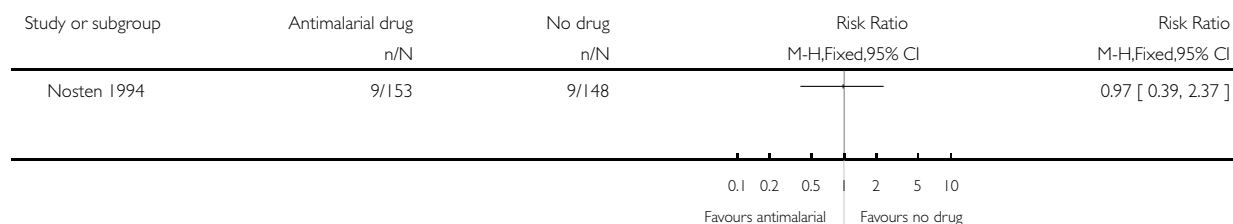


Analysis 1.3. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 3 Complicated labour.

Review: Drugs for preventing malaria in pregnant women

Comparison: 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes

Outcome: 3 Complicated labour

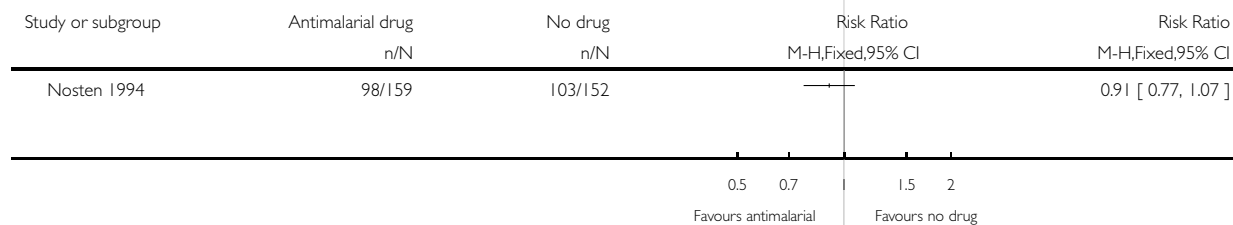


Analysis 1.4. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 4 Anaemia (any).

Review: Drugs for preventing malaria in pregnant women

Comparison: 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes

Outcome: 4 Anaemia (any)

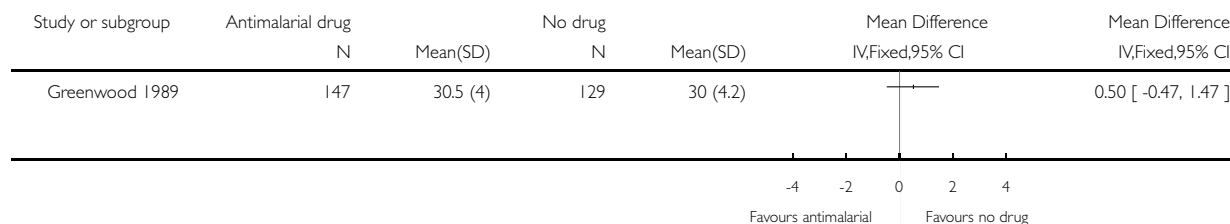


Analysis 1.5. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 5 Haematocrit.

Review: Drugs for preventing malaria in pregnant women

Comparison: 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes

Outcome: 5 Haematocrit

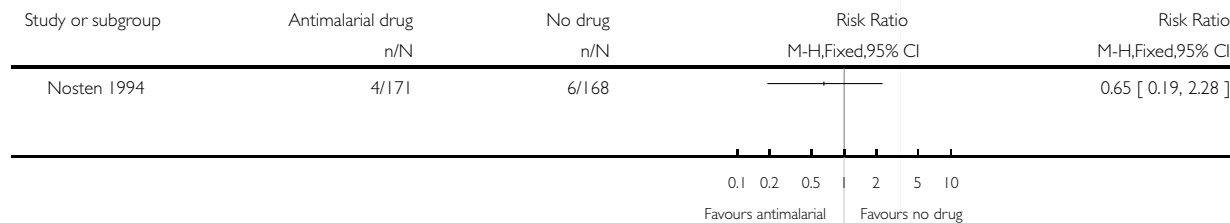


Analysis 1.6. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 6 Need for blood transfusion.

Review: Drugs for preventing malaria in pregnant women

Comparison: 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes

Outcome: 6 Need for blood transfusion

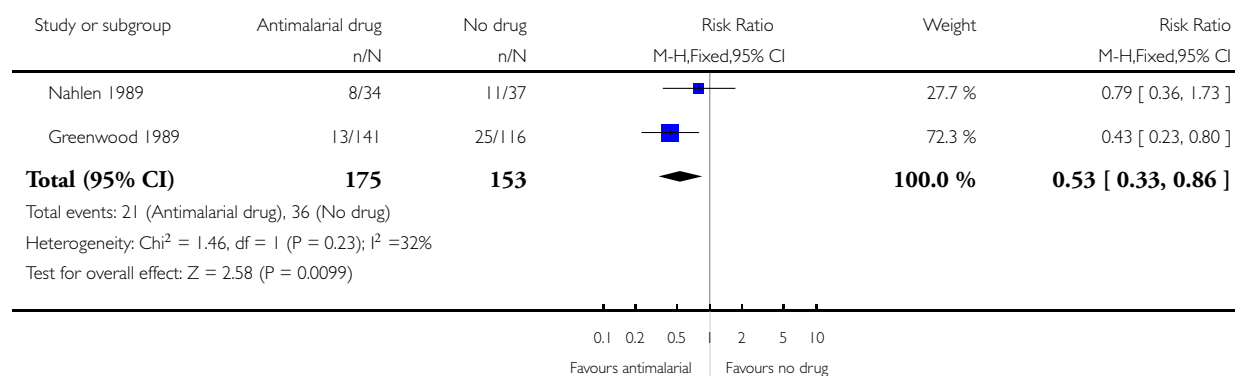


Analysis 1.7. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 7 Antenatal parasitaemia.

Review: Drugs for preventing malaria in pregnant women

Comparison: 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes

Outcome: 7 Antenatal parasitaemia

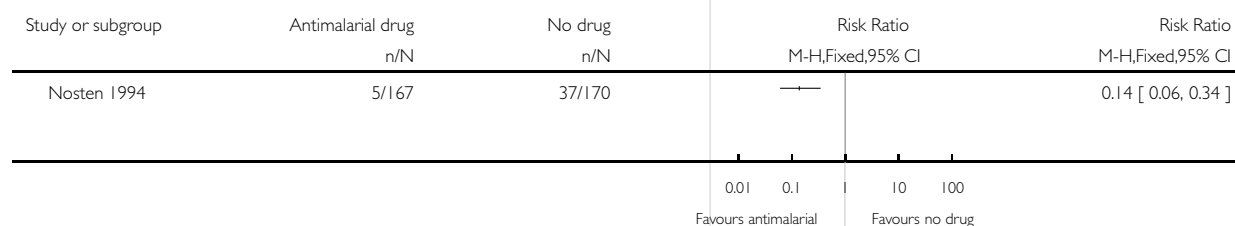


Analysis 1.8. Comparison 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 8 At least one malaria infection.

Review: Drugs for preventing malaria in pregnant women

Comparison: 1 Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes

Outcome: 8 At least one malaria infection

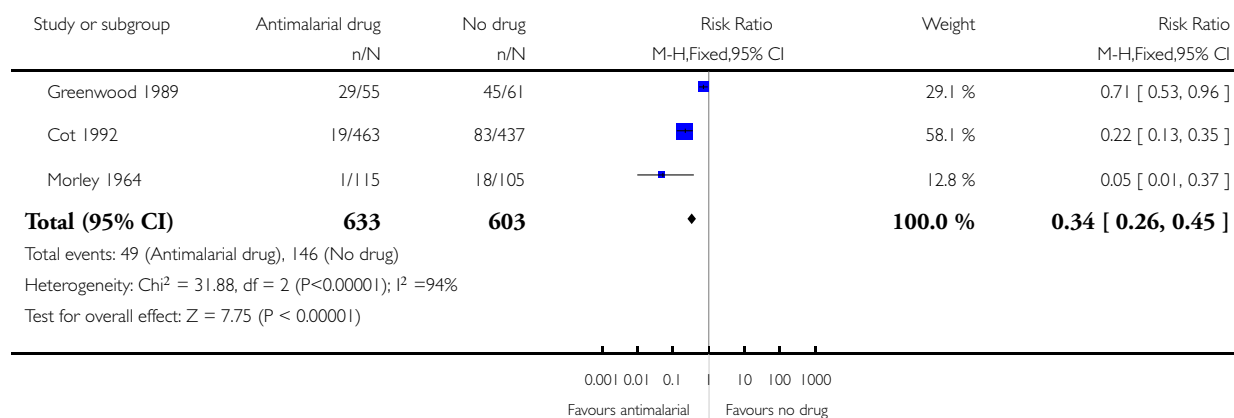


Analysis I.9. Comparison I Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 9 Placental malaria.

Review: Drugs for preventing malaria in pregnant women

Comparison: I Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes

Outcome: 9 Placental malaria

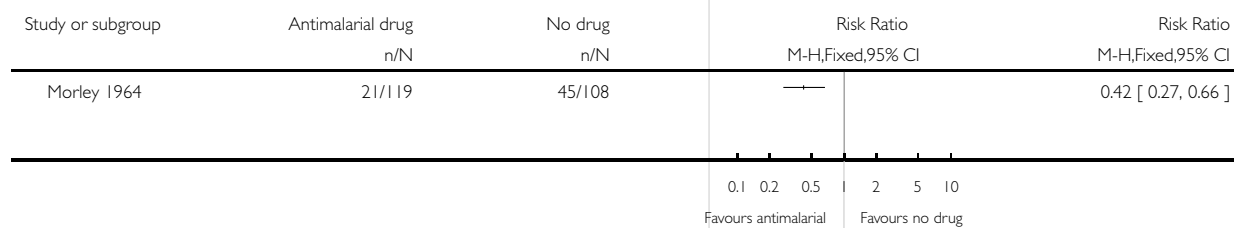


Analysis I.10. Comparison I Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes, Outcome 10 Fever episodes.

Review: Drugs for preventing malaria in pregnant women

Comparison: I Any antimalarial drug versus no drug (women of all parity groups): maternal outcomes

Outcome: 10 Fever episodes

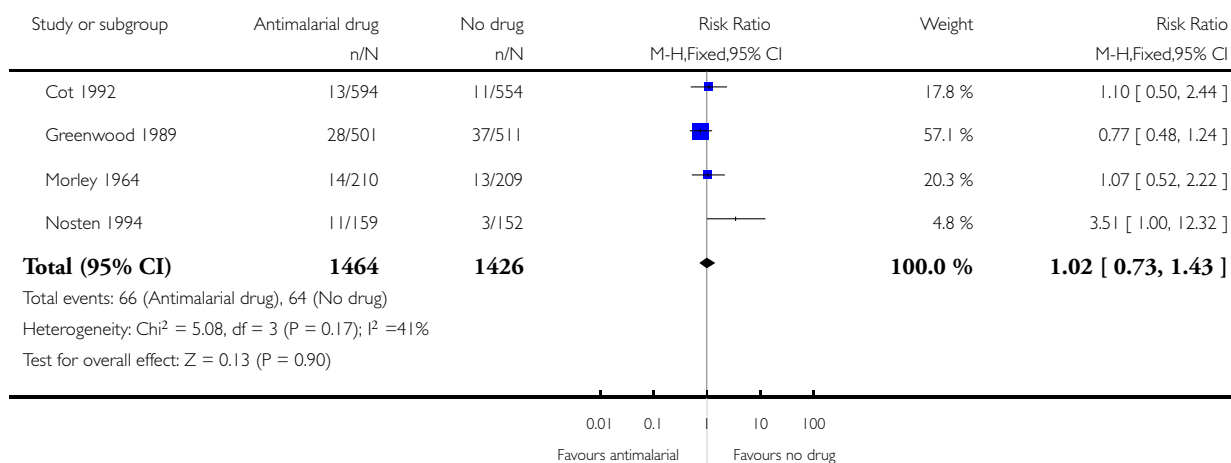


Analysis 2.1. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 1 Perinatal death.

Review: Drugs for preventing malaria in pregnant women

Comparison: 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes

Outcome: 1 Perinatal death

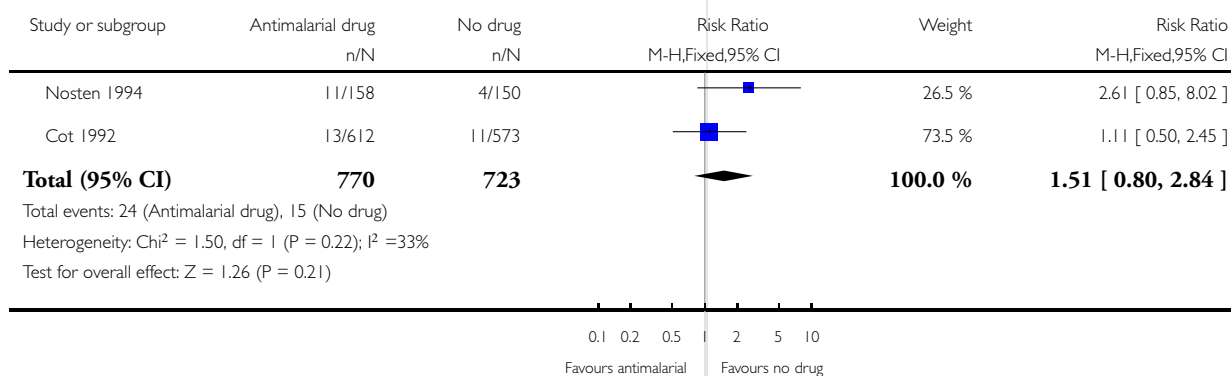


Analysis 2.2. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 2 Stillbirth.

Review: Drugs for preventing malaria in pregnant women

Comparison: 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes

Outcome: 2 Stillbirth

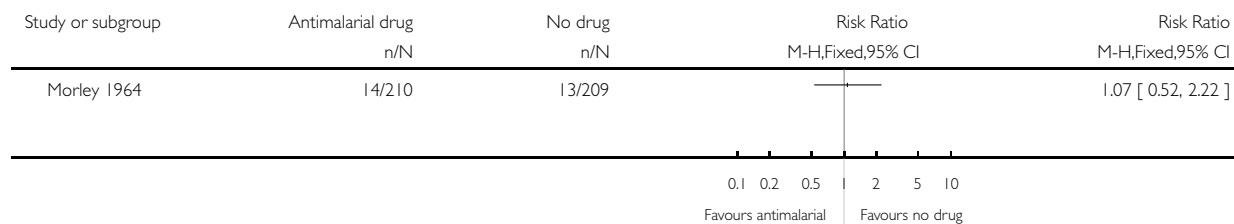


Analysis 2.3. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 3 Neonatal death.

Review: Drugs for preventing malaria in pregnant women

Comparison: 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes

Outcome: 3 Neonatal death

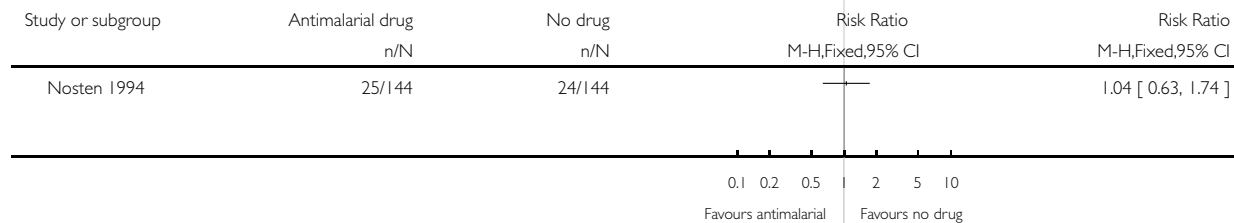


Analysis 2.4. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 4 Infant death.

Review: Drugs for preventing malaria in pregnant women

Comparison: 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes

Outcome: 4 Infant death

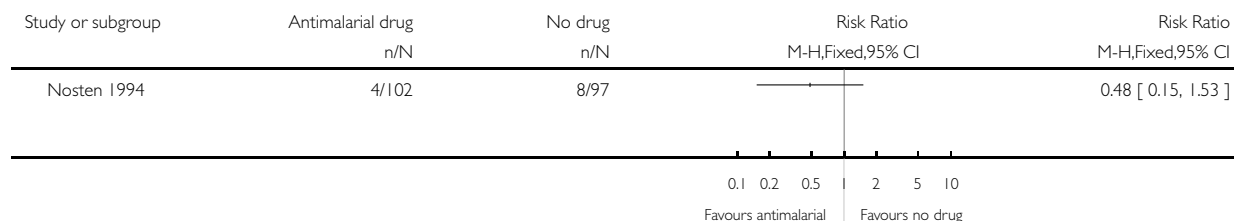


Analysis 2.5. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 5 Preterm birth.

Review: Drugs for preventing malaria in pregnant women

Comparison: 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes

Outcome: 5 Preterm birth

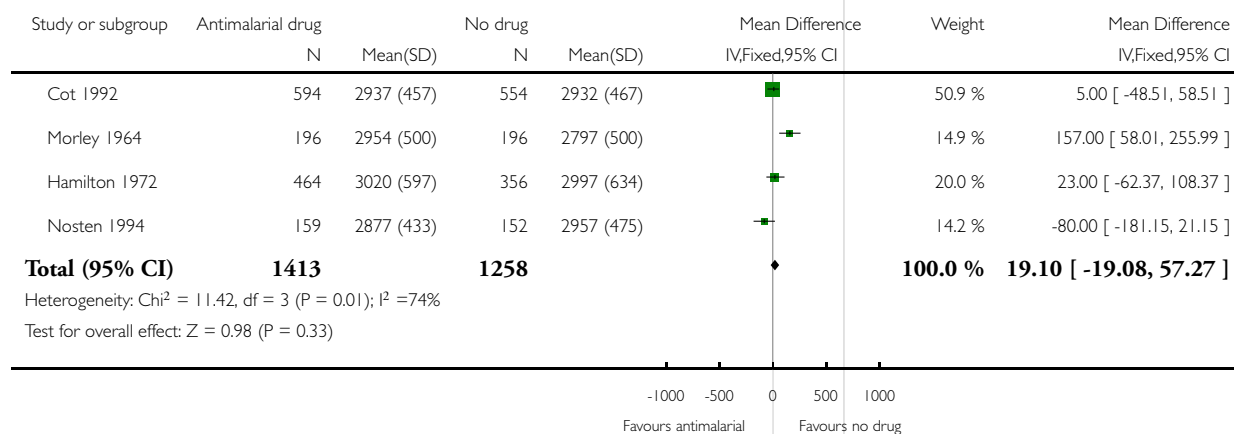


Analysis 2.6. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 6 Mean birthweight.

Review: Drugs for preventing malaria in pregnant women

Comparison: 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes

Outcome: 6 Mean birthweight

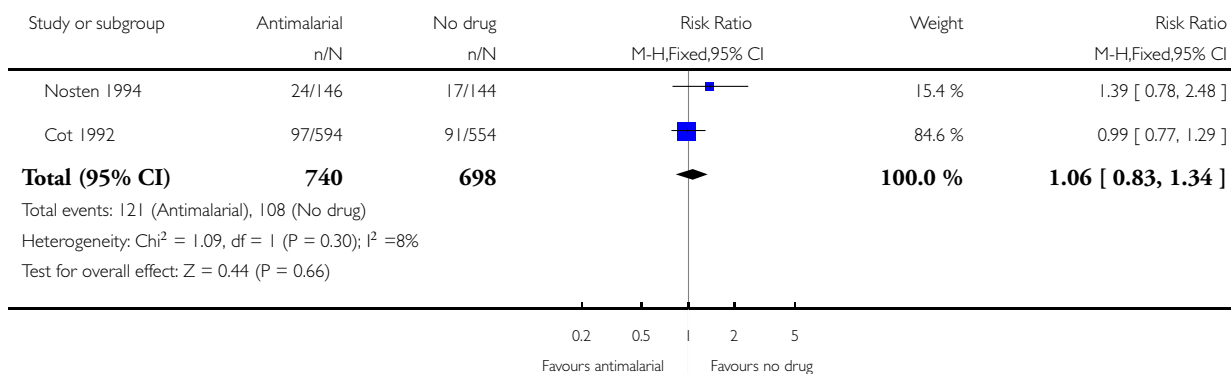


Analysis 2.7. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 7 Low birthweight.

Review: Drugs for preventing malaria in pregnant women

Comparison: 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes

Outcome: 7 Low birthweight

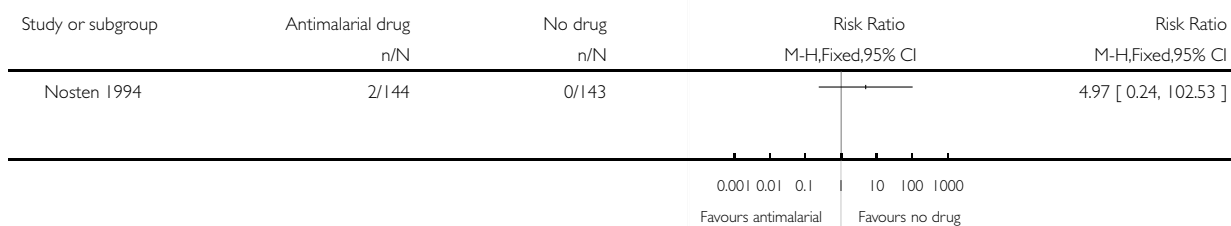


Analysis 2.8. Comparison 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes, Outcome 8 High birthweight.

Review: Drugs for preventing malaria in pregnant women

Comparison: 2 Any antimalarial drug versus no drug (women of all parity groups): fetal outcomes

Outcome: 8 High birthweight

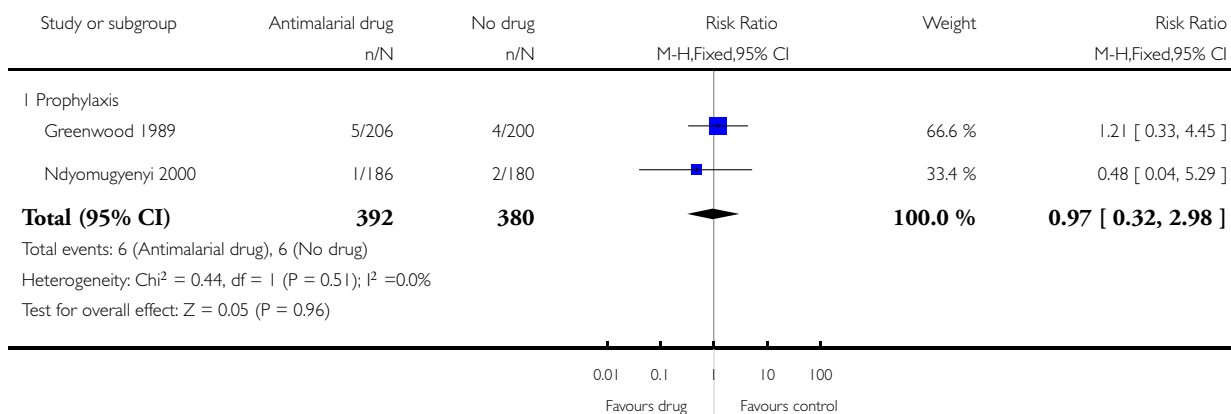


Analysis 3.1. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 1 Death.

Review: Drugs for preventing malaria in pregnant women

Comparison: 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes

Outcome: 1 Death

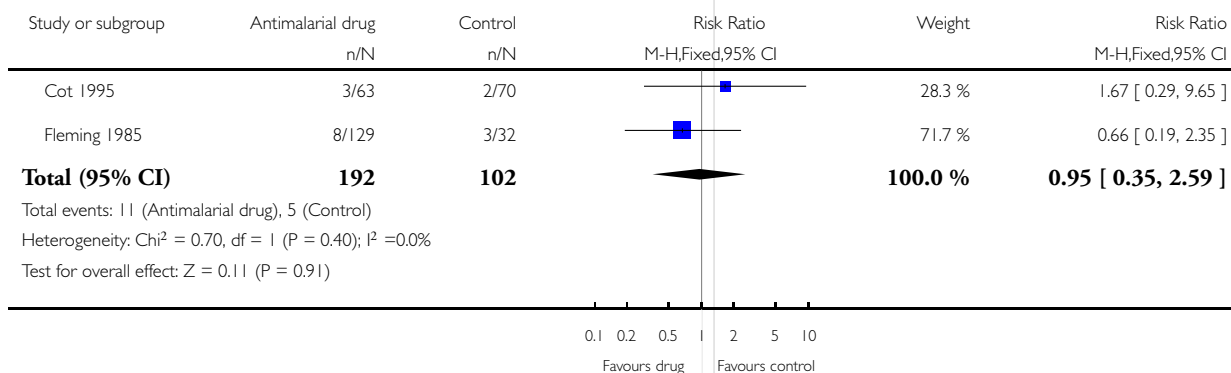


Analysis 3.2. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 2 Caesarean section (prophylaxis only).

Review: Drugs for preventing malaria in pregnant women

Comparison: 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes

Outcome: 2 Caesarean section (prophylaxis only)

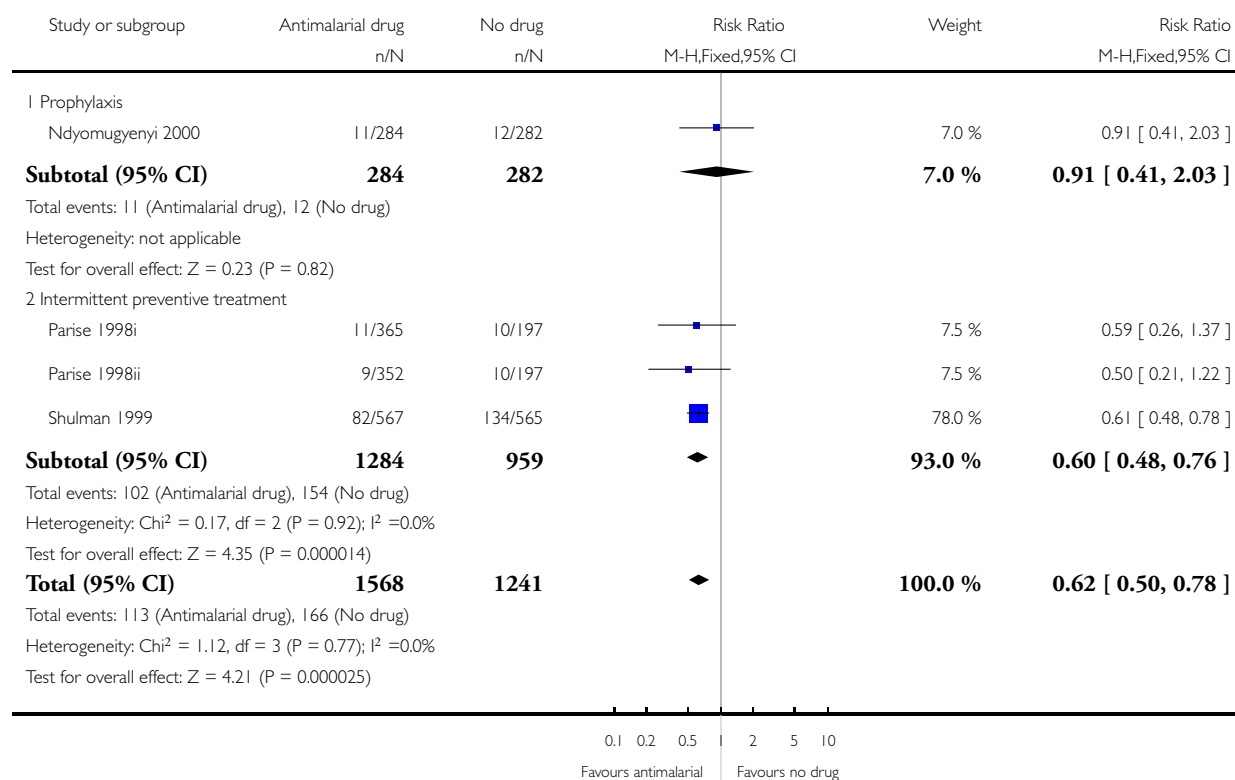


Analysis 3.3. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 3 Severe antenatal anaemia.

Review: Drugs for preventing malaria in pregnant women

Comparison: 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes

Outcome: 3 Severe antenatal anaemia

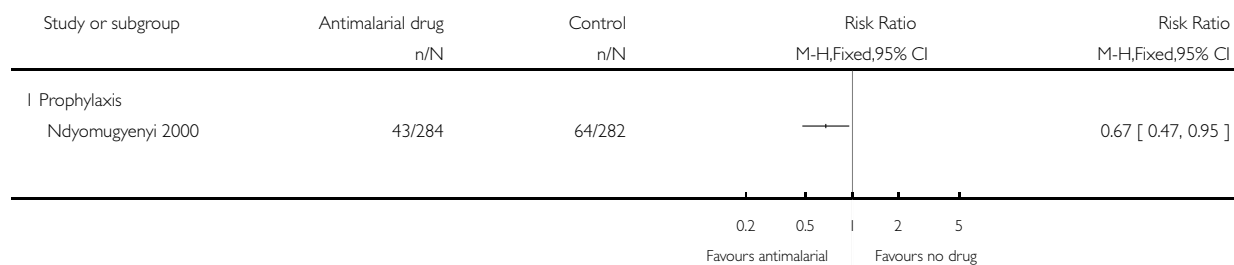


Analysis 3.4. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 4 Anaemia (any).

Review: Drugs for preventing malaria in pregnant women

Comparison: 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes

Outcome: 4 Anaemia (any)

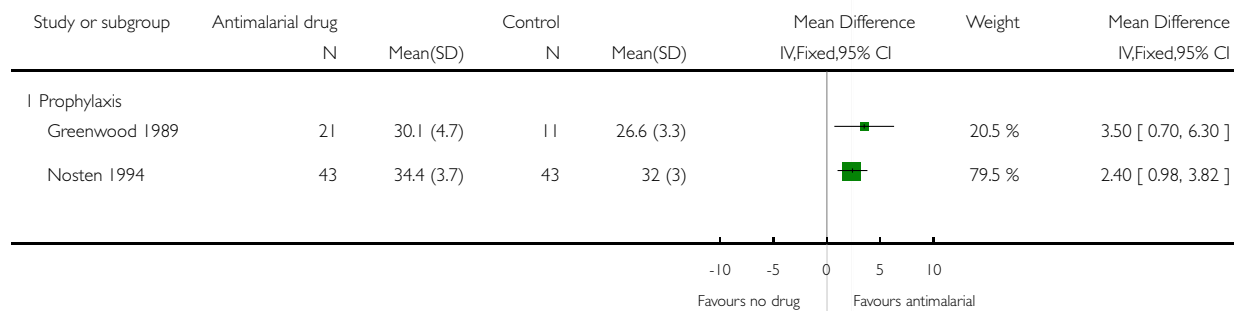


Analysis 3.5. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 5 Mean haematocrit.

Review: Drugs for preventing malaria in pregnant women

Comparison: 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes

Outcome: 5 Mean haematocrit

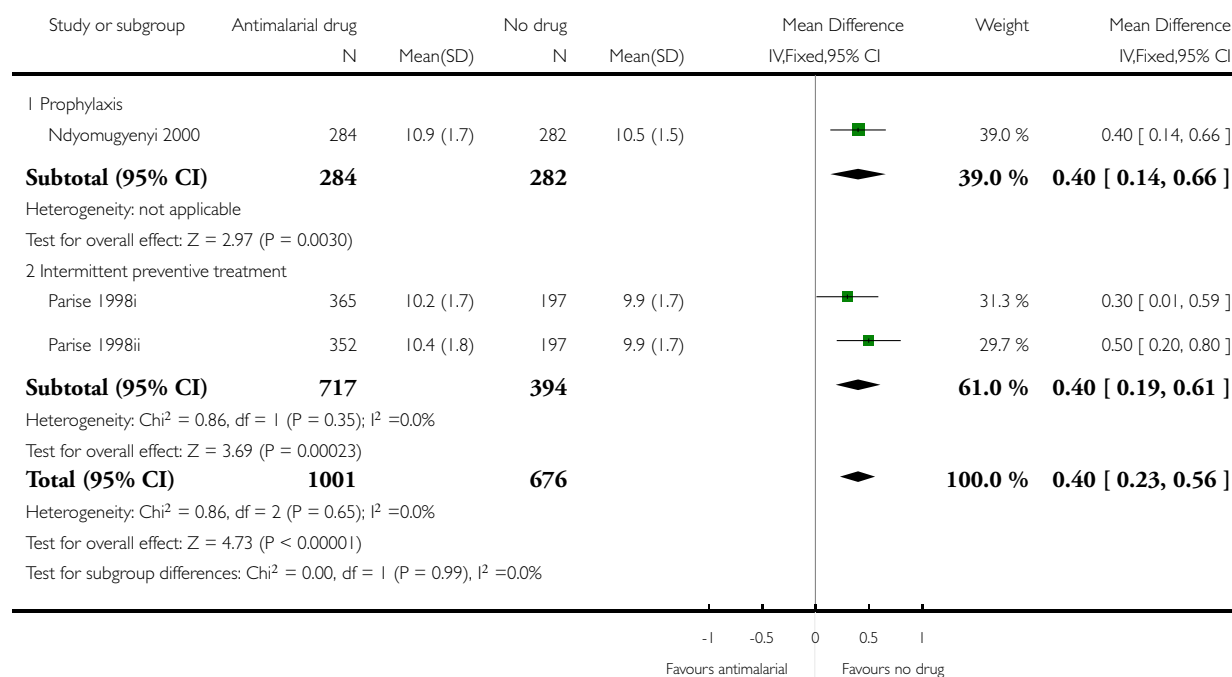


Analysis 3.6. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 6 Mean haemoglobin.

Review: Drugs for preventing malaria in pregnant women

Comparison: 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes

Outcome: 6 Mean haemoglobin

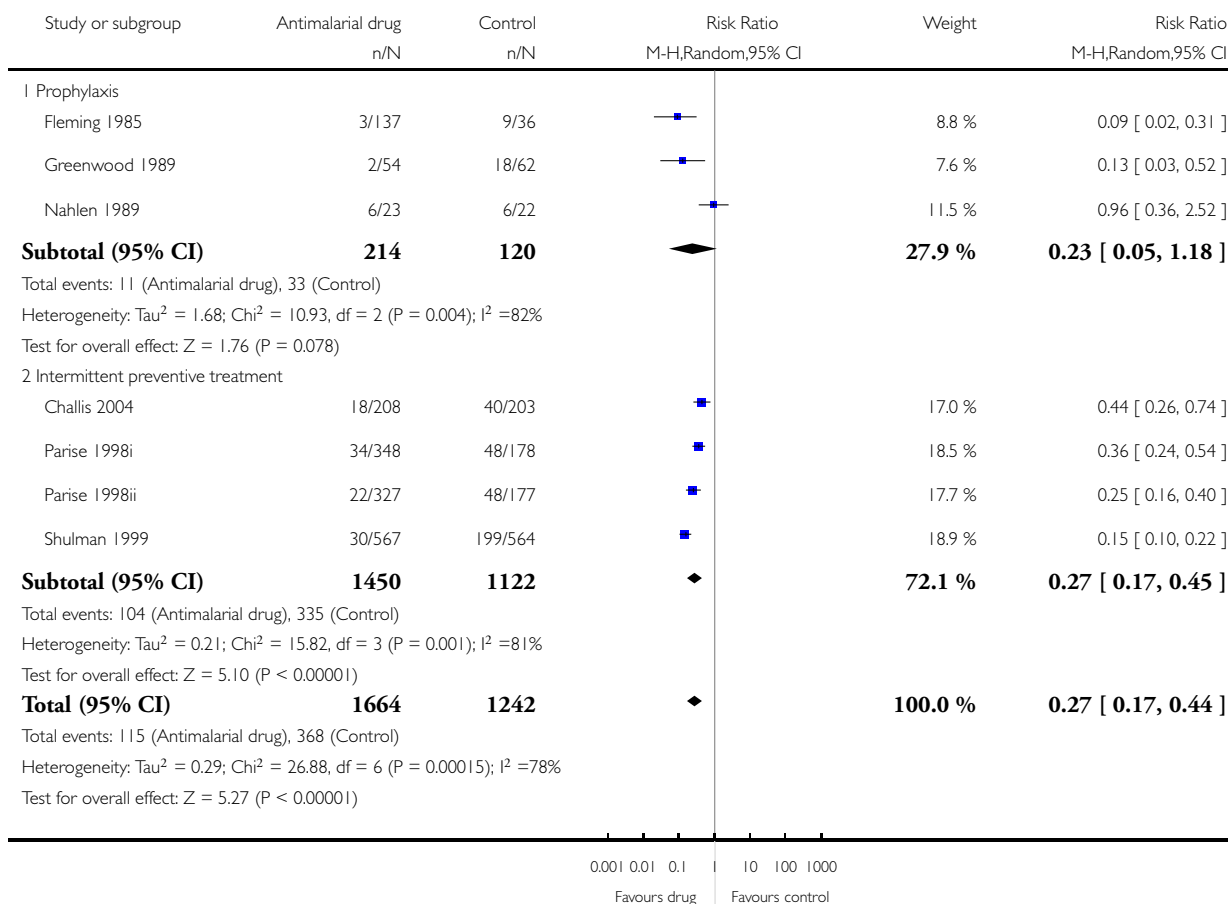


Analysis 3.7. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 7 Antenatal parasitaemia.

Review: Drugs for preventing malaria in pregnant women

Comparison: 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes

Outcome: 7 Antenatal parasitaemia

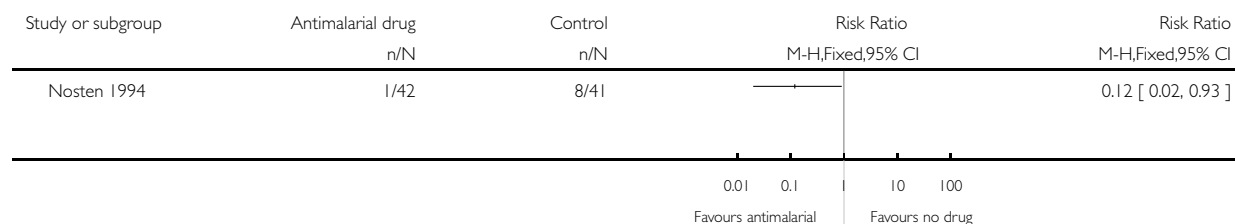


Analysis 3.8. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 8 Women infected at least once (prophylaxis only).

Review: Drugs for preventing malaria in pregnant women

Comparison: 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes

Outcome: 8 Women infected at least once (prophylaxis only)

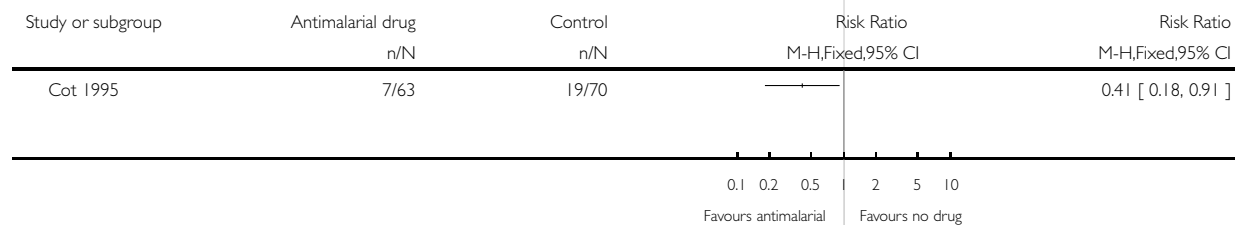


Analysis 3.9. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 9 Treatment for suspected malaria (prophylaxis only).

Review: Drugs for preventing malaria in pregnant women

Comparison: 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes

Outcome: 9 Treatment for suspected malaria (prophylaxis only)

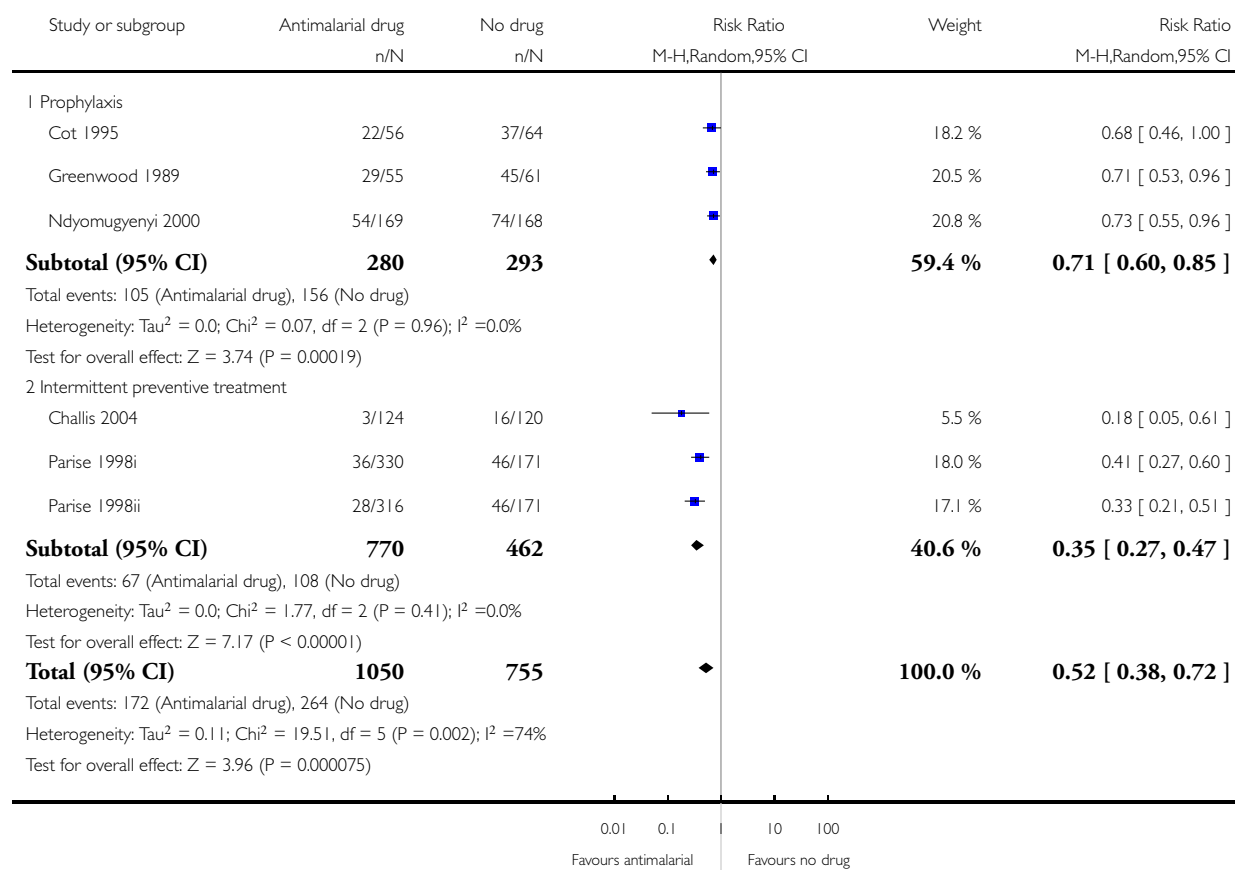


Analysis 3.10. Comparison 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes, Outcome 10 Placental malaria.

Review: Drugs for preventing malaria in pregnant women

Comparison: 3 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): maternal outcomes

Outcome: 10 Placental malaria

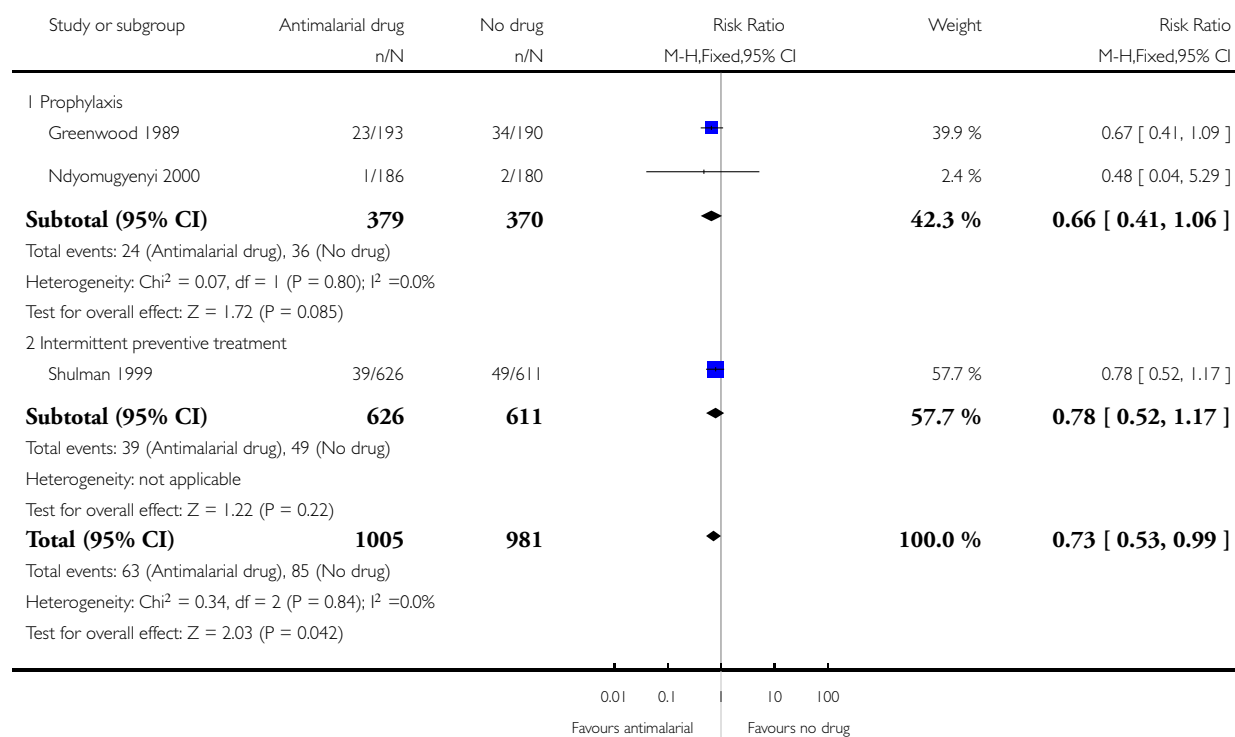


Analysis 4.1. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 1 Perinatal death.

Review: Drugs for preventing malaria in pregnant women

Comparison: 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes

Outcome: 1 Perinatal death

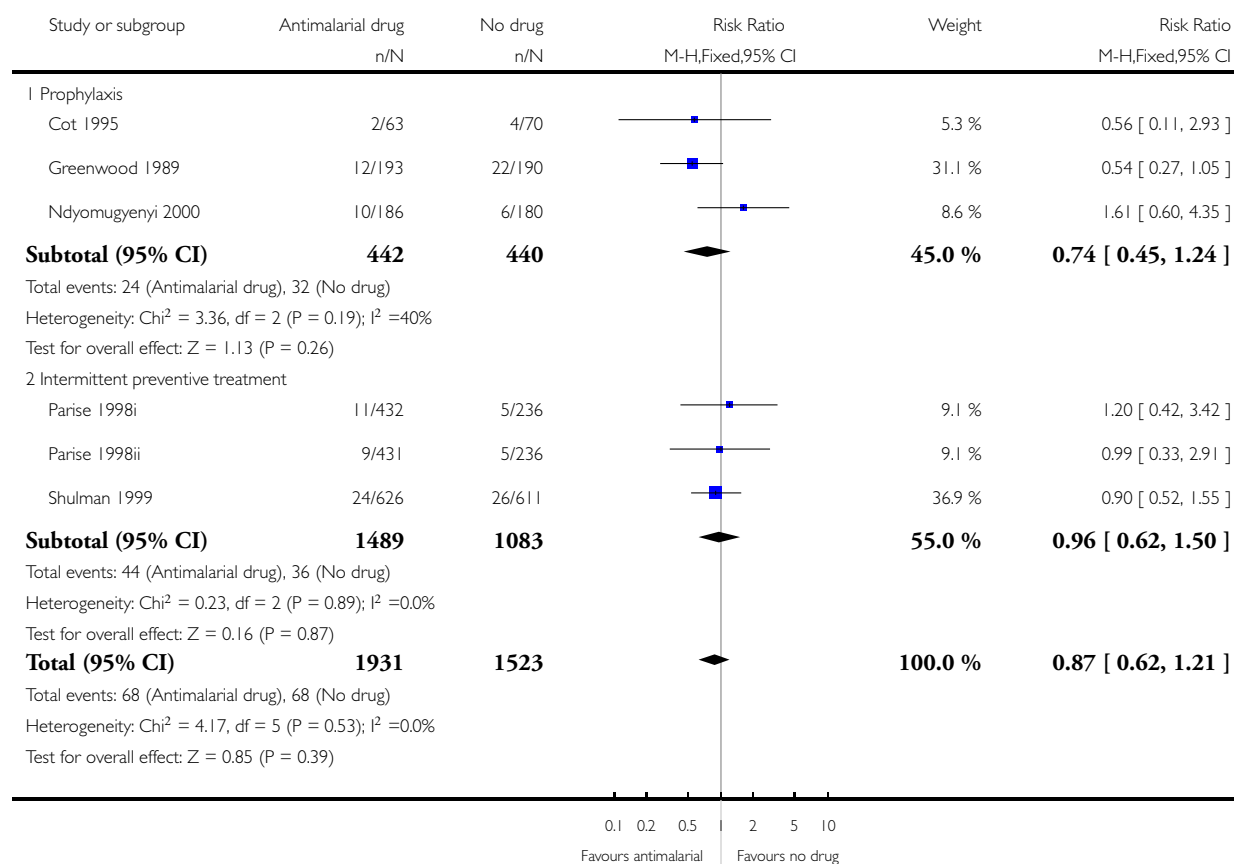


Analysis 4.2. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 2 Stillbirth.

Review: Drugs for preventing malaria in pregnant women

Comparison: 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes

Outcome: 2 Stillbirth

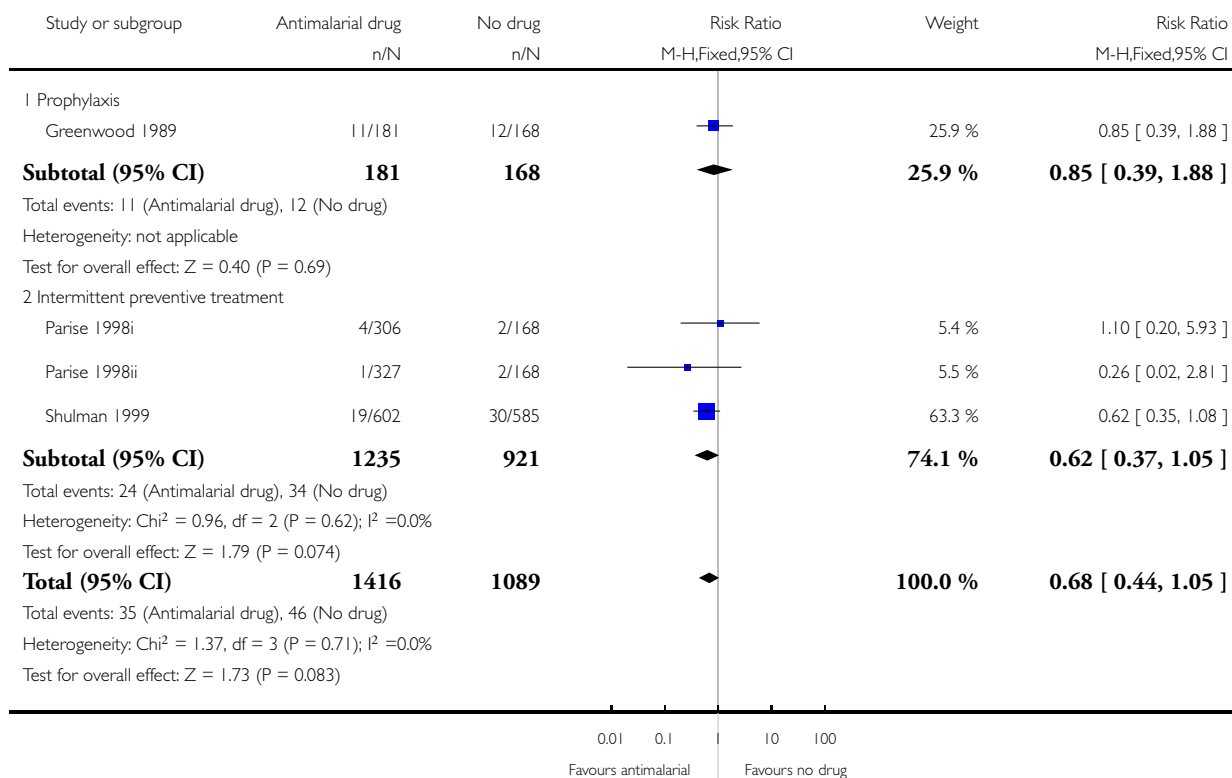


Analysis 4.3. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 3 Neonatal death.

Review: Drugs for preventing malaria in pregnant women

Comparison: 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes

Outcome: 3 Neonatal death



Analysis 4.4. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 4 Infant death.

Review: Drugs for preventing malaria in pregnant women

Comparison: 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes

Outcome: 4 Infant death

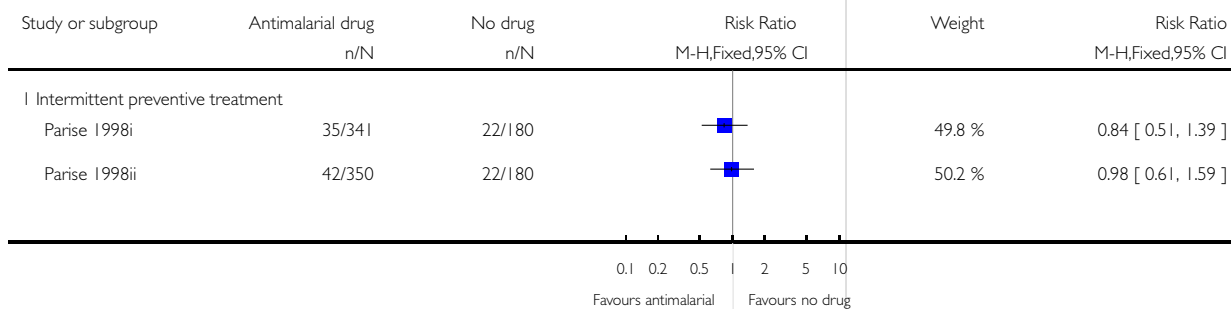


Analysis 4.5. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 5 Preterm birth.

Review: Drugs for preventing malaria in pregnant women

Comparison: 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes

Outcome: 5 Preterm birth

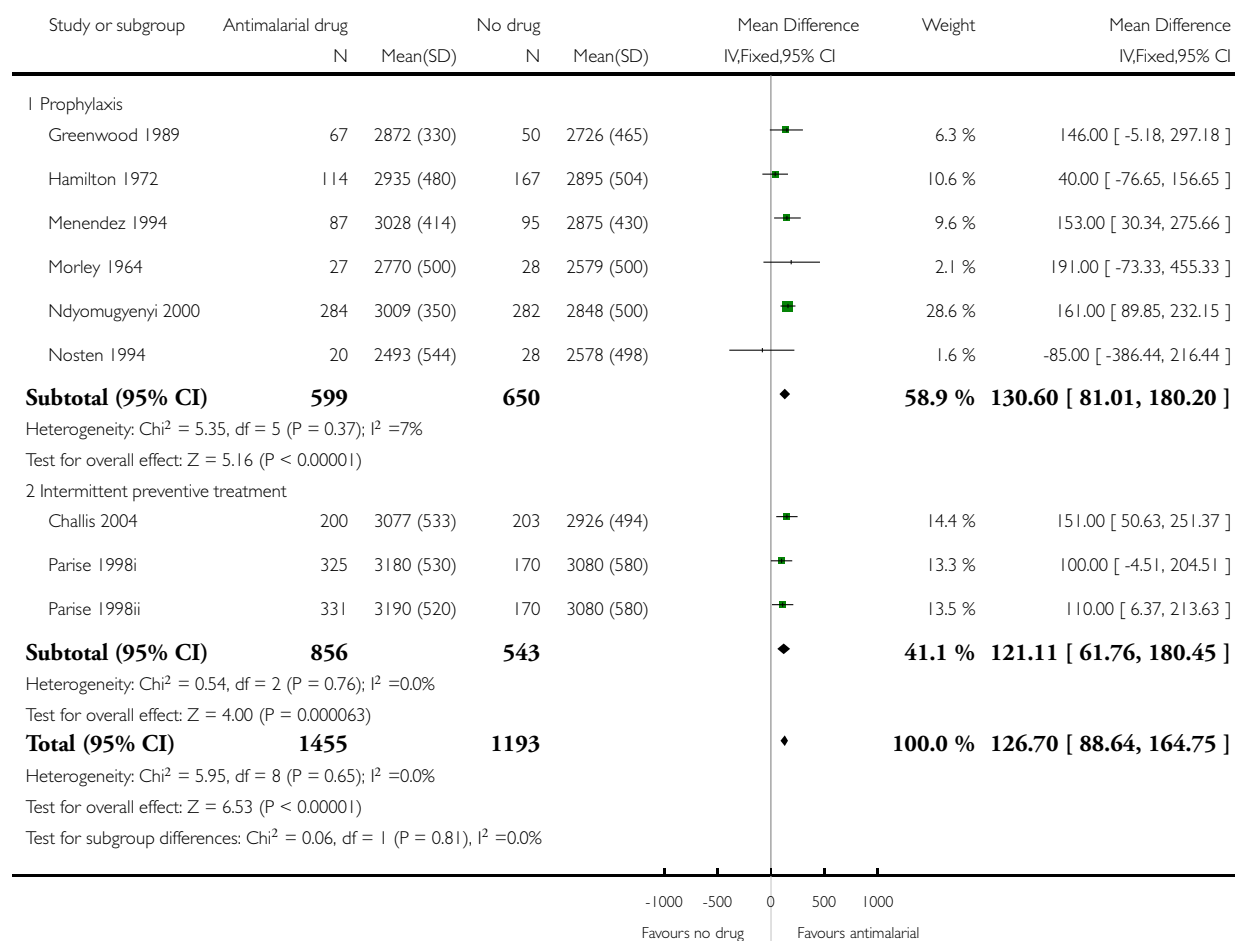


Analysis 4.6. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 6 Mean birthweight.

Review: Drugs for preventing malaria in pregnant women

Comparison: 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes

Outcome: 6 Mean birthweight

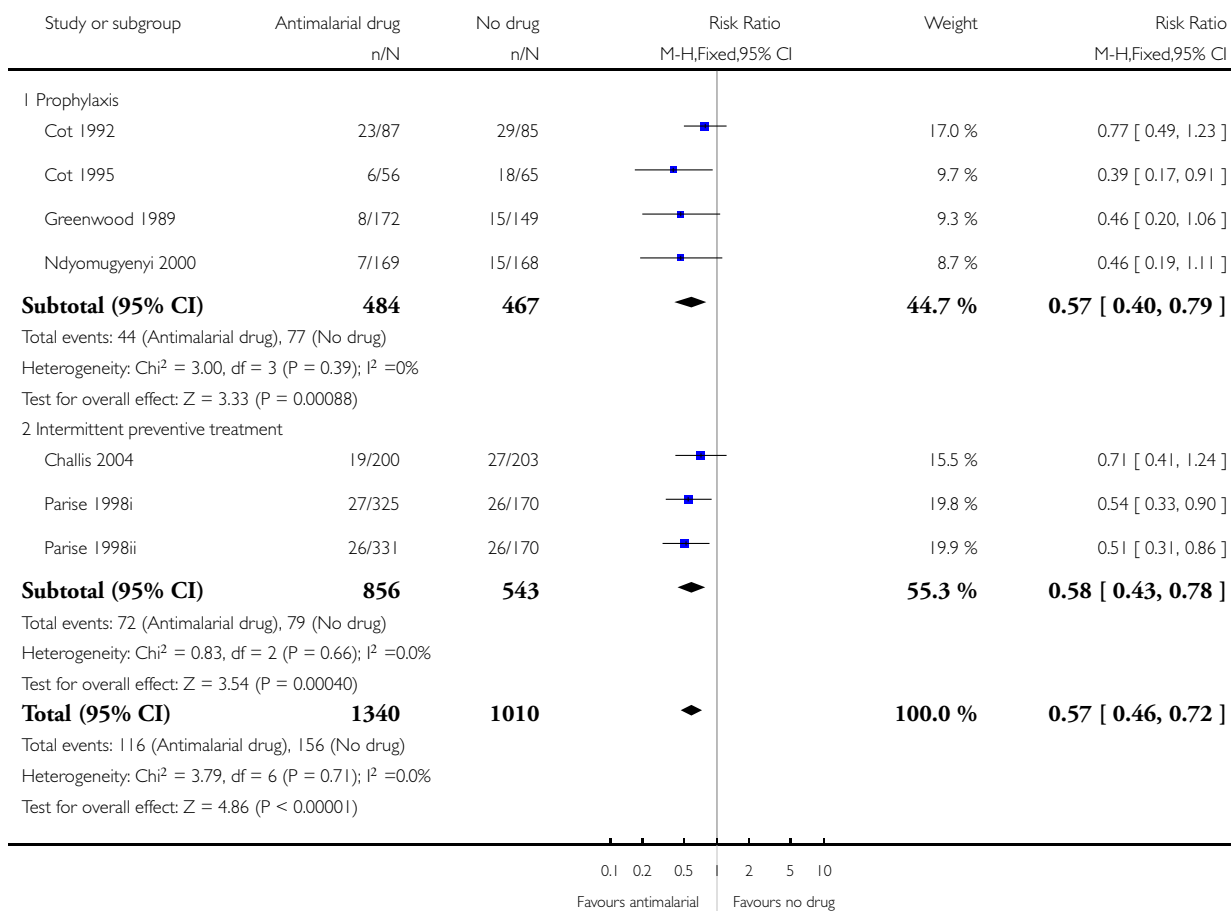


Analysis 4.7. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 7 Low birthweight.

Review: Drugs for preventing malaria in pregnant women

Comparison: 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes

Outcome: 7 Low birthweight

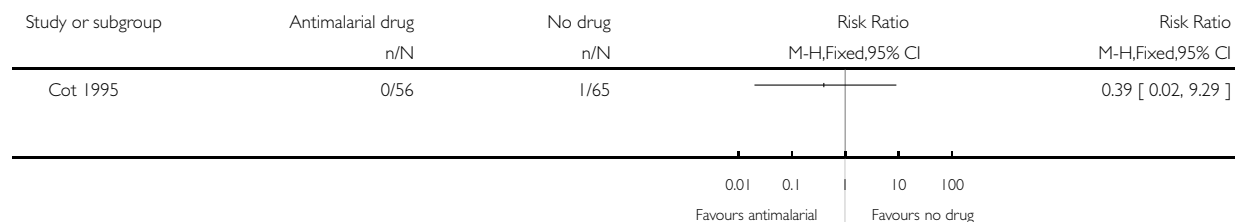


Analysis 4.8. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 8 High birthweight.

Review: Drugs for preventing malaria in pregnant women

Comparison: 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes

Outcome: 8 High birthweight

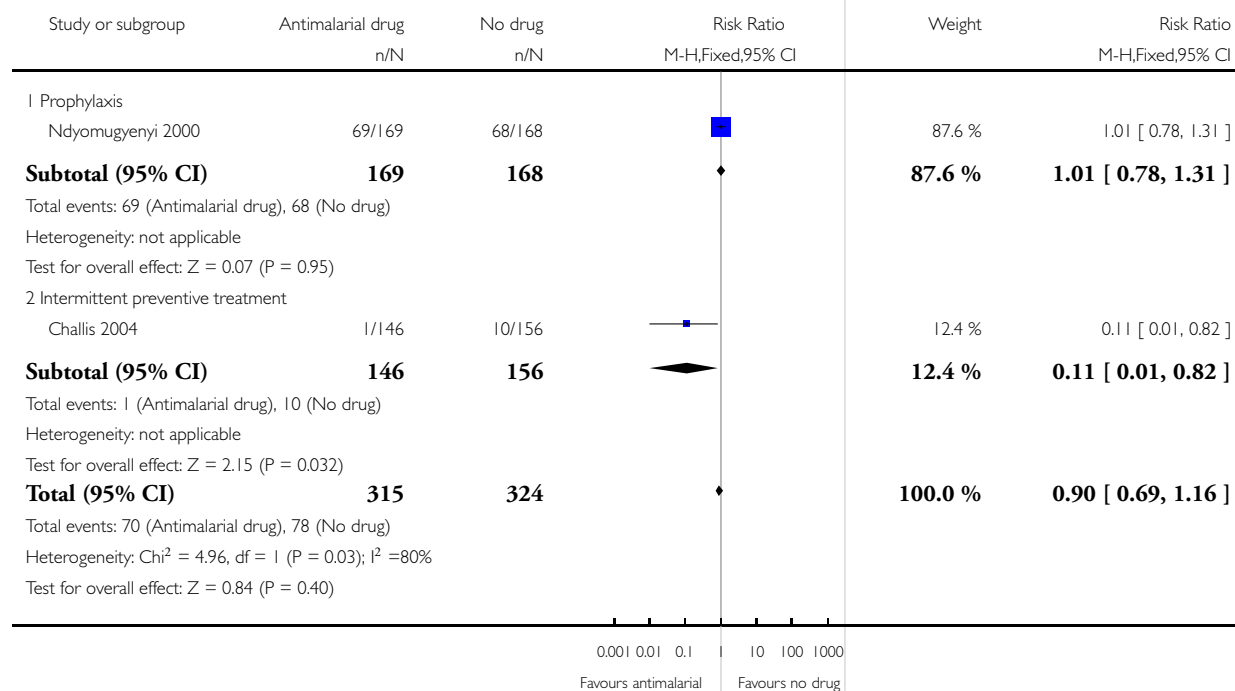


Analysis 4.9. Comparison 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes, Outcome 9 Newborn malaria infection.

Review: Drugs for preventing malaria in pregnant women

Comparison: 4 Any antimalarial drug prevention versus no drug (women in first or second pregnancy): fetal outcomes

Outcome: 9 Newborn malaria infection

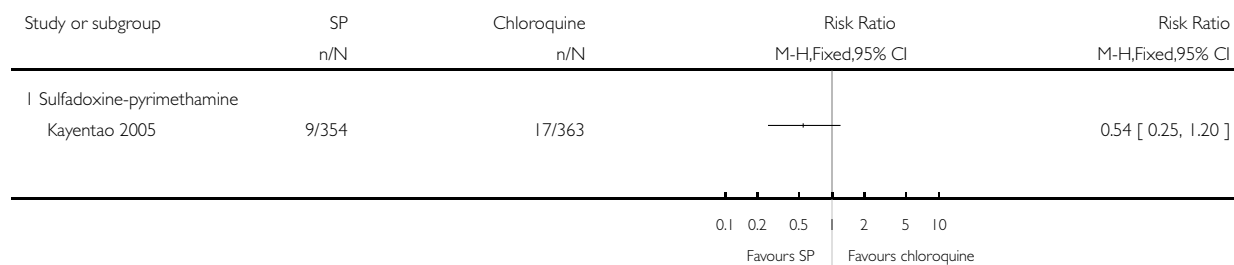


Analysis 5.1. Comparison 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes, Outcome 1 Severe anaemia.

Review: Drugs for preventing malaria in pregnant women

Comparison: 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes

Outcome: 1 Severe anaemia

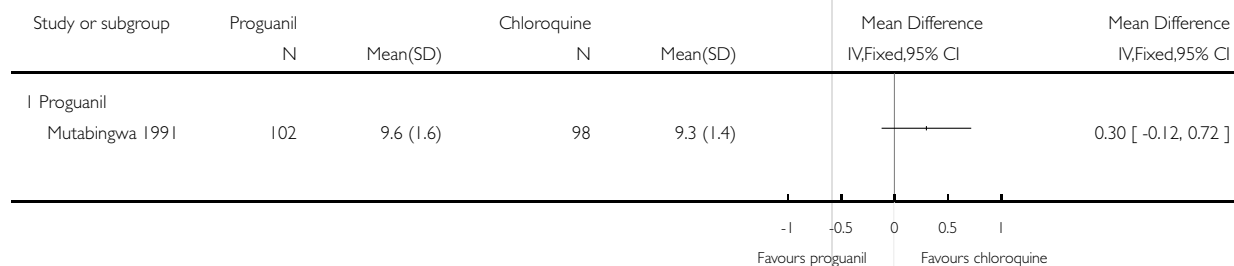


Analysis 5.2. Comparison 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes, Outcome 2 Haemoglobin.

Review: Drugs for preventing malaria in pregnant women

Comparison: 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes

Outcome: 2 Haemoglobin



Analysis 5.3. Comparison 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes, Outcome 3 Fever episodes.

Review: Drugs for preventing malaria in pregnant women

Comparison: 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes

Outcome: 3 Fever episodes

Study or subgroup	Proguanil n/N	Chloroquine n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
I Proguanil Mutabingwa 1991	72/116	96/107		0.69 [0.59, 0.81]

0.5 0.7 | 1.5 2
Favours proguanil Favours chloroquine

Analysis 5.4. Comparison 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes, Outcome 4 Antenatal parasitaemia.

Review: Drugs for preventing malaria in pregnant women

Comparison: 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes

Outcome: 4 Antenatal parasitaemia

Study or subgroup	Intervention drug n/N	Chloroquine n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
I Proguanil Mutabingwa 1991	85/116	98/107		100.0 %	0.80 [0.71, 0.91]
Subtotal (95% CI)	116	107		100.0 %	0.80 [0.71, 0.91]
Total events: 85 (Intervention drug), 98 (Chloroquine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.53 (P = 0.00042)					
2 Sulfadoxine-pyrimethamine					
Kayentao 2005	79/363	101/376		86.4 %	0.81 [0.63, 1.05]
Schultz 1994	2/71	12/38		13.6 %	0.09 [0.02, 0.38]
Subtotal (95% CI)	434	414		100.0 %	0.71 [0.56, 0.91]
Total events: 81 (Intervention drug), 113 (Chloroquine)					
Heterogeneity: Chi ² = 8.92, df = 1 (P = 0.003); I ² = 89%					
Test for overall effect: Z = 2.70 (P = 0.0069)					

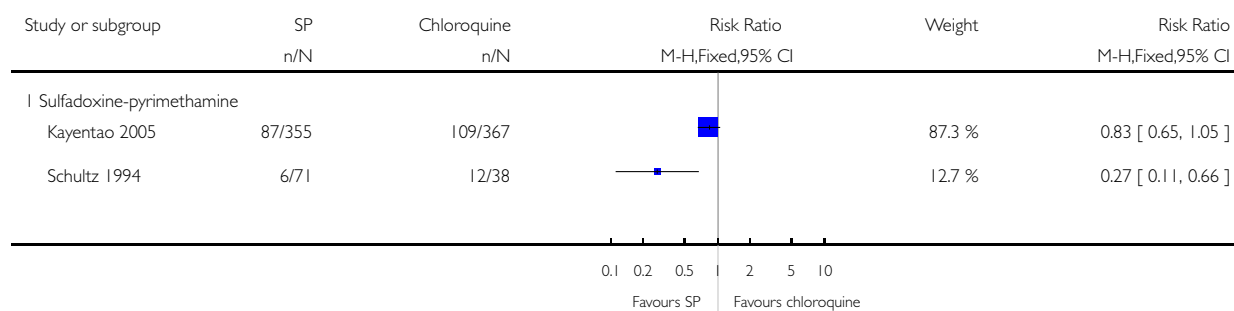
0.01 0.1 | 10 100
Favours intervention Favours chloroquine

Analysis 5.5. Comparison 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes, Outcome 5 Placental malaria.

Review: Drugs for preventing malaria in pregnant women

Comparison: 5 Any antimalarial regimen versus weekly chloroquine: maternal outcomes

Outcome: 5 Placental malaria

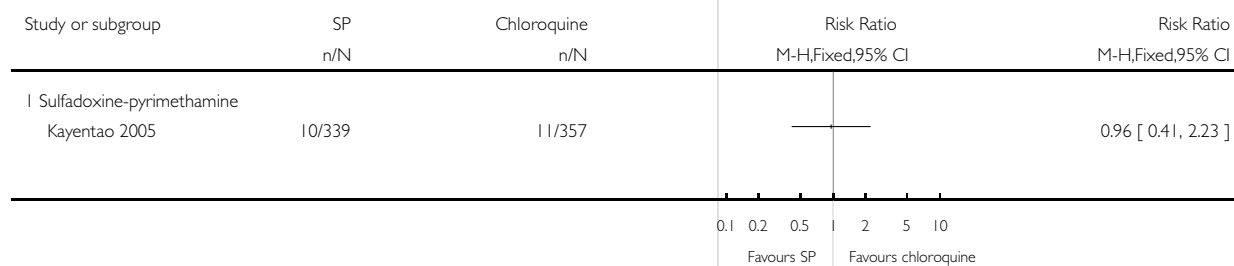


Analysis 6.1. Comparison 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes, Outcome 1 Neonatal death.

Review: Drugs for preventing malaria in pregnant women

Comparison: 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes

Outcome: 1 Neonatal death

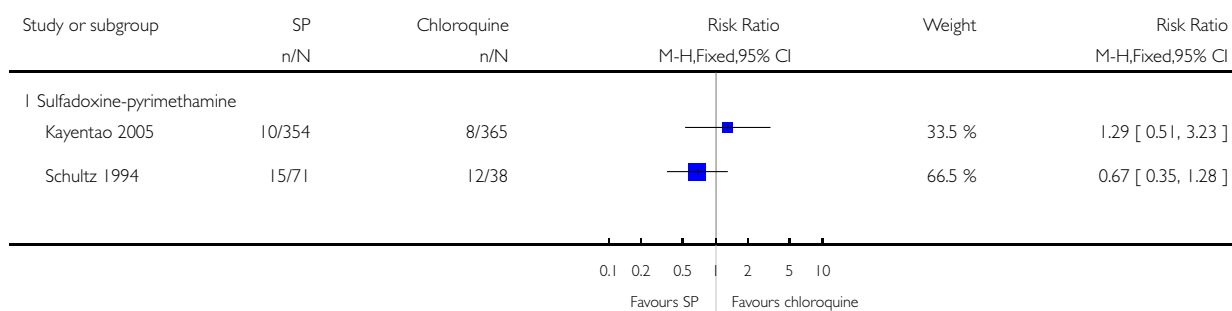


Analysis 6.2. Comparison 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes, Outcome 2 Preterm birth.

Review: Drugs for preventing malaria in pregnant women

Comparison: 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes

Outcome: 2 Preterm birth

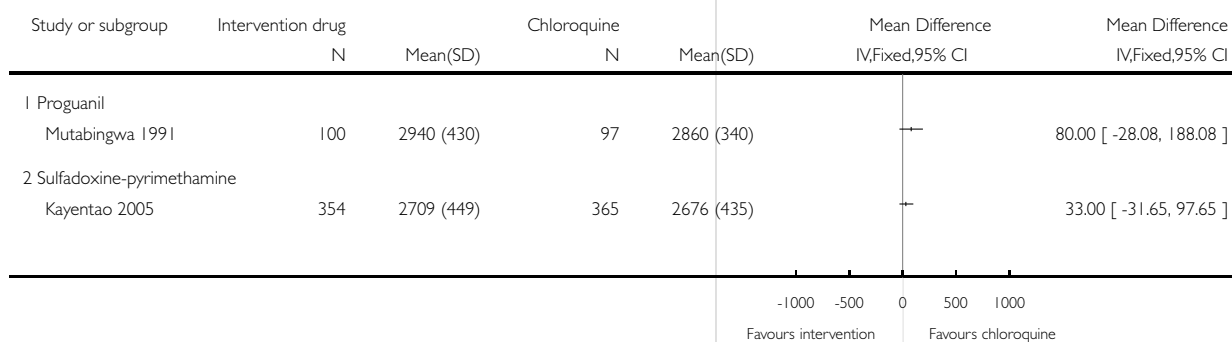


Analysis 6.3. Comparison 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes, Outcome 3 Mean birthweight.

Review: Drugs for preventing malaria in pregnant women

Comparison: 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes

Outcome: 3 Mean birthweight

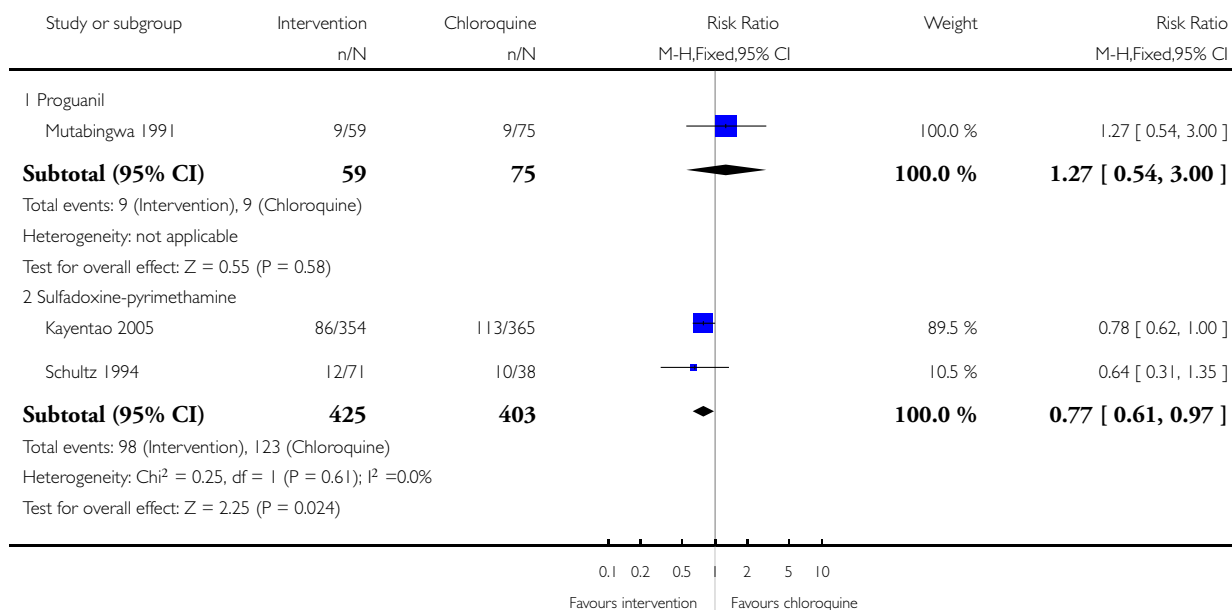


Analysis 6.4. Comparison 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes, Outcome 4 Low birthweight.

Review: Drugs for preventing malaria in pregnant women

Comparison: 6 Any antimalarial regimen versus weekly chloroquine: fetal outcomes

Outcome: 4 Low birthweight



APPENDICES

Appendix I. Search methods: detailed search strategies

Search set	CIDG SR ^a	CENTRAL	MEDLINE ^b	EMBASE ^b	LILACS ^b
1	malaria	MALARIA	MALARIA	MALARIA	malaria
2	pregnan*	malaria	malaria	malaria	pregnan*
3	1 and 2	1 or 2	1 or 2	1 or 2	1 and 2
4	-	PREGNANCY	PREGNANCY	PREGNANCY	-
5	-	pregnan*	pregnan*	pregnan\$	-

(Continued)

6	-	4 or 5	4 or 5	4 or 5	-
7	-	3 and 6	3 and 6	3 and 6	-
8	-	-	Limit 7 to human	Limit 7 to human	-

^aCochrane Infectious Diseases Group Specialized Register.

^bSearch terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2005); upper case: MeSH or Emtree heading; lower case: free text term.

Appendix 2. Trial participants: number of previous pregnancies

No. of pregnancies	Trials
All women	Morley 1964, Hamilton 1972 Nahlen 1989, Cot 1992, Nosten 1994; Greenwood 1989, and Mutabingwa 1991 selected women in their first pregnancy for follow up or reporting
First pregnancy	Fleming 1985, Menendez 1994, Cot 1995, Shulman 1998, Ndyomugenyi 2000, Challis 2004
First or second pregnancy	Schultz 1994, Parise 1998i, Parise 1998ii, Kayentao 2005

Appendix 3. Comparisons evaluated in the trials

Control	Intervention	Trials
Placebo or no active drug	Chloroquine	Hamilton 1972, Cot 1992, Cot 1995, Ndyomugenyi 2000
	Pyrimethamine	Morley 1964, Nahlen 1989
	Proguanil	Fleming 1985
	Pyrimethamine-dapsone	Greenwood 1989, Menendez 1994
	Sulfadoxine-pyrimethamine	Parise 1998i, Parise 1998ii, Shulman 1999, Challis 2004
	Mefloquine	Nosten 1994
Chloroquine	Proguanil	Mutabingwa 1991

(Continued)

	Sulfadoxine-pyrimethamine	Schultz 1994, Kayentao 2005
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Appendix 4. Methodological quality (risk of bias)

Trial	Sequence generation	Conceal allocation	Blinding
Challis 2004	Unclear	Unclear	Double (women; health worker)
Cot 1992	Inadequate (alternate allocation)	Inadequate (not concealed)	None
Cot 1995	Inadequate (alternate allocation)	Inadequate (not concealed)	None
Fleming 1985	Adequate (random-number table)	Unclear	Patients blind; not clear if health staff blinded
Greenwood 1989	Unclear (allocated by compound)	Inadequate (not concealed)	None
Hamilton 1972	Inadequate (day of the week attending clinic; based on referral to 1 of 3 clinics)	Inadequate (not concealed)	None
Kayentao 2005	Unclear (“by block”)	Unclear	None
Menendez 1994	Unclear (allocated by compound)	Inadequate (not concealed)	None
Morley 1964	Inadequate (alternate assignment at registration)	Inadequate	None
Mutabingwa 1991	Inadequate (alternate allocation)	Inadequate (not concealed)	None
Nahlen 1989	Unclear	Inadequate (not concealed)	None
Ndyomugenyi 2000	Adequate (“using a random sequence”)	Unclear	Double
Nosten 1994	Unclear	Adequate (investigators unaware of randomization)	Patients and health staff blind
Parise 1998i, Parise 1998ii	Inadequate (based on day of clinic attendance)	Inadequate (not concealed)	None

(Continued)

Shulman 1999	Adequate (blocks of 10) from statistician	Adequate (code held by statistician)	Patients, investigator, and health staff blind
Schultz 1994	Inadequate (sequential assignment based on the day of clinic attendance)	Inadequate (not concealed)	None

Appendix 5. Percentage of randomized participants included in the analyses

Trial	Women			Newborns		
	Outcome	n/N ^a	% in analysis	Outcome	n/N ^a	% in analysis
Challis 2004	Parasitaemia	411/600	69	Low birthweight	403/600	67
Cot 1992	Placental malaria	904/1464	62	Birthweight	1148/1148	100
Cot 1995	Placental malaria	120/266	57	Birthweight	209/266	79
Fleming 1985	Haemoglobin	107/200	45	Perinatal death	152/200	76
Greenwood 1989	Parasitaemia	257/1049	24	Birthweight	877/1034	85
Hamilton 1972	-	-	-	Birthweight	1149/1846	62
Kayentao 2005	Severe anaemia	717/1163	61	Birthweight	Appears complete	Appears complete
Menendez 1994	Placental malaria	116/230	50	Birthweight	182/203	90
Morley 1964	Antenatal parasitaemia	227/429	53	Birthweight	429/429	100
Mutabingwa 1991	Antenatal parasitaemia	367/423	87	Birthweight	312/423	74
Nahlen 1989	Parasitaemia	71/71	100	-	-	-
Ndyomugenyi 2000	Anaemia	510/860	59	Congenital malaria	337/510	66
Nosten 1994	Parasitaemia	399/399	100	Birthweight	290/290	100

(Continued)

Parise 1998i , Parise 1998ii	Haemoglobin	1378/2077	66	-	-	-
Shulman 1999	Severe anaemia	1132/1264	90	-	-	-
Schultz 1994	Parasitaemia	159/357	44	Birthweight	Not known	Not known

^aNumber analysed/number randomized.

WHAT'S NEW

Last assessed as up-to-date: 19 August 2006.

16 September 2008	Amended	Converted to new review format with minor editing.
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HISTORY

Protocol first published: Issue 1, 1995

Review first published: Issue 1, 1995

20 August 2006	Amended	2006, Issue 4: added Challis 2004 and Kayentao 2005 ; meta-analysis stratified by prophylaxis and intermittent preventive treatment; review title shortened.
20 November 2002	Amended	2003, Issue 1: Review overhauled to reflect current methods; title was altered to "Drugs for preventing malaria-related illness in pregnant women and death in the newborn" (from "Prevention versus treatment for malaria in pregnant women"); we excluded mosquito nets as these are now covered by Gamble 2006 ; primary outcome measures were adjusted following feedback from readers; methodological quality of trials reassessed; Martin 1982 trial previously included, but now excluded because it is not randomized.
28 February 2001	Amended	Primary outcome measures defined; Parise 1998 trial added.

CONTRIBUTIONS OF AUTHORS

Paul Garner wrote the first version of this review in 1995. Metin Gülmezoglu carried out the first update, and Paul Garner has been updating the review since then in consultation with Metin Gülmezoglu.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- HRP-UNDP/UNFPA/WHO/World Bank Special Programme in Human Reproduction, Geneva, Switzerland.

External sources

- Department for International Development (DFID), UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*therapeutic use]; Infant, Newborn; Malaria [drug therapy; *prevention & control]; Mosquito Control; Pregnancy Complications, Parasitic [drug therapy; *prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy