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Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment (Review)

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[Intervention Review]

Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment

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ABSTRACT

Background

Pregnancy increases the risk of malaria and this is associated with poor health outcomes for both the mother and the infant, especially during the first or second pregnancy. To reduce these effects, the World Health Organization recommends that pregnant women living in malaria endemic areas sleep under insecticide-treated bednets, are treated for malaria illness and anaemia, and receive chemoprevention with an effective antimalarial drug during the second and third trimesters.

Objectives

To assess the effects of malaria chemoprevention given to pregnant women living in malaria endemic areas on substantive maternal and infant health outcomes. We also summarised the effects of intermittent preventive treatment with sulfadoxine-pyrimethamine (SP) alone, and preventive regimens for *Plasmodium vivax.*

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, EMBASE, LILACS, and reference lists up to 1 June 2014.

Selection criteria

Randomized controlled trials (RCTs) and quasi-RCTs of any antimalarial drug regimen for preventing malaria in pregnant women living in malaria-endemic areas compared to placebo or no intervention. In the mother, we sought outcomes that included mortality, severe anaemia, and severe malaria; anaemia, haemoglobin values, and malaria episodes; indicators of malaria infection, and adverse events. In the baby, we sought foetal loss, perinatal, neonatal and infant mortality; preterm birth and birthweight measures; and indicators of malaria infection. We included regimens that were known to be effective against the malaria parasite at the time but may no longer be used because of parasite drug resistance.

Data collection and analysis

Two review authors applied inclusion criteria, assessed risk of bias and extracted data. Dichotomous outcomes were compared using risk ratios (RR), and continuous outcomes using mean differences (MD); both are presented with 95% confidence intervals (CI). We assessed the quality of evidence using the GRADE approach.

Main results

Seventeen trials enrolling 14,481 pregnant women met our inclusion criteria. These trials were conducted between 1957 and 2008, in Nigeria (three trials), The Gambia (three trials), Kenya (three trials), Mozambique (two trials), Uganda (two trials), Cameroon (one trial), Burkina Faso (one trial), and Thailand (two trials). Six different antimalarials were evaluated against placebo or no intervention; chloroquine (given weekly), pyrimethamine (weekly or monthly), proguanil (daily), pyrimethamine-dapsone (weekly or fortnightly), and mefloquine (weekly), or intermittent preventive therapy with SP (given twice, three times or monthly). Trials recruited women in their first or second pregnancy (eight trials); only multigravid women (one trial); or all women (eight trials). Only six trials had adequate allocation concealment.

For women in their first or second pregnancy, malaria chemoprevention reduces the risk of moderate to severe anaemia by around 40% (RR 0.60, 95% CI 0.47 to 0.75; three trials, 2503 participants, *high quality evidence*), and the risk of any anaemia by around 17% (RR 0.83, 95% CI 0.74 to 0.93; five trials,, 3662 participants, *high quality evidence*). Malaria chemoprevention reduces the risk of antenatal parasitaemia by around 61% (RR 0.39, 95% CI 0.26 to 0.58; seven trials, 3663 participants, *high quality evidence*), and two trials reported a reduction in febrile illness (*low quality evidence*). There were only 16 maternal deaths and these trials were underpowered to detect an effect on maternal mortality (*very low quality evidence*).

For infants of women in their first and second pregnancies, malaria chemoprevention probably increases mean birthweight by around 93 g (MD 92.72 g, 95% CI 62.05 to 123.39; nine trials, 3936 participants, *moderate quality evidence*), reduces low birthweight by around 27% (RR 0.73, 95% CI 0.61 to 0.87; eight trials, 3619 participants, *moderate quality evidence*), and reduces placental parasitaemia by around 46% (RR 0.54, 95% CI 0.43 to 0.69; seven trials, 2830 participants, *high quality evidence*). Fewer trials evaluated spontaneous abortions, still births, perinatal deaths, or neonatal deaths, and these analyses were underpowered to detect clinically important differences.

In multigravid women, chemoprevention has similar effects on antenatal parasitaemia (RR 0.38, 95% CI 0.28 to 0.50; three trials, 977 participants, *high quality evidence*)but there are too few trials to evaluate effects on other outcomes.

In trials giving chemoprevention to all pregnant women irrespective of parity, the average effects of chemoprevention measured in all women indicated it may prevent severe anaemia (defined by authors, but at least < 8 g/L: RR 0.19, 95% CI 0.05 to 0.75; two trials, 1327 participants, *low quality evidence),* but consistent benefits have not been shown for other outcomes.

In an analysis confined only to intermittent preventive therapy with SP, the estimates of effect and the quality of the evidence were similar.

A summary of a single trial in Thailand of prophylaxis against *P. vivax* showed chloroquine prevented vivax infection (RR 0.01, 95% CI 0.00 to 0.20; one trial, 942 participants).

Authors' conclusions

Routine chemoprevention to prevent malaria and its consequences has been extensively tested in RCTs, with clinically important benefits on anaemia and parasitaemia in the mother, and on birthweight in infants.

8 May 2019

No update planned

Review superseded

The intervention is clearly effective. The questions now are around head-to-head comparisons not included in this review.

PLAIN LANGUAGE SUMMARY

The effect of taking antimalarial drugs routinely to prevent malaria in pregnancy

Pregnancy increases the risk of malaria and this is associated with poor health outcomes for both the mother and the infant, especially during the first or second pregnancy. For this reason, women are encouraged to try and prevent malaria infection during pregnancy by sleeping under mosquito bed-nets, and by taking drugs effective against malaria throughout pregnancy as chemoprevention.

This Cochrane Review looked at all drug regimens compared to placebo. The review authors sought to summarise and quantify the overall effects of chemoprevention. Seventeen trials were included, all conducted between 1957 and 2008, and all but two in countries of Africa.

For women in their first or second pregnancy, malaria chemoprevention prevents moderate to severe anaemia (*high quality evidence*); and prevents malaria parasites being detected in the blood (*high quality evidence*). It may also prevent malaria illness. We don't know if it prevents maternal deaths, as this would require very large studies to detect an effect.

In their infants, malaria chemoprevention improves the average birthweight (*moderate quality evidence*), and reduces the number of low birthweight infants (*moderate quality evidence*). We are not sure if chemoprevention reduces mortality of babies in the first week, month and year, as again studies would need to be very large to show these effects.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings table 1

Malaria chemoprevention for pregnant women (parity 0-1) living in endemic areas: maternal outcomes

Patient or population: Pregnant women (parity 0-1)
Settings: Malaria-endemic areas
Intervention: Malaria chemoprevention (any regimen)
Control: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Chemoprevention			
Mortality All-cause death	**7 per 1000**	**8 per 1000** (3 to 20)	**RR 1.15** (0.44 to 3.06)	2097 (3 trials)	⊕⊝⊝⊝ **very low** [1,2]
Severe anaemia During the third trimester	**145 per 1000**	**87 per 1000** (68 to 108)	**RR 0.60** (0.47 to 0.75)	2503 (3 trials)	⊕⊕⊕⊕ **high** [3,4,5,6]
Anaemia	**649 per 1000**	**539 per 1000** (480 to 604)	**RR 0.83** (0.74 to 0.93)	3662 (5 trials)	⊕⊕⊕⊕ **high** [3,6,7,8]
Uncomplicated clinical malaria	**173 per 1000**	**64 per 1000** (31 to 128)	**RR 0.37** (0.18 to 0.74)	307 (2 trials)	⊕⊕⊝⊝ **low** [4,9,10]
Antenatal parasitaemia	**286 per 1000**	**111 per 1000** (74 to 165)	**RR 0.39** (0.26 to 0.58)	3663 (8 trials)	⊕⊕⊕⊕ **high** [3,6,7,11]
Severe adverse effects [12]	-	-	-	-	-

*The basis for the **assumed risk** (eg, the median control group risk across trials) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by 1 for risk of bias: Only one of these trials adequately described allocation concealment to be considered at low risk of selection bias.
[2] Downgraded by 2 for imprecision: These trials were not adequately powered to detect a difference in mortality. Only 15 deaths occurred in these three trials.To confidently detect a 25% reduction in maternal mortality in a setting of 350 deaths/100,000 would require a sample size of over 100,000.
[3] No serious risk of bias: Exclusion of the trials at high risk of bias did not change the statistical significance or clinical importance of the result.
[4] No serious inconsistency: This finding was consistent across all trials and statistical heterogeneity was low.
[5] No serious indirectness: These trials were conducted in Kenya and Mozambique between 1996 and 2005, all three trials administered IPT with SP. The definition of severe anaemia was variable; Hb < 8 g/dL, Hb < 7 g/dL, or PCV < 21%.
[6] No serious imprecision: This result is statistically significant and the meta-analysis is adequately powered to detect this effect.
[7] No serious inconsistency: Although statistical heterogeneity was high, all trials favoured chemoprevention but there was variability in the size of the effect.
[8] No serious indirectness: These trials were conducted in Nigeria, Kenya and Uganda between 1978 and 1999. Three trials administered IPT as SP, one gave weekly chloroquine, and one gave daily proguanil. The definition of anaemia was variable: Hb < 12 g/dL, Hb < 11 g/dL, Hb < 10 g/dL, PCV < 33% and PCV < 30%.
[9] Downgraded by 1 for risk of bias. Both trials had high or unclear risk of selection bias and an attrition rate above 20%.
[10] Downgraded by 1 for indirectness: Both these trials, from Cameroon 1993 and Mozambique 2002, measured fever history only as proxy for malaria illness.
[11] Not downgraded for inconsistency. Despite substantive quantitative heterogeneity (I^2 69% across six trials), all show at least a reduction of 23%, often more
[11] No serious indirectness: These trials were conducted in The Gambia, Nigeria, Kenya and Mozambique between 1978 and 2005. Five trials gave IPT as SP, one gave pyrimethamine-dapsone, one pyrimethamine, and one proguanil.
[12] Reporting of adverse events was generally poor. No severe adverse events were reported.

Summary of findings 2. Summary of findings table 2

Malaria chemoprevention for pregnant women (parity 0-1) living in endemic areas: infant outcomes

Patient or population: Pregnant women (parity 0-1)
Settings: Malaria-endemic areas
Intervention: Malaria chemoprevention (any regimen)
Control: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Chemoprevention			
Spontaneous abortion	**33 per 1000**	**21 per 1000** (13 to 33)	**RR 0.65** (0.41 to 1.02)	2876 (5 trials)	⊕⊕⊖⊖ **low** [1,2,3,4]
Stillbirth	**33 per 1000**	**32 per 1000** (21 to 49)	**RR 0.97** (0.64 to 1.49)	2703 (3 trials)	⊕⊕⊖⊖ **low** [2,4,5,6,]
Perinatal mortality	**104 per 1000**	**76 per 1000** (56 to 104)	**RR 0.73** (0.54 to 1.00)	1620 (2 trials)	⊕⊕⊖⊖ **low** [2,4,5,7,]

Neonatal mortality	**37 per 1000**	**23 per 1000** (14 to 39)	**RR 0.62** (0.37 to 1.05)	2156 (2 trials)	⊕⊕⊖⊖ **low** [2,4,5,7,]
Preterm birth	**164 per 1000**	**140 per 1000** (108 to 181)	**RR 0.85** (0.66 to 1.10)	1493 (2 trials)	⊕⊕⊖⊖ **low** [1,2,4]
Low birthweight	**152 per 1000**	**110 per 1000** (92.7 to 132.2)	**RR 0.73** (0.61 to 0.87)	3619 (8 trials)	⊕⊕⊕⊖ **moderate** [9,10]
Mean birthweight	The mean birthweight in the control groups ranged from **2723 g to 3079 g**	The mean birthweight in the intervention groups was **92.72 g higher** (62.05 higher to 123.39 higher)	-	3936 (9 trials)	⊕⊕⊕⊖ **moderate** [5,10]
Placental parasitaemia	**307 per 1000**	**160 per 1000** (132 to 211)	**RR 0.54** (0.43 to 0.69)	2830 (7 trials)	⊕⊕⊕⊕ **high** [3,11,12]
Cord blood haemoglobin	The mean haemoglobin in the control group was **15.8 g/dL**	The mean haemoglobin in the intervention groups was **1.8 g/dL lower** (3.46 lower to 0.14 lower)	-	64 (1 trial)	⊕⊖⊖⊖ **very low** [1,13,14]

*The basis for the **assumed risk** (eg the median control group risk across trials) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by 1 for serious risk of bias: None of the trials described adequate measures to prevent selection bias.
[2] No serious inconsistency: The effect is consistent across trials and statistical heterogeneity is low.
[3] No serious indirectness: These trials were conducted in The Gambia, Cameroon, Kenya and Mozambique between 1990 and 2002. One gave chemoprevention as weekly chloroquine and four trials gave IPT with SP.
[4] Downgraded by 1 for serious imprecision: The 95% CI is wide and sample remains underpowered to detect or rule out an effect.
[5] Downgraded by 1 for serious risk of bias: Only one trial adequately described methods to prevent selection bias.
[6] No serious indirectness: Trials were conducted in Cameroon and Kenya between 1993 and 1997. One trial gave weekly chloroquine and the others gave IPT as SP.
[7] No serious indirectness: The trials were conducted in The Gambia and Kenya between 1984 and 1997. One trial used IPT with SP and one gave pyrimethamine-dapsone which is no longer in use.
[8] No serious indirectness: Both trials were conducted in Kenya and used IPT with SP.

[9] Downgraded by 1 for serious risk of bias: Only two of these trials were at low risk of selection bias.
[10] No serious indirectness: These trials were conducted in The Gambia, Cameroon, Kenya, Uganda and Mozambique between 1986 and 2005. The majority of trials used IPT with SP.
[11] No serious inconsistency: Although statistical heterogeneity was high, all trials favoured chemoprevention but there was variability in the size of the effect.
[12] No serious indirectness: These trials were conducted in The Gambia, Cameroon, Kenya, Uganda and Mozambique between 1990 and 2002. The majority of trials used IPT with SP.
[13] Downgraded by 1 for serious indirectness: This single trial used a regimen that is no longer in use (proguanil).
[14] Downgraded by 1 for serious imprecision: Only a single small trial has evaluated this comparison.

Summary of findings 3. Summary of findings table 3

Malaria chemoprevention for pregnant women (parity 2+) living in endemic areas: maternal outcomes

Patient or population: Pregnant women (parity 2+)
Settings: Malaria-endemic areas
Intervention: Malaria chemoprevention (any regimen)
Control: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Chemoprevention			
Mortality All-cause death	**5 per 1000**	**7 per 1000** (2 to 26	**RR 1.47** (0.42 to 5.21)	2239 (1 trial)	⊕⊝⊝⊝ **very low** [1,2,3]
Severe anaemia During the third trimester	**68 per 1000**	**65 per 1000** (28 to 153)	**RR 0.96** (0.41 to 2.25)	2682 (2 trials)	⊕⊕⊝⊝ **low** [1,4,5]
Anaemia	The mean PCV in the control group was **30.4 %**	The mean PCV in the intervention group was **0.3 % higher** (0.7 lower to 1.3 higher)	-	244 (1 trial)	⊕⊝⊝⊝ **very low** [6,7,8]
Uncomplicated clinical malaria	-	-	-	- (0 trials)	-
Antenatal parasitaemia	**108 per 1000**	**41 per 1000** (30 to 54)	**RR 0.38** (0.28 to 0.50)	3022 (4 trials)	⊕⊕⊕⊕ **high** [9,10]
Severe adverse events [11]	-	-	-	-	-

*The basis for the **assumed risk** (eg the median control group risk across trials) is provided in footnotes. The **corresponding risk** (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).

CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: These trials are at low risk of bias.
[2] Downgraded by 1 for serious indirectness: This single trial was conducted in The Gambia between 2002 and 2004 and administered IPT as monthly SP. The findings may not be easily generalised to elsewhere.
[3] Downgraded by 2 for very serious imprecision: Only ten deaths occurred in this trial. Much larger trials would be needed to detect or exclude effects on maternal mortality.
[4] No serious indirectness: These two trials were conducted in The Gambia in 2002-2004 and Mozambique between 2003 and 2005.
[5] Downgraded by 2 for very serious imprecision: The 95% CI are very wide and include the possibility of both clinically important benefits and harms.
[6] Downgraded by 1 for serious risk of bias: This single trial is at unclear risk of selection bias.
[7] Downgraded by 1 for serious indirectness: This trial administered chemoprevention as pyrimethamine-dapsone which is no longer in use.
[8] Downgraded by 1 for serious imprecision: A much larger sample size is required to confidently detect or exclude an effect.
[9] No serious risk of bias: Two of the four trials were at low risk of selection bias and exclusion of the other two trials did not change the size of the effect.
[10] No serious indirectness: These three trials were conducted in The Gambia, Nigeria and Mozambique between 1986 and 2005. The biggest and most recent trial administered IPT with SP (two doses)
[11] Reporting of adverse events was generally poor. No severe adverse events were reported.

Summary of findings 4. Summary of findings table 4

Malaria chemoprevention for pregnant women (parity 2+) living in endemic areas: infant outcomes

Patient or population: Pregnant women (parity 2+)
Settings: Malaria-endemic areas
Intervention: Malaria chemoprevention (any regimen)
Control: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Chemoprevention			
Spontaneous abortion	-	-	-	- (0 trials)	-
Stillbirth	-	-	-	-	-

				(0 trials)	
Perinatal deaths	-	-	-	- (0 trials)	-
Neonatal mortality	**26 per 1000**	**38 per 1000** (23 to 62)	**RR 1.46** (0.90 to 2.38)	2017 (1 trial)	⊕⊝⊝⊝ **very low** [1,2,3]
Preterm birth	-	-	-	- (0 trials)	-
Low birthweight	**60 per 1000**	**63 per 1000** (46 to 85)	**RR 0.86** (0.63 to 1.17)	2743 (3 trials)	⊕⊕⊝⊝ **low** [3,4,5]
Mean birthweight	-	-	-	- (0 trials)	-
Placental parasitaemia	-	-	-	- (0 trials)	-
Cord blood haemoglobin	-	-	-	- (0 trials)	-

*The basis for the **assumed risk** (eg the median control group risk across trials) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: This single trial was at low risk of selection bias.
[2] Downgraded by 1 for serious indirectness: This single trial was conducted in The Gambia between 2002 and 2004 and administered IPT as monthly SP. The findings may not be easily generalised to elsewhere.
[3] Downgraded by 2 for serious imprecision: The 95% CI is very wide and includes clinically important effects and no effect. A much larger sample size is required to confidently detect or exclude an effect.
[4] No serious risk of bias: These trials are at low risk of selection bias.

[5] No serious indirectness: These trials were conducted in The Gambia, Mozambique, and Uganda between 2002 and 2008.

Summary of findings 5. Summary of findings table 5

Malaria chemoprevention for all pregnant women (all parities) living in endemic areas: maternal outcomes

Patient or population: Pregnant women (all parities)
Settings: Malaria-endemic areas
Intervention: Malaria chemoprevention (any regimen)
Control: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Chemoprevention			
Mortality All-cause death	**1 per 1000**	**1 per 1000** (0 to 3)	**RR 0.84** (0.25 to 2.74)	6026 (4 trials)	⊕⊕⊝⊝ **low** [1,2,3]
Severe anaemia During the third trimester	**26 per 1000**	**5 per 1000** (1 to 19)	**RR 0.19** (0.05 to 0.75)	1327 (2 trials)	⊕⊕⊝⊝ **low** [2,4,5,6]
Anaemia	**206 per 1000**	**212 per 1000** (179 to 253)	**RR 1.03** (0.87 to 1.23)	3027 (3 trials)	⊕⊕⊕⊝ **moderate** [1,2,7,8]
Uncomplicated clinical malaria	**114 per 1000**	**42 per 1000** (13 to 140)	**RR 0.37** (0.11 to 1.23)	3455 (4 trials)	⊕⊕⊝⊝ **low** [1,9,10]
Antenatal parasitaemia	**152 per 1000**	**106 per 1000** (67 to 172)	**RR 0.70** (0.44 to 1.13)	3455 (4 trials)	⊕⊕⊝⊝ **low** [1,8,11]
Severe adverse effects [12]	-	-	-	- (0 trials)	-

*The basis for the **assumed risk** (eg the median control group risk across trials) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: The two most recent trials adequately described allocation concealment to be considered at low risk of selection bias.
[2] No serious inconsistency: This finding was consistent across all trials and statistical heterogeneity was low.
[3] Downgraded by 2 for very serious imprecision: These trials were not adequately powered to detect a difference in mortality. Only nine deaths occurred in these four trials. To confidently detect a 25% reduction in maternal mortality in a setting of 350 deaths/100,000 would require a sample size of over 100,000.
[4] No serious risk of bias: One of these two trials adequately described allocation concealment to be at low risk of bias.
[5] Downgraded by 1 for serious indirectness: Only a single trial from Mozambique provides data on the currently used regimen of IPT as two doses of SP. The definition of severe anaemia was PCV <21%.
[6] Downgraded by 1 for serious imprecision: The number of events is very low and the trials underpowered to be confident in these results.
[7] No serious indirectness: These trials were conducted in Thailand, Mozambique and Uganda between 1988 and 2008. The two recent trials administered IPT as two doses of SP. The definition of anaemia was variable; Hb < 11 g/dL, PCV < 33% and PCV <30%.
[8] Downgraded by 1 for serious imprecision: Although the finding is of no effect. The 95% CI includes what may be clinically important differences.
[9] Downgraded by 1 for serious inconsistency: The two old trials from 1957 and 1988 suggest clinically important benefits with chemoprophylaxis - however, the two recent trials providing two doses of SP find no evidence of an effect.
[10] Downgraded by 1 for serious indirectness: The finding of no effect in the two recent trials may be due to the declining efficacy of two doses of SP.
[11] Downgraded for by 1 for serious inconsistency. There is substantive heterogeneity between trials (I^2 = 79%), and this finding of no effect is in contrast to findings of benefit in both women of low parity and multigravidae. The finding of no effect in two of the recent trials may reflect declining efficacy in the regimens used.
[12] Reporting of adverse events was generally poor. No severe adverse events were reported.

Summary of findings 6. Summary of findings table 6

Malaria chemoprevention for pregnant women (all parities) living in endemic areas: infant outcomes

Patient or population: Pregnant women (all parities)
Settings: Malaria-endemic areas
Intervention: Malaria chemoprevention (any regimen)
Control: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Chemoprevention			
Spontaneous abortion	**12 per 1000**	**11 per 1000** (7 to 16)	**RR 0.89** (0.58 to 1.36)	5767 (3 trials)	⊕⊕⊙⊙ **low** [1,2,3,4]
Stillbirth	**22 per 1000**	**22 per 1000** (17 to 30)	**RR 1.02** (0.76 to 1.36)	7130 (5 trials)	⊕⊕⊕⊙ **moderate** [1,2,5]

Perinatal mortality	**33 per 1000**	**41 per 1000** (31 to 54)	**RR 1.24** (0.94 to 1.63)	5216 (4 trials)	⊕⊕⊕⊖ **moderate** [1,2,5]
Neonatal mortality	**62 per 1000**	**56 per 1000** (44 to 72)	**RR 0.91** (0.71 to 1.16)	6313 (5 trials)	⊕⊕⊕⊖ **moderate** [1,2,5]
Preterm birth	**85 per 1000**	**81 per 1000** (55 to 117)	**RR 0.95** (0.65 to 1.38)	1174 (2 trials)	⊕⊕⊖⊖ **low** [2,5,6,10]
Low birthweight	**119 per 1000**	**126 per 1000** (106 to 151)	**RR 1.06** (0.89 to 1.27)	3644 (4 trials)	⊕⊕⊖⊖ **low** [1,2,5,10]
Mean birthweight	The mean birthweight in the control groups ranged from **2797 g to 3161 g**	The mean birthweight in the intervention groups was **0.54 g lower** (24.6 g lower to 23.6 g higher)	-	6007 (5 trials)	⊕⊕⊕⊖ **moderate** [1,7,8,10]
Placental parasitaemia	**181 per 1000**	**80 per 1000** (27 to 233)	**RR 0.44** (0.15 to 1.29)	3200 (4 trials)	⊕⊕⊖⊖ **low** [1,9,10]

*The basis for the **assumed risk** (eg the median control group risk across trials) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No serious risk of bias: The two most recent trials adequately described allocation concealment to be considered at low risk of selection bias.
[2] No serious inconsistency: The finding of no difference is consistent across trials and statistical heterogeneity is low
[3] No serious indirectness: These trials were conducted in the Burkina Faso, Mozambique and Uganda between 1988 and 2008. One gave chemoprevention as weekly chloroquine and two trials gave IPT with SP.
[4] Downgraded by 2 for very serious imprecision: The 95% CI is wide and sample remains underpowered to detect or rule out an effect.
[5] Downgraded by 1 for serious imprecision: The 95% CI is wide and sample remains underpowered to detect or rule out an effect.
[6] No serious risk of bias: The most recent trial adequately described allocation concealment to be considered at low risk of selection bias.
[7] No serious inconsistency: Although substantial statistical heterogeneity is present (I^2 = 72%), this relates to the oldest trial which found a benefit with chemoprevention. The subsequent four trials have consistently found no clinically important difference.
[8] No serious imprecision: The 95% CI probably excludes clinically important benefits.
[9] Downgraded by 1 for serious inconsistency: The two old trials from 1957 and 1988 suggest clinically important benefits with chemoprophylaxis - however, the two recent trials providing two doses of SP find no evidence of an effect.

[10] Downgraded by 1 for serious indirectness: The finding of no effect in the recent trials may be due to the declining efficacy of two doses of SP which is no longer recommended.

Summary of findings 7. Summary of findings table 7

Intermittent preventive treatment with SP for pregnant women (parity 0-1) living in malaria endemic areas: maternal outcomes

Patient or population: Pregnant women (parity 0-1)
Settings: Malaria-endemic areas
Intervention: Intermittent preventive treatment with SP (2 doses, 3 doses, or monthly dosing)
Control: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	IPT (SP)			
Mortality All-cause death	**7 per 1000**	**8 per 1000** (3 to 20)	**RR 1.15** (0.44 to 3.06)	2097 (2 trials)	⊕⊝⊝⊝ **very low** [1,2]
Severe anaemia During the third trimester	**145 per 1000**	**87 per 1000** (68 to 108)	**RR 0.60** (0.47 to 0.75)	2503 (3 trials)	⊕⊕⊕⊕ **high** [3,4,5,6]
Anaemia	**617 per 1000**	**543 per 1000** (480 to 604)	**RR 0.88** (0.81 to 0.96)	3291 (4 trials)	⊕⊕⊕⊝ **moderate** [1,6,7,8]
Uncomplicated clinical malaria	**9 per 100**	**2 per 100** (0 to 10)	**RR 0.24** (0.05 to 1.12)	174 (1 trial)	⊕⊝⊝⊝ **very low** [9,10,11]
Antenatal parasitaemia	**286 per 1000**	**108 per 1000** (69 to 169)	**RR 0.38** (0.24 to 0.59)	2832 (4 trials)	⊕⊕⊕⊕ **high** [3,6,7,12]
Severe adverse effects [13]	-	-	-	- (0 trials)	-

*The basis for the **assumed risk** (eg the median control group risk across trials) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Downgraded by 1 for risk of bias: Only one of these trials adequately described allocation concealment to be considered at low risk of selection bias.
[2] Downgraded by 2 for imprecision: These trials were not adequately powered to detect a difference in mortality. Only 15 deaths occurred in these two trials. To confidently detect a 50% reduction in maternal mortality in a setting of 350 deaths/100,000 would require a sample size of over 100,000.
[3] No serious risk of bias: Exclusion of the trials at high risk of bias did not change the statistical significance or clinical importance of the result.
[4] No serious inconsistency: This finding was consistent across all trials and statistical heterogeneity was low.
[5] No serious indirectness: These trials were conducted in Kenya and Mozambique between 1996 and 2005, all three trials administered IPT with SP. The definition of severe anaemia was variable; Hb < 8 g/dL, Hb < 7g/dL, or PCV < 21%.
[6] No serious imprecision: This result is statistically significant and the meta-analysis is adequately powered to detect this effect.
[7] No serious inconsistency: Although statistical heterogeneity was high, all trials favoured IPT with SP but there was variability in the size of the effect.
[8] No serious indirectness: These trials were conducted Kenya between 1996 and 1999. The definition of anaemia was variable; Hb < 11 g/dL, Hb < 10 g/dL.
[9] Downgraded by 1 for risk of bias: This trial is at unclear risk of selection bias.
[10] Downgraded by 1 for indirectness: This trial from Mozambique 2002, measured fever history only as proxy for malaria illness.
[11] Downgraded by 1 for serious imprecision: The 95% CI is wide and includes clinically important benefits and no effect.
[12] No serious indirectness: These trials were conducted in the Kenya and Mozambique between 1996 and 2005.
[13]Reporting of adverse events was generally poor. No severe adverse events were reported.

Summary of findings 8. Summary of findings table 8

Intermittent preventive treatment with SP for pregnant women (parity 0-1) living in malaria endemic areas: infant outcomes

Patient or population: Pregnant women (parity 0-1)
Settings: Malaria-endemic areas
Intervention: Intermittent preventive treatment with SP (2 doses, 3 doses, or monthly dosing)
Control: Placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	IPT (SP)			
Spontaneous abortion	**34 per 1000**	**21 per 1000** (13 to 33)	**RR 0.61** (0.38 to 0.99)	2567 (3 trials)	⊕⊕⊖⊖ **low** [1,2,3,4]
Stillbirth	**33 per 1000**	**32 per 1000** (21 to 49)	**RR 0.97** (0.64 to 1.47)	2703 (3 trials)	⊕⊕⊖⊖ **low** [2,4,5,6]
Perinatal mortality	**80 per 1000**	**62 per 1000** (42 to 94)	**RR 0.78** (0.52 to 1.17)	1237 (1 trial)	⊕⊕⊖⊖ **low** [7]

Neonatal mortality	**37 per 1000**	**23 per 1000** (14 to 39)	**RR 0.62** (0.37 to 1.05)	2156 (2 trials)	⊕⊕⊖⊖ **low** [2,4,5,6]
Preterm birth	**164 per 1000**	**140 per 1000** (108 to 181)	**RR 0.85** (0.66 to 1.10)	1493 (2 trials)	⊕⊕⊖⊖ **low** [1,2,4]
Low birthweight	**128 per 1000**	**104 per 1000** (86 to 127)	**RR 0.81** (0.67 to 0.99)	3043 (4 trials)	⊕⊕⊕⊖ **moderate** [8,9]
Mean birthweight	The mean birthweight in the control groups ranged from **2908 g to 3079 g**	The mean birthweight in the intervention groups was **84.18 g higher** (40.1 to 128.3 higher)	-	2127 (3 trials)	⊕⊕⊕⊖ **moderate** [5,9]
Placental parasitaemia	**225 per 1000**	**101 per 1000** (74 to 137)	**RR 0.45** (0.33 to 0.61)	1633 (3 trials)	⊕⊕⊕⊖ **moderate** [5,10]
Cord blood haemoglobin	-	-	-	- (0 trials)	-

*The basis for the **assumed risk** (eg the median control group risk across trials) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded by 1 for serious risk of bias: None of the trials described adequate measures to prevent selection bias.
[2] No serious inconsistency: The effect is consistent across trials and statistical heterogeneity is low
[3] No serious indirectness: These trials were conducted in the Kenya and Mozambique between 1996 and 2002.
[4] Downgraded by 1 for serious imprecision: The 95% CI is wide and sample remains underpowered to detect or rule out an effect.
[5] Downgraded by 1 for serious risk of bias: Only one trial adequately described methods to prevent selection bias.
[6] No serious indirectness: Trials were conducted in Kenya between 1996 and 1997.
[7] Downgraded by 2 for serious imprecision: The 95% CI is wide and sample remains underpowered to detect or rule out an effect.
[8] Downgraded by 1 for serious risk of bias: Only two of these trials were at low risk of selection bias.
[9] No serious indirectness: These trials were conducted in the Kenya, Uganda and Mozambique between 1996 and 2008.
[10] No serious inconsistency: Although statistical heterogeneity was high, all trials favoured chemoprevention but there was variability in the size of the effect.

BACKGROUND

Description of the condition

Approximately 125 million women living in malaria-endemic areas become pregnant each year (Dellicour 2010), and pregnancy is known to increase the risk of malaria infection and the severity of the illness compared to non-pregnant women in the same age group (Desai 2007). Studies have also shown a strong association between malaria infection in pregnancy and consequent maternal anaemia, and low birthweight in infants, particularly in women in their first or second pregnancy (Desai 2007; Steketee 2001).

To reduce the burden and consequences of malaria in pregnancy, the World Health Organization (WHO) recommends that all pregnant women living in malaria-endemic areas: i) sleep under a long lasting insecticide-treated bednet (ITN; Gamble 2006; WHO 2012); ii) are treated when anaemic or when ill with malaria; and iii) receive some form of malaria chemoprevention. Currently the WHO recommends 'intermittent-preventive therapy' with sulfadoxine-pyrimethamine (SP) during the second and third trimesters in Africa (WHO 2013).

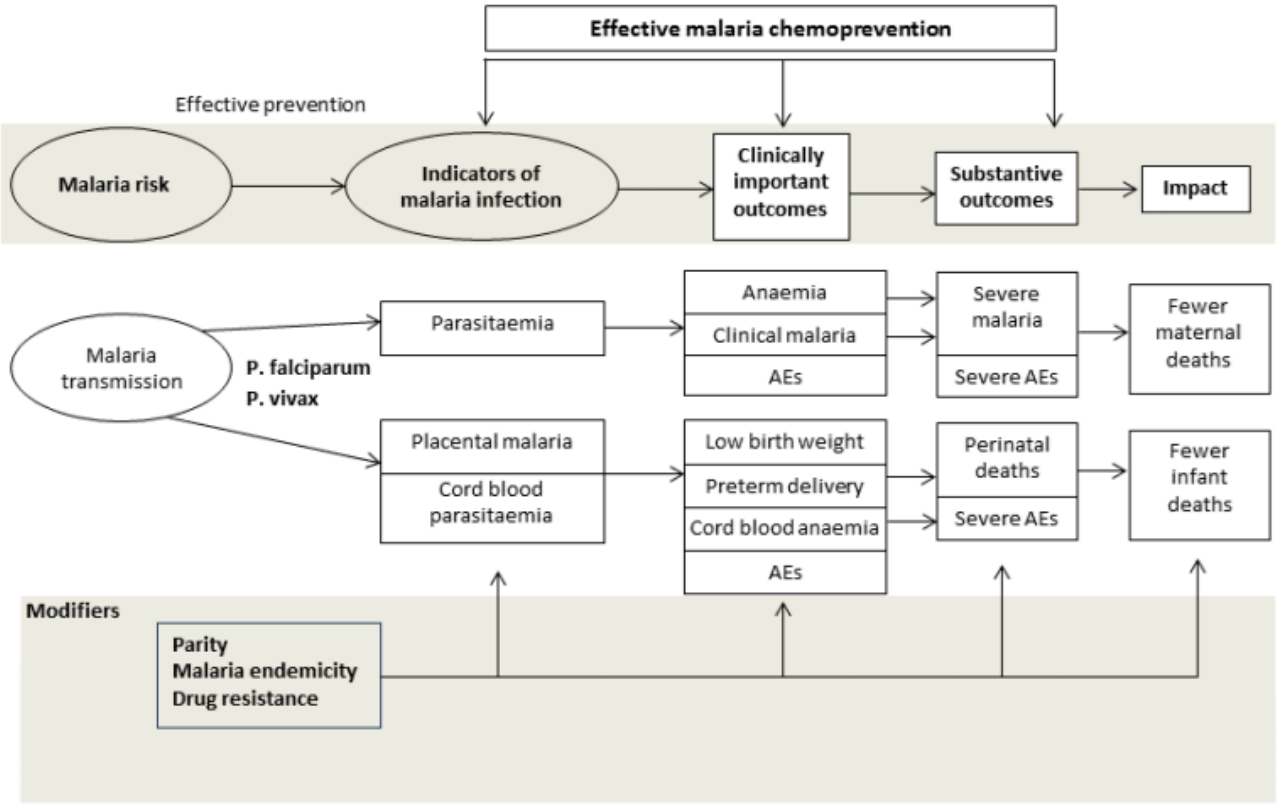
Description of the intervention

Over the years a variety of drugs have been evaluated for malaria chemoprevention in pregnancy, including amodiaquine, chloroquine, dapsone-pyrimethamine, mefloquine, proguanil, pyrimethamine as monotherapy and as the fixed dose combination SP, and others. All have specific toxic and adverse effects, which are outlined in standard texts (WHO 2010), and these may be important factors influencing maternal adherence. For example, proguanil can cause mouth ulcers, chloroquine can cause itch, and mefloquine can cause dizziness and headaches.

How the intervention might work

Chemoprevention encompasses malaria chemoprophylaxis, and also the use of treatment courses given regularly to women. This is termed intermittent preventive treatment (IPT), defined as a full therapeutic course of antimalarial medicine given to pregnant women at routine prenatal visits, regardless of whether the recipient is infected with malaria. combines elements of a treatment effect through clearance or suppression of existing malaria infections in the placental and peripheral blood of mother, and a post-treatment prophylactic effect by preventing new infections for several weeks after each dose (White 2005). Daily, weekly, or bi-weekly malaria chemoprophylaxis is thought to work primarily through the prevention of new malaria infections. However, a reduction in malaria infections per se may be insufficient to justify the use of chemoprevention for widespread use without subsequent benefits on clinically important outcomes in the mother and her baby. These may include a reduction in clinical malaria episodes, a reduced risk of anaemia, improved birthweight, or more substantive outcomes such as a reduction in severe maternal illness, or fewer deaths in the mother and infant (see Figure 1).

Figure 1. Drugs for preventing malaria in pregnancy: conceptual framework.



The effects of malaria chemoprevention may differ between settings dependent on the local malaria epidemiology. In highly endemic areas with stable transmission, mothers may have partial immunity to malaria, and chronic subclinical placental infection

are common leading to maternal anaemia and low birthweight, especially in primi- and secundigravidae. In contrast, where malaria transmission is low or unstable, the degree of life-long acquired and pregnancy-specific protective immunity may be lower and malaria infections are more likely to result in clinical episodes or severe illness, leading to low birthweight due to a preterm birth, foetal loss or maternal death.

Another potential effect modifier is HIV status. Many malaria-endemic areas, especially in east and southern Africa, also have a high prevalence of HIV infection among pregnant women. Compared to HIV negative women, HIV positive women are more likely to carry malaria parasites in their blood, have higher parasite densities, and are more likely to have placental parasitaemia, anaemia, and malaria symptoms and deliver low birthweight babies (Nkhoma 2012a; Nkhoma 2012b; ter Kuile 2004).

Why it is important to do this review

This Cochrane Review aims to address the following questions:

1. Does chemoprevention reduce mortality and substantive outcomes in the mother and infant?
2. What is the potential reduction in the burden of malaria in pregnancy that can be achieved by successful malaria chemoprevention in pregnancy?
3. Are the effects consistent in low parity and high parity women?

This review summarises the underpinning evidence of the protective efficacy achieved with antimalarial chemoprevention regimens on the effects on malaria and its consequences on the mother and baby when compared against placebo or no chemoprevention (case-management strategies only). It does not compare different regimens. These were included in earlier editions of this Cochrane Review (Garner 2006); a more recent review has examined the effects of different IPT regimens in pregnant women (Kayentao 2013).

OBJECTIVES

In malaria-endemic areas, to assess the effects in pregnant women of:

1. Malaria chemoprevention versus no chemoprevention irrespective of the regimen;
2. Malaria chemoprevention with SP (called intermittent preventive treatment) with no chemoprevention;
3. Preventive regimens for *Plasmodium vivax*.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs.

Types of participants

Pregnant women of any gravidity living in malaria-endemic areas, defined as regions where transmission occurs and malaria is a characteristic of the region.

Types of interventions

Interventions

Any antimalarial drug chemoprevention regimen given to pregnant women.

Controls

Placebo or no intervention,

Types of outcome measures

For the conceptual framework, see Figure 1.

Maternal outcomes

- Impact: maternal deaths (number of maternal deaths reported: death of a pregnant woman during pregnancy or within 42 days of termination of pregnancy).
- Substantive outcomes: severe malaria, which includes severe anaemia (defined as Hb < 8 g/dL, < 7 g/dL, < 6 g/dL); severe adverse events.
- Clinically important outcomes: anaemia (anaemia defined as Hb < between 10 and 12 g/dL); mean haemoglobin (g/dL) or mean PCV (%); clinical malaria (history of fever episodes prior to delivery); adverse events.
- Indicators of malaria infection: parasitaemia (defined as the presence of asexual stage parasites in thick smears in peripheral, placental, or cord blood).

Infant outcomes

- Impact: neonatal and Infant mortality.
- Substantive outcomes: foetal loss (including spontaneous abortion (spontaneous expulsion of a fetus before it is able to survive independently); stillbirth (birth of a foetus with no vital signs, born after the 28th week of pregnancy); perinatal mortality; severe adverse events, including congenital anomalies (a defect that is present at birth).
- Clinically important outcomes: preterm birth (delivery at < 37 weeks gestation); low birthweight (< 2500 g); mean birthweight; cord blood anaemia; adverse events.
- Indicators of malaria infection: placental malaria; haemoglobin levels (infant), cord blood haemoglobin (g/dL), and cord blood PCV; cord blood parasitaemia.

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 (1 June 2014); Central Register of Controlled Trials (CENTRAL); MEDLINE (1966 to 1 June 2014); EMBASE (1974 to February 2012); and LILACS (1982 to February 2012).

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, 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

We applied inclusion criteria to all trials, including those in the previous edition of this Cochrane Review. DR-P and PG independently screened all trials identified by the search strategy (Appendix 1). Using a form based on the inclusion criteria, DR-P and PG assessed eligibility independently. FK checked the completeness of the included trials. We retrieved full text articles for all potentially relevant trials, applied the inclusion criteria, and then compared decisions. We resolved any differences by discussion and, when necessary, consulted with co-authors.Trials identified in the initial abstract screening which did not meet the inclusion criteria are listed in the 'Characteristics of excluded studies'.

Data extraction and management

DR-P and PG independently extracted data using a data extraction form. We extracted data on trial characteristics, including trial site, year, local malaria transmission and resistance, trial methods, participants, interventions, doses and outcomes and entered this data into Review Manager 5.1. The number of participants randomized and the number analysed in the experimental and control arms were extracted in each group for each outcome. For dichotomous outcomes, we recorded the number of participants experiencing the event and the number assessed in each treatment group. For continuous outcomes, we extracted the arithmetic means, standard deviations for each treatment group and the number of participants assessed in each group. We calculated and reported the loss to follow-up in each group.

Assessment of risk of bias in included studies

We independently assessed the trials' methodological quality (risk of bias) of each trial, using the Cochrane Collaboration's tool for assessing the risk of bias (Higgins 2011). The following six components were assessed for each trial: generation of allocation sequence, allocation concealment, blinding (of participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. Each component was classified by 'yes' (low risk of bias), 'no' (high risk of bias), or 'unclear' to indicate level of bias. Where our judgement was 'unclear', we attempted to contact the trial authors for clarification.

Measures of treatment effect

We used the risk ratio (RR) to summarise dichotomous outcomes, reported the mean difference for continuous outcomes, and used the rate ratio for count outcomes. We presented all measures of effect with 95% confidence intervals (CI). One trial had four arms: one a comparison of IPT with nets, and a second comparison with no nets, and these were treated as separate comparisons (Njagi 2003i KEN; Njagi 2003ii KEN); a second trial had two intervention comparisons, so in meta-analysis we split the control group in half for dichotomous outcomes. For continuous outcomes, we split the denominator of the control in half, but applied no correction to the standard deviation.

Unit of analysis issues

If the original trial analyses had not adjusted for clustering, we planned to adjust the results for clustering by multiplying the standard errors of the treatment effect by the square root of the design effect. The design effect would be calculated as 1+(m-1)*ICC where m was the average cluster size and ICC was the intra-cluster correlation coefficient. We planned to estimate the ICC from other trials included in the review or by contacting trial investigators. We also planned to include trials with multiple treatment arms if relevant to any of the comparisons. One trial randomized by compound in The Gambia (Greenwood 1989 GMB). However, we know that compounds are quite small, are grouped around families, and that, even if two women were pregnant at the same time in one family, this would not be quantitatively important in terms of overestimating the precision of the effect estimate.

Dealing with missing data

We planned to use intention-to-treat (ITT) data from the original trials, but it was more practical to use a complete-case analysis, such that we excluded participants for whom no outcome was reported from the analysis. This analysis assumes that the participants for whom an outcome is available are representative of the original randomized patients. If data from the trial reports were insufficient, unclear, or missing, we attempted to contact the trial authors for additional information. In one trial with no standard deviation for birthweight, we used the average of the standard deviation for the other included trials.

Assessment of heterogeneity

We inspected the forest plots to detect overlapping CIs, applying the Chi^2 test and a P value of 0.10 as the cut-off value to determine statistical significance. We also estimated the I^2-statistic and categorized the degree of heterogeneity using standard cut-offs (Higgins 2011).

Data synthesis

We used Review Manager 5.1 for the analysis.

Our primary analysis is stratified by parity, with results grouped into women of low parity (0-1) and multigravidae (1+).

We included a category called 'all women'. This included trials that recruited women irrespective of parity. This analysis included the trials which had stratified the analysis by parity (and were therefore included in the primary analysis), and a second set of trials, which had not. This analysis provides information on the population effects of a policy of providing chemoprevention to all pregnant women.

We used RRs for dichotomous variables and mean differences (MD) for continuous variables; all results are presented with 95% CIs. In the absence of heterogeneity, we used a fixed-effect model for the meta-analysis, and where we detected heterogeneity we used a random-effects model. Weighted averages were calculated where required. We converted Packed Cell Volume (PCV) values to haemoglobin values by dividing by three.

Subgroup analysis and investigation of heterogeneity

We grouped the analysis by parity. Although we intended to investigate heterogeneity by a variety of factors (including HIV

status, risk of bias, geographical region, malaria transmission pattern, antimalarial resistance, ITN use, drug regimen), there were insufficient data to do this.

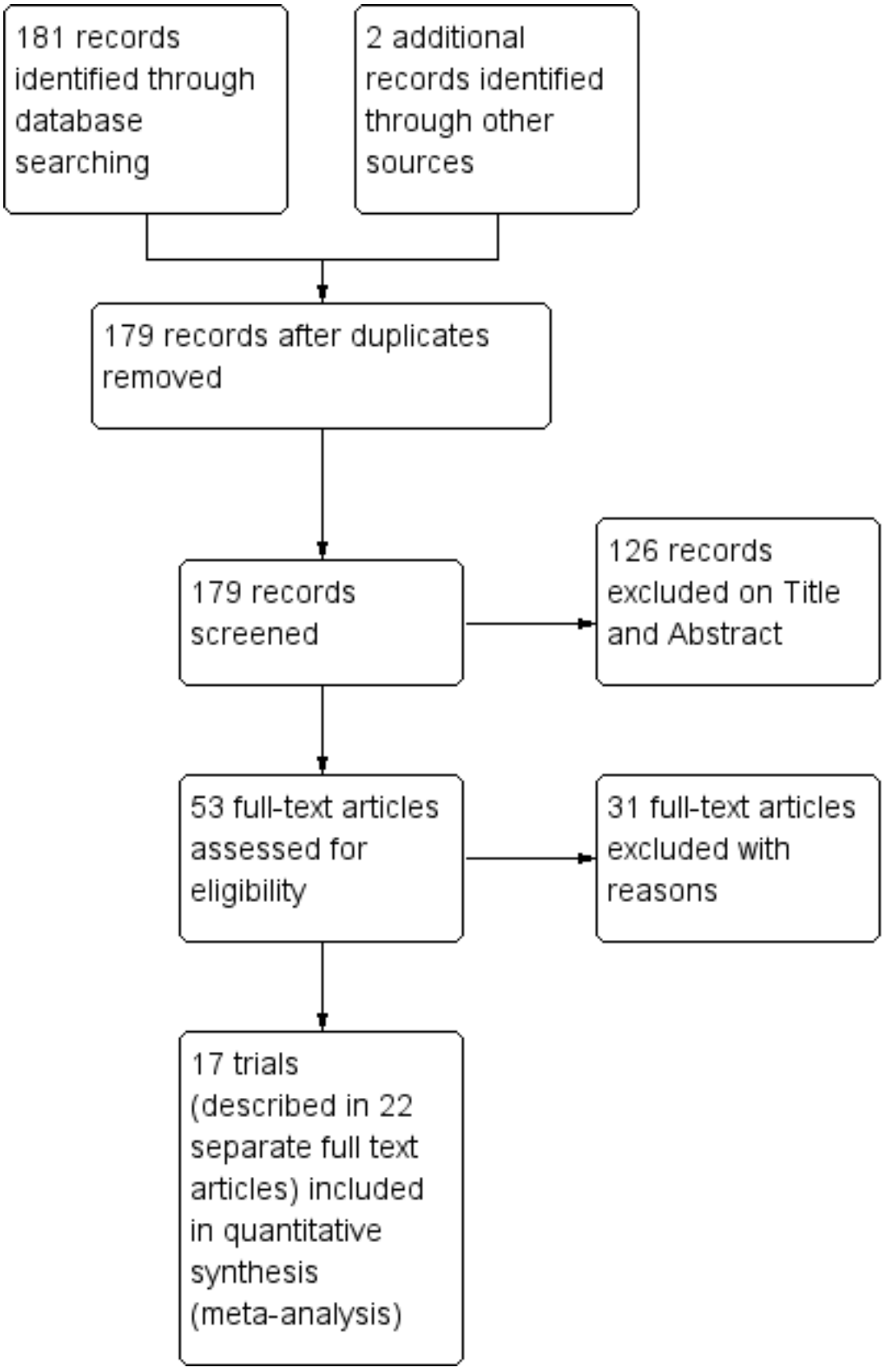
RESULTS

Description of studies

Results of the search

The search was conducted up to 01 June 2014 for the time period 1964 to 2014, and identified 181 references of which two were duplicate trial reports. Out of 179, we retrieved 53 full-text articles for eligibility screening (Figure 2).

Figure 2. Study flow diagram.



Included studies

Seventeen chemoprevention trials, enrolling 20,256 pregnant women, met our inclusion criteria (see 'Characteristics of included studies'). These trials were conducted between 1957 and 2008, in Nigeria (three trials), The Gambia (three trials), Kenya (three trials), Mozambique (two trials), Uganda (two trials), Cameroon (one trial), Burkina Faso (one trial), and Thailand (two trials).

Six different antimalarials were evaluated against placebo or no preventive intervention (ie passive case detection and treatment of clinical cases only); chloroquine (given weekly), pyrimethamine (weekly or monthly), proguanil (daily), pyrimethamine-dapsone (weekly or fortnightly), SP (given twice, monthly or intermittently for up to four doses at least one month apart), and mefloquine (weekly) (see Appendix 2). Fifteen trials reported that drug administration was supervised, and in two trials it was unsupervised (Fleming 1986 NGA; Ndyomugyenyi 2000 UGA).

Eight trials recruited women in all parity groups; four reported aggregate results, and four disaggregated by parity. The rest only recruited low parity women: six were parity 0, and two were women of parity 0-1. One trial only recruited multigravidae (see Appendix 3).

In four trials, all women in both intervention and control groups received a long-lasting ITNs at recruitment (Menendez 2008 MOZ; Ndyomugyenyi 2000 UGA; Ndyomugyenyi 2011 UGA; Njagi 2003i KEN). One additional trial mentioned that ITNs were in use in the area, with a use of 26% (Shulman 1999 KEN; ter Kuile 2007). In six trials iron and folic acid were routinely administered to all pregnant women (Fleming 1986 NGA; Mbaye 2006 GMB; Nahlen 1989 NGA; Njagi 2003i KEN; Njagi 2003ii KEN; Parise 1998i KEN; Parise 1998ii KEN; Villegas 2007 THA), in one trial only iron was administered (Shulman 1999 KEN), and in one trial both iron and folic acid were given to anaemic women (Nosten 1994 THA). The remaining trials did not comment on use of iron or folic acid.

One trial was randomized by compound, but for the analysis we assumed that it was individually randomized (Greenwood 1989 GMB). Two trials with multiple intervention arms were presented by individual arms, and the placebo patients split between the two arms where the treatment arms were both included in the meta-analysis; Parise 1998i KEN compared two doses of SP versus no intervention while Parise 1998ii KEN compared monthly SP versus no intervention; Njagi 2003i KEN compared SP + ITNs versus placebo + ITNs; and Njagi 2003ii KEN compared SP alone versus placebo.

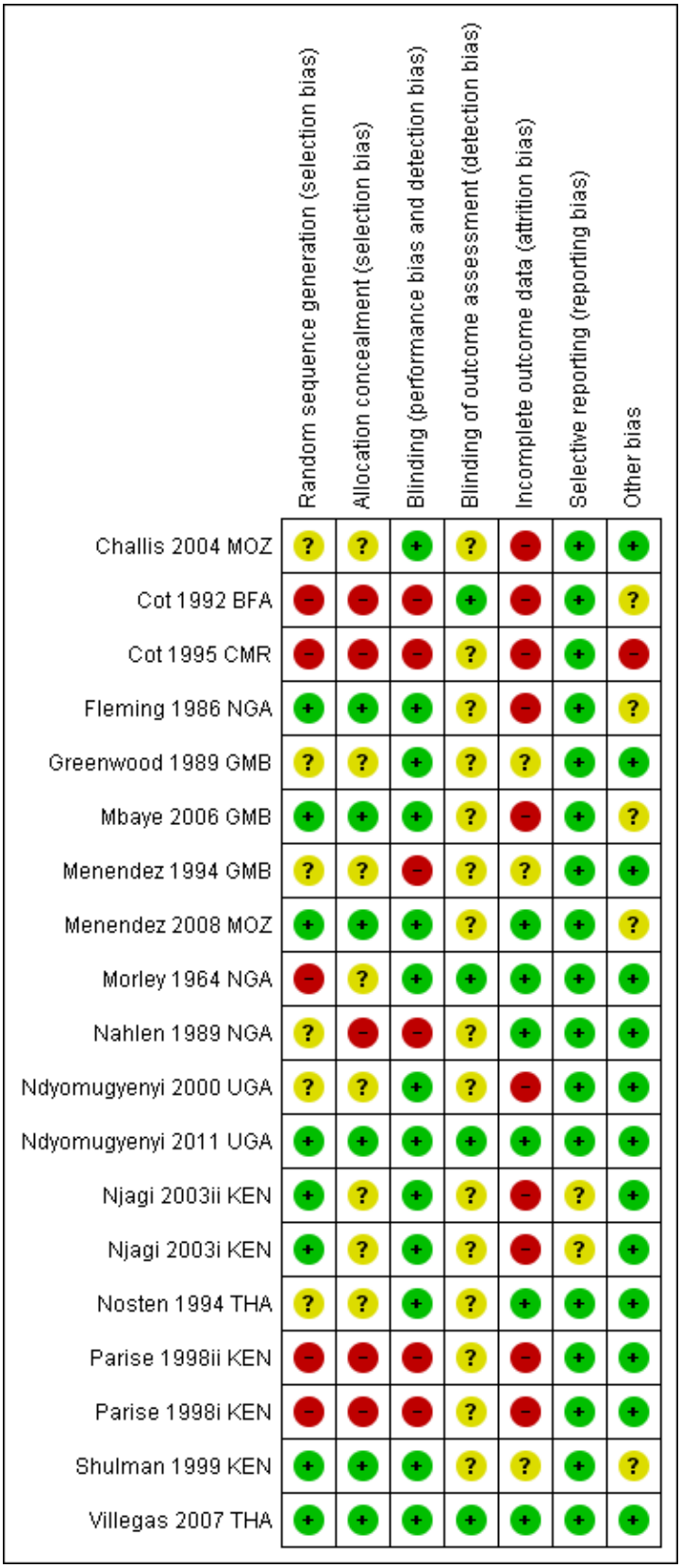
Excluded studies

We excluded 32 trials for the reasons given in the 'Characteristics of excluded studies' table. Also in this review update, we excluded one previously included trial (Hamilton 1972 UGA) as iron was administered to one of the control groups and folic acid to the other, but nothing was mentioned of iron and folates being administered to women in the intervention group (chloroquine).

Risk of bias in included studies

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

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.



Allocation

Six trials adequately described methods of sequence generation and allocation concealment to be considered at low risk of selection bias (Fleming 1986 NGA; Mbaye 2006 GMB; Menendez 2008 MOZ; Ndyomugyenyi 2011 UGA; Shulman 1999 KEN; Villegas 2007 THA). Four trials were quasi-RCT and so at high risk of selection bias (Cot 1992 BFA; Cot 1995 CMR; Morley 1964 NGA; Parise 1998i KEN; Parise 1998ii KEN), and in the remaining seven trials the risk was unclear.

Blinding

Eleven trials used placebo tablets, identical in taste and appearance to the active drug, and were assessed as having low risk of performance bias.

Four trials explicitly stated that outcome assessors were blinded and were assessed as having low risk of detection bias (Cot 1992 BFA; Morley 1964 NGA; Ndyomugyenyi 2011 UGA; Villegas 2007 THA). In the remaining included trials the risk was unclear.

Incomplete outcome data

Six trials had an attrition rate lower than 10% in both the intervention and control arm (Menendez 2008 MOZ; Morley 1964 NGA; Nahlen 1989 NGA; Ndyomugyenyi 2011 UGA; Nosten 1994 THA; Villegas 2007 THA). The remaining 11 trials were at high or unclear risk of attrition bias.

Selective reporting

Birthweight data were not available in one trial, but we obtained this data from a subsequent review (Njagi 2003i KEN; Njagi 2003ii KEN; ter Kuile 2007).

Other potential sources of bias

In one trial, 18 participants were replaced by others after randomization (Fleming 1986 NGA). We sought differences in baseline values with haemoglobin (Analysis 1.4) and detected no obvious difference.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table 1; **Summary of findings 2** Summary of findings table 2; **Summary of findings 3** Summary of findings table 3; **Summary of findings 4** Summary of findings table 4; **Summary of findings 5** Summary of findings table 5; **Summary of findings 6** Summary of findings table 6; **Summary of findings 7** Summary of findings table 7; **Summary of findings 8** Summary of findings table 8

Comparison 1: Chemoprevention (any drug regimen) versus placebo/no chemoprevention

Chemoprevention for women in their first or second pregnancy

Maternal outcomes (see Summary of findings for the main comparison)

Only 15 maternal deaths were reported across all trials with no difference between groups (three trials, 2097 participants, Analysis 1.1, *very low quality evidence*). Maternal death, even in these settings, is a relatively rare event occurring in less than five women per 1000 pregnancies. Consequently trials would need to enrol over 125,000 women to be adequately powered to detect or exclude effects as large as a 25% relative reduction (see Table 1).

No trials reported on episodes of severe malaria, but three trials reported moderate to severe anaemia (defined as Hb < 7/8 g/dL or PCV < 21%). Overall, chemoprevention was associated with a 40% reduction in the risk of moderate to severe anaemia in the third trimester (RR 0.60, 95% CI 0.47 to 0.75; three trials, 2503 participants, Analysis 1.2, *high quality evidence*). This effect was consistent despite variation in doses, and differences in the definition and timing of assessment for severe anaemia (I^2 =0); Parise 1998ii KEN recorded severe anaemia at delivery (after three doses of SP); Shulman 1999 KEN at 34 weeks (after three doses of SP); Menendez 2008 MOZ at delivery (after two doses of SP), and Parise 1998i KEN at the beginning of the third trimester clinic visit (when the second dose of SP was due, and these women had only had one SP dose).

Chemoprevention was also associated with a reduction in the risk of any anaemia (defined as Hb < 10/11/12 g/dL or PCV < 33%/30%), although this reduction was generally of smaller magnitude (RR 0.83, 95% CI 0.74 to 0.93; five trials, 3662 participants, Analysis 1.3, *high quality evidence*). In addition, measures of mean haemoglobin in the third trimester were higher in those receiving chemoprevention (MD 0.41 g/dL, 95% CI 0.29 to 0.54; five trials, 3363 participants, Analysis 1.4).

Chemoprevention was associated with fewer episodes of presumed clinical malaria (history of fever), but this outcome was only reported in two small trials (RR 0.37, 95% CI 0.18 to 0.74; two trials, 307 participants, Analysis 1.5, *low quality evidence*). Instead most trials reported antenatal parasitaemia, defined as either parasitaemia at delivery or parasitaemia at 34 to 36 weeks, with most trials showing benefits but wide variation in the size of the reduction (RR 0.39, 95% CI 0.26 to 0.58; eight trials, 3663 participants, I^2 = 82; Analysis 1.6, *high quality evidence*) This heterogeneity is probably not unexpected given the differences in chemoprevention regimens and malaria endemicity.

Infant outcomes (see Summary of findings 2).

The trials and the meta-analyses are underpowered to confidently detect or exclude effects on spontaneous abortion, perinatal deaths, or neonatal deaths (see Table 1). The CIs range from important benefits to no evidence of any harm in four outcomes: spontaneous abortions (RR 0.65, 95% CI 0.41 to 1.02; five trials, 2876 participants, Analysis 1.9, *low quality evidence*); perinatal deaths (RR 0.73, 95% CI 0.54 to 1.00; two trials, 1620 participants, Analysis 1.11, *low quality evidence*); neonatal deaths (RR 0.62, 95% CI 0.37 to 1.05; two trials, 2156 participants, Analysis 1.12, *low quality evidence*). The preterm births analysis was (RR 0.85, 95% CI 0.66 to 1.10; two trials, 1493 participants, Analysis 1.13, *low quality evidence*).

Chemoprevention was associated with fewer low birthweight infants (RR 0.73, 95% CI 0.61 to 0.87; eight trials, 3619 participants, Analysis 1.14, *moderate quality evidence*). and mean birthweight was higher with chemoprevention (MD 92.72 g, 95% CI 62.05 to 123.39; nine trials, 3936 participants, Analysis 1.15, *moderate quality evidence*).

One very small trial reported no difference in the prevalence of cord blood anaemia (64 participants, Analysis 1.16), and a lower cord blood haemoglobin in babies born to women receiving chemoprevention (MD -1.80 g/dL, 95% CI -3.46 to -0.14; one trial, 64 participants, Analysis 1.17, *very low quality evidence*).

Chemoprevention resulted in fewer cases of placental parasitaemia (RR 0.54, 95% CI 0.43 to 0.69; seven trials, 2830 participants, Analysis 1.17, *high quality evidence*). Only one trial examined cord blood parasitaemia, but there were too few events to be confident of the result (RR 0.47, 95% CI 0.22 to 1.01; one trial, 1335 participants, Analysis 1.19). The children born to mothers receiving monthly SP had reduced cord parasitaemia, whereas those born to mothers receiving two doses of SP did not (Parise 1998i KEN).

Chemoprevention for multigravidae

Maternal outcomes (see Summary of findings 3).

Four trials provided data on multigravidae women. Only one trial assessed mortality with six deaths in the chemoprevention group and four in the control group (RR 1.47, 95% CI 0.42 to 5.21; one trial, 2239 participants, Analysis 1.1, *very low quality evidence*).

No trials reported episodes of severe malaria, but two reported severe anaemia. In one trial more women had severe anaemia in the chemoprevention group (RR 1.20, 95% CI 0.91 to 1.57; one trial, 1954 participants), and the second trial had few events and consequently very wide CIs (RR 0.41, 95% CI 0.08 to 2.09; one trial, 728 participants). The 95% CIs of the overall meta-analysis does not exclude effects as large as those seen in women in their first or second pregnancy but this is probably unlikely (RR 0.96, 95% CI 0.41 to 2.25; two trials, 2682 participants, Analysis 1.2).

No trials reported the risk of mild anaemia, but two trials reported mean haemoglobin at delivery without clinically important differences between groups (MD 0.01 g/dL, 95% CI -0.23 to 0.24; two trials, 676 participants, Analysis 1.4).

No trial measured malaria or febrile episodes in the mother. Four trials reported antenatal parasitaemia, and all four trials report large effects of a similar magnitude to those seen in women in their first or second pregnancy (RR 0.38, 95% CI 0.28 to 0.50; four trials, 3022 participants, Analysis 1.6, *high quality evidence*).

Infant outcomes (see Summary of findings 4).

Two trials included information on infant outcomes after chemoprevention given to multigravid women.

Spontaneous abortions, stillbirths and perinatal deaths were not reported. One trial reported deaths in the first six weeks of life with slightly higher deaths following chemoprevention, but with wide CIs including the possibility of no difference between groups (RR 1.46, 95% CI 0.90 to 2.38; one trial, 2017 participants, Analysis 1.12).

No trials reported mean birthweight in infants born to multigravid women, but three reported the risk of low birthweight. The trend is in favour of chemoprevention but neither the trials, or the meta-analysis reached standard levels of statistical significance (RR 0.86, 95% CI 0.64 to 1.17; three trials, 2743 participants, Analysis 1.14, *very low quality evidence).*

No trials reported measures of placental parasitaemia, cord blood parasitaemia, or cord blood haemoglobin.

Chemoprevention for all women

To evaluate the population effects of a policy of chemoprevention for all pregnant women, regardless of parity, this third analysis includes all trials which recruited women of any parity. Some of these presented results stratified by parity and were included in the analyses above, but a few additional trials did not provide their outcome data stratified by parity.

Maternal outcomes (see Summary of findings 5).

For maternal mortality, only nine maternal deaths were recorded in trials recruiting women of all parities; 4/3019 with chemoprevention and 5/3007 without (four trials, 6026 participants, Analysis 1.1, *low quality evidence*).

For severe anaemia in the mother, there were very few events recorded in the two trials but the risk was lower with chemoprevention (RR 0.19, 95% CI 0.05 to 0.75; two trials, 1327 participants, Analysis 1.2, *low quality evidence*). For any anaemia, no population differences were demonstrated (RR 1.03, 95% CI 0.87 to 1.23; three trials, 3027 participants, Analysis 1.3, *moderate quality evidence*). Three trials reported mean haemoglobin, with only one very small trial from the early 1990s finding benefit with chemoprevention (three trials, 2223 participants, Analysis 1.4).

Clinical malaria (or history of fever) was reported in four of the trials across all parity groups. The older, and smaller trials, suggested a population benefit on clinical malaria but this was not seen in the two recent and much larger trials using two doses of SP (four trials, 3455 participants, Analysis 1.5, *low quality evidence*).

For parasitaemia at delivery, there was considerable heterogeneity between trials (I^2 = 79%). Of the two most recent trials, both large, and both administering two doses of SP, one trial from Mozambique demonstrated a benefit with chemoprevention and one from Uganda did not (five trials, 3961 participants, Analysis 1.6, *low quality evidence*).

Infant outcomes (see Summary of findings 6).

In trials recruiting women of all parities, no differences were demonstrated for spontaneous abortions (three trials, 5767 participants, Analysis 1.9, *low quality evidence*), stillbirths (five trials, 7130 participants, Analysis 1.10, *moderate quality evidence*), perinatal deaths (four trials, 5216 participants, Analysis 1.11, *moderate quality evidence*), or neonatal and infant deaths (five trials, 6313 participants, Analysis 1.12, *moderate quality evidence*). We also pooled across all trials for these outcomes (including those which only recruited women in their first or second pregnancies), and no differences were demonstrated.

Population benefits for the infants were not demonstrated for pre-term birth (two trials, 1174 participants, Analysis 1.13, *low quality evidence*), low birthweight (four trials, 3644 participants, Analysis 1.14, *low quality evidence*), or mean birthweight (five trials, 6007 participants, Analysis 1.15, *moderate quality evidence*).

The effects of chemoprevention on placental parasitaemia were mixed (I^2 = 94%), with large effects in two older trials administering monthly pyrimethamine or weekly chloroquine, and no effect demonstrated in the two more recent trials administering two doses of SP (four trials, 3200 participants, Analysis 1.18, *low quality evidence*).

One trial in Mozambique found a large effect in reducing the risk of cord blood anaemia (RR 0.49, 95% CI 0.30 to 0.80; one trial, 870 participants, Analysis 1.16), and increase in mean cord PCV (MD 1.01%, 95% CI 0.05 to 1.97; one trial, 990 participants, Analysis 1.17).

Adverse effects

We aggregated adverse effects across all parity groups. Reporting of adverse effects was generally poor. Only five trials specifically stated that no adverse effects attributable to the drugs were observed in the mothers, and the rest either did not report adverse effects or the information was unclear. Four trials reported adverse events following SP (Analysis 1.7), and one trial following mefloquine (Analysis 1.8). No differences were seen between the treatment and control groups.

Again, reporting of adverse events in the neonate was generally poor. Episodes of neonatal kernicterus were reported in two trials, and congenital anomalies in two trials, with no differences detected (Analysis 1.20).

Comparison 2. SP IPT chemoprevention for women in their first or second pregnancy

The above analysis examines the effects of drugs known to be effective in preventing malaria at the particular time the trials were carried out. As the WHO currently recommends intermittent dosing with SP, we performed an additional analysis to provide the effect estimates for SP compared to no drug or placebo. The analysis is exactly the same as comparison one, but we included only the six SP trials. These trials administered SP in two doses (Parise 1998i KEN; Njagi 2003i KEN; Njagi 2003ii KEN; Challis 2004 MOZ; Menendez 2008 MOZ; Ndyomugyenyi 2011 UGA), three doses (Shulman 1999 KEN), or monthly (Parise 1998ii KEN).

Maternal outcomes (see Summary of findings 7).

For maternal death, no effect was demonstrated but the analysis is underpowered (Analysis 2.1).

For women of low parity, restricting the analysis to trials of SP did not substantially change the estimates of benefit on severe anaemia (RR 0.60, 95% CI 0.47 to 0.75; three trials, 2503 participants, Analysis 2.2, *high quality evidence*), mild anaemia (RR 0.88, 95% CI 0.88 to 0.96; three trials, 3219 participants, Analysis 2.3, *moderate quality evidence*), or mean haemoglobin (MD 0.41 g higher, 95% CI 0.27 to 0.54; three trials, 2995 participants, Analysis 2.4).

Similarly, the reduction in antenatal parasitaemia is consistent with the overall effect from trials of any chemoprevention (RR 0.38, 95% 0.24 to 0.59; four trials, 2832 participants, Analysis 2.5, *high quality evidence*), but there is insufficient data to draw conclusions on clinical malaria (RR 0.24, 95% CI 0.05 to 1.12; one trial, 174 participants, *very low quality evidence* (Analysis 2.6).

Infant outcomes (see Summary of findings 8).

The trials and the meta-analyses are underpowered to confidently detect or exclude effects on spontaneous abortion, stillbirth, perinatal deaths, or neonatal deaths, but restricting the analysis to trials of SP did not substantially change the estimates of effect (see Analysis 2.7; Analysis 2.8; Analysis 2.9; Analysis 2.10; *low quality evidence*). The trend is towards a reduction in pre-term birth but the 95% CI is wide and includes the possibility of no effect (RR 0.85, 95% CI 0.66 to 1.10; two trials, 1493 participants, Analysis 2.11, *low quality evidence*).

Overall, chemoprevention with SP reduced the incidence of low birthweight but this effect seems to be reducing over time, with large effects in the older trials and no effect seen in the more recent trials using two doses of SP (four trials, 3043 participants, Analysis 2.12, *moderate quality evidence*). However, mean birthweight was higher with SP, and this effect was still present in the most recent trials (MD 105.5 g, 95% CI 68.02 to 142.9, four trials, 2693 participants, Analysis 2.13, *moderate quality evidence*).

Chemoprevention with SP reduced placental parasitaemia (RR 0.45, 95% CI 0.33 to 0.61; three trials, 1633 participants, Analysis 2.14, *high quality evidence*) but only one trial of SP reported cord parasitaemia (RR 0.47, 95% CI 0.22 to 1.01; one trial, 1335 participants, Analysis 2.15).

Adverse effects

No effects were detected with icterus (two trials, 2233 participants, Analysis 2.16) or congenital abnormalities (one trial, 1017 participants, Analysis 2.16).

Comparison 3. Chemoprevention for P. vivax

Only one trial reported on chemoprevention for *P. vivax*, conducted in Thailand with weekly prophylaxis with chloroquine. It was rated at low risk of bias on all criteria. It seemed to prevent completely all episodes of *P. vivax* malaria (RR 0.01, 95% CI 0.00 to 0.20; 942 participants, see Table 2), but had no effect on maternal anaemia, low birthweight, or mean birthweight. It was underpowered to assess effects on mortality.

DISCUSSION

Summary of main results

We included 17 trials, enrolling 14,481 pregnant women, in this Cochrane Review.

For women in their first or second pregnancy, malaria chemoprevention reduces the risk of moderate to severe anaemia by around 40% (*high quality evidence*), and the risk of any anaemia by around 17% (*high quality evidence*). Malaria chemoprevention reduces the risk of antenatal parasitaemia by around 61% (*high quality evidence*), and two trials reported a reduction in febrile illness (*low quality evidence*). There were only 16 maternal deaths and these trials were underpowered to detect an effect on maternal mortality (*very low quality evidence*).

For infants of women in their first and second pregnancies, malaria chemoprevention probably increases mean birthweight by around 93 g (*moderate quality evidence*), reduces low birthweight by around 27% (*moderate quality evidence*), and reduces placental parasitaemia by around 46% (*high quality evidence*). Fewer trials evaluated spontaneous abortions, still births, perinatal deaths, or neonatal deaths, and these analyses were underpowered to detect clinically important differences.

In multigravid women, chemoprevention has similar effects on antenatal parasitaemia (*high quality evidence*) but there are too few trials to evaluate effects on other outcomes.

In trials giving chemoprevention to all pregnant women irrespective of parity, the average effects of chemoprevention measured in all women indicated it may prevent severe anaemia (*low quality evidence),* but consistent benefits have not been shown for other outcomes.

In an analysis confined only to intermittent preventive therapy with SP, the estimates of effect and the quality of the evidence were similar.

A summary of a single trial in Thailand of prophylaxis against vivax showed chloroquine prevented vivax infection (RR 0.01, 95% CI 0.00 to 0.20; 942 participants).

Overall completeness and applicability of evidence

Trials were almost exclusively from Africa and published between 1964 and 2011. These trials, from a variety of settings and using varied chemoprevention regimens, found fairly consistent clinically important benefits for low parity women and their infants.

However, it is possible that with the introduction of ACTs, declining malaria transmission in some areas of Africa, and increasing quality of antenatal services, that the attributable fraction of malaria towards maternal anaemia and low birthweight has been reduced and the large effects seen in these trials may be attenuated by less malaria and better individualized care of women during pregnancy.

Quality of the evidence

The evidence for effects on maternal, foetal and neonatal mortality is generally considered of low or very low quality because the trials and the meta-analysis remain significantly underpowered to confidently prove or exclude clinically important effects.

For women of low parity, we considered the evidence of clinically important effects on anaemia and antenatal parasitaemia to be of high quality, meaning we can have confidence in these results. For the infants of women of low parity, we considered the effects on birthweight to only be of moderate quality because of the high risk of bias of most of the older trials. This means we can have only moderate confidence in the magnitude of these effects.

Trials did not describe the routine health services available to detect and treat malaria infection in both intervention and control arms, but many trials were done some years ago in areas with very basic curative health services available. However, in the future with declining levels of malaria the individual management of illness and malaria at clinic may become an important option to control malaria in pregnancy.

Potential biases in the review process

It seems unlikely that we have missed any trials. As trials did not systematically document adverse effects, it is likely that these have been underestimated in this review.

Agreements and disagreements with other studies or reviews

The findings of this Cochrane Review are consistent with previous editions (Garner 2006; ter Kuile 2007). The findings are also consistent with the findings of a review comparing observational and randomized evidence (McClure 2013). McClure 2013 points out that the fairly modest effects seen in RCTs, where delivery of care is often strengthened and adherence assured, were attenuated in the observational studies where, the authors surmise, delivery of the intervention and adherence to it may be attenuated. However, this contrasts with a study estimating the effects of IPT with SP on low birthweight and neonatal mortality from survey data: the trial estimates are remarkably similar to the results observed with IPT with SP from the trial data reported in this and previous analysis (Eisele 2012; ter Kuile 2007).

AUTHORS' CONCLUSIONS

Implications for practice

Routine chemoprevention to prevent malaria and its consequences has been extensively tested in RCTs, with clinically important benefits on anaemia and parasitaemia in the mother, and on birthweight in infants.

The data also assists in showing the potential attribution of malaria towards key endpoints, and what can be achieved by successful prevention to assist in modelling studies examining the impact of malaria on pregnancy.

Implications for research

Identifying current effective chemoprevention regimens remains a challenge, especially with the spread of drug-resistant malaria, in particular against SP which is the only antimalarial currently recommended for IPT in pregnant women. There is justification for assessing the safety and efficacy of effects of alternative drugs that can replace SP in areas with high SP resistance, or alternative strategies that could replace IPT during pregnancy, such as intermittent screen and treat (IST) approaches that focus on prompt accessible treatment for anaemia and asymptomatic parasitaemia (Tagbor 2010).

All new trials should systematically and carefully collect adverse effects of regimens.

The data on the longer term impact on infants is poor and needs further study: currently the evidence mainly relates to effects on clinically important outcomes, such as preterm birth and birthweight.

There is a dearth of data from endemic areas outside of Africa, such as Asia and Latin America.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Challis 2004 MOZ

Methods	Trial design: RCT Data collected: 2001 to 2002 Length of follow-up: from first antenatal visit to first week after delivery Frequency of follow-up: monthly
Participants	Parity: 0-1 Number: 600 Inclusion criteria: nulliparous and primiparous women under 21 years Excluded: none stated
Interventions	1. SP (3 tablets): at enrolment and in third trimester 2. Placebo Other: clinical malaria symptoms treated with CQ, SP or quinine and tetracycline irrespective of allotment Administration supervised: yes
Outcomes	1. Parasitaemia at second visit 2. Placenta malaria 3. Birthweight
Notes	Location: Mozambique Urban/rural: both (women from Matola - town and Boane - village) Malaria transmission: 20% prevalence Drug resistance: chloroquine resistance present HIV prevalence: 10% Funding: Department of Research Co-operation with Developing countries (SAREC) at the Swedish International Development Authority (Sida) and from Mid Sweden Research and Development Centre (FoU)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The data were analysed on an ITT basis. ITT includes a random allocation procedure producing comparable groups and an analysis of the data according to the way we intended to treat the subjects". Women were "randomly assigned" to receive SP or placebo. No sufficient information provided how the allocation sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Packages of SP or placebo tablets.

Challis 2004 MOZ *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	"Three tablets (SP or placebo) were given in a double-blind manner: either SP/SP – an initial treatment dose of SP at enrolment with a second dose at the beginning of the third trimester; or placebo/placebo…The placebo dose was three similar tablets in shape and colour as SP tablets."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided, except that all slides were analysed and double checked at the malaria laboratory at the Ministry of Health.
Incomplete outcome data (attrition bias) All outcomes	High risk	At second dose: 189/600 = 31.5% lost to follow-up. At delivery: 309/600 women = 51.5% lost to the follow-up peripheral blood analyses (153/300 = 51% from the placebo group and 156/300 = 52% from the SP group).
Selective reporting (reporting bias)	Low risk	No selective reporting observed.
Other bias	Low risk	None identified.

Cot 1992 BFA

Methods	Trial design: Quasi-RCT Data collected: 1987 to 1988 Length of follow-up: approximately five months (from the first visit to the clinic which was for most women before the 5th month of pregnancy, until delivery) Frequency of follow-up: twice a week
Participants	Parity: all women Number: 1464 Inclusion criteria: every pregnant woman attending urban maternal and child health centre Excluded: none stated
Interventions	1. Chloroquine: weekly 2. Nothing Other: no information Administration supervised: yes
Outcomes	1. Placental parasitaemia 2. Mean birthweight and low birthweight
Notes	Location: Burkina Faso Urban/rural: urban (the city of Banfora) Malaria transmission: hyperendemic, with seasonal transmission Drug resistance: chloroquine resistance may be present 19% parasitaemia in trial population

Cot 1992 BFA *(Continued)*

	Funding: INSERM (Institut National de Ia Santé et de Ia Recherche Médicale): Reseau Nord-Sud no. 486 NS2.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"For the sake of simplicity, an alternate allocation of treatment was performed, in which the women were divided into two groups (treated and control)." No specific procedure used to generate allocation sequence.
Allocation concealment (selection bias)	High risk	Allocation not concealed.
Blinding (performance bias and detection bias) All outcomes	High risk	"For technical reasons, it was not possible to give a placebo to women in the control group." Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Laboratory technicians had no information on the status of the individuals from whom the samples had been taken, as did the midwives who weighed the newborn babies" Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition rate: 263/1464 (17.96%). There were 20.3 % (151/745 women) with no outcome in the experimental arm (chloroquine): 29 excluded after randomization (stillbirths, abortions, multiple pregnancies). The other 122/745 women (16.4%) delivered outside of the hospital. There were 22.9% (165/719 women) with no outcome in the control arm: 24 excluded, 141/719 (19.6%) delivered outside of the hospital.
Selective reporting (reporting bias)	Low risk	No selective reporting observed.
Other bias	Unclear risk	Approximately 20 women were allocated to the control group at the beginning of the trial and reclassified in the treated group a few days later. "These subjects were not clearly identified, and it was impossible to exclude them afterwards."

Cot 1995 CMR

Methods	Trial design: Quasi-RCT Data collected: 1991 to 1993 Length of follow-up: from first prenatal visit until delivery (two to five months) Frequency of follow-up: weekly
Participants	Parity: para 0 Number: 266 Inclusion criteria: primigravidae antenatal clinic attendees

Cot 1995 CMR *(Continued)*

	Excluded: none stated
Interventions	1. Chloroquine: 300 mg per week until delivery 2. Nothing Other: no information Administration supervised: yes
Outcomes	1. Antenatal parasitaemia 2. Placental malaria 3. Birthweight
Notes	Location: Cameroon Urban/rural: urban (town of Ebolowa) Malaria transmission: hyperendemic area with high transmission all year round Drug resistance: moderate chloroquine resistance Funding: Ministère Français de la Coopération (FAC paludisme)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"After being examined by the hospital physician, any primigravida living in the study area and attending the clinic for a first prenatal visit… was introduced to an investigator who obtained their informed consent and allocated them alternately to a chloroquine treatment (CQ) group or a control (CT) group." Trial described as "randomized, double-blind", but participants were "alternately allocated".
Allocation concealment (selection bias)	High risk	Allocation not concealed.
Blinding (performance bias and detection bias) All outcomes	High risk	"Women in the control group followed the usual hospital procedures; placebos were not used". Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors were blinded. No information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rate was 21.4% (28/131) in the experimental arm (chloroquine) and 21.5% (29/135) in the control arm for the duration of the pregnancy.
Selective reporting (reporting bias)	Low risk	No selective reporting observed. Antenatal parasitaemia not clearly reported.
Other bias	High risk	"Of the CT group women, 39 (56%) declared that on their own initiative, they had taken one or more short treatments of either chloroquine or amodiaquine during the course of their pregnancy because they thought they had contracted malaria." Possible protocol violation.

Fleming 1986 NGA

Methods	Trial design: RCT Data collected: unclear (before 1985). First attendance to the clinic: 1977 to 1978 Length of follow-up: from first prenatal visit until 6 weeks after delivery Frequency of follow-up: at least once every two weeks up to the 36th week of gestation and subsequently, weekly until delivery Haematological observations were performed at first attendance, 28 weeks and 36 weeks of gestation, at delivery and 6 weeks postpartum
Participants	Parity: para 0 Number: 200 Inclusion criteria: primigravidae under 16 years attending antenatal clinic; Hausa tribe Excluded: 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 Administration supervised: no
Outcomes	1. Antenatal parasitaemia and haemoglobin 2. Birthweight
Notes	Location: Nigeria Urban/rural: urban (Zaria) Malaria transmission: unstable area with seasonal transmission Drug resistance: none Funding: WHO, Ahmadu Bello University, Smith Kline and French Laboratories Ltd (UK) and Imperial Chemical Industries

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants "randomly allocated" to one of five treatment groups, using random numbers table.
Allocation concealment (selection bias)	Low risk	"Neither the researchers nor the patients were aware of the treatment allocated until after the completion of the study." Treatment allocation code was used.
Blinding (performance bias and detection bias) All outcomes	Low risk	"The manufacturers supplied active tablets or spansules and the placebos, which could not be distinguished by sight."

Fleming 1986 NGA *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors were blinded. No information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	"Only 89 women out of 200 delivered in the hospital... 12/200 (6%) did not attend again (the clinic) after the first or second visits; a further 72/200 (36%) did not continue until the postnatal visit." Inadequate details but there is evidence to suggest that the attrition rate was quite high.
Selective reporting (reporting bias)	Low risk	No selective reporting observed.
Other bias	Unclear risk	"18 patients were replaced in the trial by others; this was arranged by a moderator (Dr. B. M. Greenwood), who was not otherwise involved in the research, but had access to the treatment allocation code for this purpose…Eighteen patients were replaced in the trial by others."

Greenwood 1989 GMB

Methods	Trial design: Trial randomized by compound Data collected: 1984 to 1987 Length of follow-up: from first prenatal visit until one week after delivery Frequency of follow-up: unclear but administration was on weekly basis
Participants	Parity: all women Number: 1049 Inclusion criteria: all women in trial villages who became pregnant; some sub-studies only followed up primigravidae Excluded: none stated
Interventions	1. Pyrimethamine 25 mg and dapsone 100 mg: fortnightly 2. Placebo Given by village people employed by the project Other: no information Administration supervised: yes
Outcomes	1. Antenatal parasitaemia 2. Birthweight 3. Packed cell volume 4. Maternal death 5. Perinatal death 6. Infant death
Notes	Location: The Gambia Urban/rural: urban

Greenwood 1989 GMB *(Continued)*

	Malaria transmission: seasonal Drug resistance: none reported Funding: Unclear For the analysis we assumed that it is individually RCT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Once a woman had reported to a traditional birth attendant that she was pregnant, she was allocated to receive one tablet of Maloprim fortnightly or placebo and issued with a record card by an MRC field worker. Randomization was by compound." No details provided of a specific procedure used to generate allocation sequence.
Allocation concealment (selection bias)	Unclear risk	"Treatment was indicated on the record card by a pictorial representation of a coloured tablet (white for Maloprim, pink for placebo)". Insufficient details provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo tablets used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"1208 pregnancies which progressed beyond the 28th week were recorded during the 3 years of the survey. During 1049 (87%) of these pregnancies women reported to the TBA resident and received one or more doses of Maloprim or placebo." Unclear risk. Assumption is that attrition rate was 13.2% (159/1208, where 159 = 1208-1049).
Selective reporting (reporting bias)	Low risk	No apparent risk.
Other bias	Low risk	None identified.

Mbaye 2006 GMB

Methods	Trial design: RCT Data collected: 2002 to 2004 Length of follow-up: From the 1st antenatal visit to 1 year after delivery Frequency of follow-up: twice per week before delivery; 6 weeks and 1 year after delivery
Participants	Parity: multigravidae only Number: 2688

Mbaye 2006 GMB *(Continued)*

	Inclusion criteria: pregnancy of more than 15 weeks duration Excluded: Hb concentration of < 7 g/dL; allergy to sulphonamides; severe or chronic disease
Interventions	1. 3 tablets of SP (up to 4 drug administrations; mean gap 29 days) 2. 3 tablets of placebo (up to 4 administrations; mean gap 28 days) Other: iron and folic acid for all Administration supervised: yes
Outcomes	1. Maternal mortality 2. Prevalence of peripheral parasitaemia after delivery 3. Anaemia/Hb 4. Birth outcomes 5. Infant death (death by 6 weeks)
Notes	Location: The Gambia Urban/rural: urban (around the town Farafenni) Malaria transmission: seasonal Drug resistance: unknown HIV: HIV negative women; prevalence of HIV infection among antenatal clinic attenders < 1% Funding: The Medical Research Council and the Gates Malaria Partnership, funded by the Bill and Melinda Gates foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Women were individually randomized in blocks of 12".
Allocation concealment (selection bias)	Low risk	"Tablets were pre-packed in envelopes…pre-labelled with the same packet number and placed in a wallet bearing the subject's number and packet number."
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical SP and placebo tablets used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rate quite high: 459/2688 (17.1 %): Loss to follow-up in SP group 223/1346 (16.6%) and in the placebo group 236/1342 (17.6%).
Selective reporting (reporting bias)	Low risk	No apparent risk.
Other bias	Unclear risk	Limited information obtained on bednet use (an important variable in determining the efficacy of IPT). Actual birthweights obtained from only 5% of

Mbaye 2006 GMB *(Continued)*

	women (87% of the newborn babies were weighed between 3 and 5 days after birth).

Menendez 1994 GMB

Methods	Trial design: Cluster-RCT Data collected: 1987 to 1990 Length of follow-up: from first antenatal visit to third day after delivery Frequency of follow-up: unclear but administration by traditional birth attendants was on weekly basis
Participants	Parity: 0 Number: 230 Inclusion criteria: primigravidae resident in trial area Excluded: none stated
Interventions	1. Pyrimethamine and dapsone: weekly (one tablet of Maloprim weekly: pyrimethamine 12.5 mg and dapsone 100 mg) 2. Placebo Given by village people employed by the project Other: no information Administration supervised: yes
Outcomes	1. Placental malaria 2. Pregnancy outcomes 3. Birthweight 4. Neonatal mortality
Notes	Location: The Gambia Urban/rural: rural (trial area: 15 villages and 3 hamlets, 12 to 35 km from the town of Farafenni) Malaria transmission: seasonal HIV: no information provided Drug resistance: none reported Funding: no information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "a randomized, double-blind, placebo-controlled community based trial" but no details of the way allocation sequence was generated are provided.
Allocation concealment (selection bias)	Unclear risk	"After consent had been obtained, women were randomized by compound of residence to receive weekly either one tablet of Maloprim or placebo."

Menendez 1994 GMB *(Continued)*

		Comment: insufficient detail.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear. "Two hundred and thirty women were recruited into the study over a 3-year period…" Afterwards, only 82 women are mentioned as participants in the maloprim group and 89 women in the placebo group. Overall attrition rate 59/230 (25.7%) The total number of women with incomplete outcome data 28/230 (12.2%). Four women had an abortion, 17 had stillbirths, five women died, and 2 other women (0.9%) were lost to follow-up.
Selective reporting (reporting bias)	Low risk	No selective reporting observed.
Other bias	Low risk	No other source of bias identified.

Menendez 2008 MOZ

Methods	Trial design: RCT Data collected: August 2003 to April 2005 Length of follow-up: from recruitment until 8 weeks postpartum Frequency of follow-up: unclear. Mean number of outpatient visits during pregnancy 1.64 in the SP and 1.83 in the placebo group. Mean number of visits post-partum 0.69 in the SP group and 0.68 in the placebo group
Participants	Parity: all Number: 1030 Inclusion criteria: permanent residents of the CISM trial area with gestational age ≤ 28 weeks Excluded: allergic to sulpha drugs
Interventions	1. Two doses of SP given at least one month apart 2. Placebo - same Other: ITNs Administration supervised: yes
Outcomes	1. Maternal mortality 2. Peripheral parasitaemia 3. Any placental malaria infection (fever episode) 4. Severe anaemia (PCV < 21%)

Menendez 2008 MOZ *(Continued)*

5. Pregnancy outcomes
6. Perinatal mortality
7. Neonatal mortality
8. Birthweight
9. Pre-term birth
10. Cord blood parasitaemia
11. Cord blood anaemia (PCV < 37%)
12. Newborn gestational age

Notes	Location: Mozambique Urban/rural: urban Malaria transmission: perennial malaria transmission with some seasonality Drug resistance: evidence suggests that SP was highly effective in the area during the trial HIV: In the SP group, 26.5% (117/441 women), and in the placebo group, 21.2% (91/429 women). Overall: 23.9% Funding: Fondo de Investigaciones Sanitarias del Instituto de Salud Carlos III (grant number CM03/00125); Banco de Bilbao, Vizcaya, Argentaria Foundation (grant number BBVA 02-0); Spanish Agency for International Cooperation (AECI)

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".
Allocation concealment (selection bias)	Low risk	"Tablets of SP or placebo... were stored in 10 bottles labelled only with a single treatment identification letter."
Blinding (performance bias and detection bias) All outcomes	Low risk	SP and placebo tablets "identical in shape and colour".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the SP group 35/515 (6.8%) did not receive 2 doses and birthweight was not measured for 7/501 (1.4%) live births. In the placebo group 29/515 (5.6%) did not receive 2 doses and birthweight was not measured for 7/503 (1.4%) live births.
Selective reporting (reporting bias)	Low risk	None identified (trial protocol available).
Other bias	Unclear risk	Data were analysed by ITT analysis whereby all randomized women were included regardless of whether or not they had received the intervention and the number of doses. Women with a multiple delivery (twins or triplets) as well as those who did not receive all three doses were also included in the analysis.

Morley 1964 NGA

Methods	Trial design: Quasi-RCT Data collected: 1957 Length of follow-up: from first antenatal visit to delivery Frequency of follow-up: insufficient detail (drugs given monthly)
Participants	All women Number: 429 Inclusion criteria: all pregnant women registered at dispensary Excluded: none stated
Interventions	1. Pyrimethamine: monthly 2. Placebo Other: fever treated with chloroquine sulphate in both groups Administration supervised: women were given drugs during antenatal visits
Outcomes	1. Antenatal weight gain 2. Fever episodes 3. Parasitaemia 4. Placental infection 5. Birthweight 6. Perinatal mortality
Notes	Location: Nigeria Urban/rural: rural (the village of Imesi) Malaria transmission: holoendemic area Drug resistance: none Funding: no information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"As the pregnant women were registered at the dispensary, they were given consecutive numbers and allotted to one or other of two groups. All women with even numbers were given 2 tablets (50 mg) of pyrimethamine once a month… The control group (the odd numbers) were given two tablets of placebo". Comment: not randomized.
Allocation concealment (selection bias)	Unclear risk	Insufficient detail provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Pyrimethamine and "similar tablets" placebo were used

Morley 1964 NGA *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Blood films were examined in the hospital laboratory… The technicians did not know to which group a mother belonged." Assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Birthweight: data available for 93.7% (402/429 women). Incomplete data outcome for 6.3% (27/429) women: 17 stillbirths and 10 twin deliveries were excluded.
Selective reporting (reporting bias)	Low risk	No selective reporting observed.
Other bias	Low risk	None identified.

Nahlen 1989 NGA

Methods	Trial design: RCT Data collected: from January to June 1988 Length of follow-up: 77 days (mean interval from day 7 post-chloroquine treatment to documentation of parasitaemia was 74 days for pyrimethamine group) Frequency of follow-up: weekly. Follow-up examinations and blood smears were obtained on days 2, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, and 77
Participants	Parity: all Number: 71 Inclusion criteria: antenatal and attending hospital and health centre; < 34 weeks gestation; no recent chloroquine taken; parasitaemic > 500 parasites/µL blood Excluded: history of antimalarial drug ingestion during the previous week
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 Administration supervised: yes
Outcomes	1. Antenatal parasitaemia
Notes	Location: Nigeria Urban/rural: urban (Ilorin, the capital of Kwara State) Malaria transmission: endemic area Drug resistance: possible pyrimethamine resistance present Funding: US Agency for International Development, Africa Child Survival-Initiative-Combatting Childhood Communicable Diseases Project, 698-0421

Risk of bias

Bias	Authors' judgement	Support for judgement

Nahlen 1989 NGA *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Women in group 2 were assigned randomly to a pyrimethamine treatment or a control group." The statement that women were randomly assigned is insufficient to be confident that the allocation sequence was genuinely randomized.
Allocation concealment (selection bias)	High risk	"The treated group was observed to take 25 mg of pyrimethamine weekly and was instructed to take folic acid and iron supplements daily, while the control group took only folic acid and iron daily." Allocation not concealed.
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"In vivo tests were completed successfully in all 71 women enrolled." Comment: There were no missing outcome data.
Selective reporting (reporting bias)	Low risk	No apparent risk.
Other bias	Low risk	None identified.

Ndyomugyenyi 2000 UGA

Methods	Trial design: RCT Data collected: 1996 to 1998 Length of follow-up: from first antenatal visit to first week postpartum Frequency of follow-up: monthly
Participants	Parity: 0 Number: 860 Inclusion criteria: primigravidae Excluded: severe anaemia (< 8 g)
Interventions	1. Chloroquine 2. Placebo 3. Iron + folate (not included in the analysis) Other: clinical malaria symptoms treated with 25 mg/kg of chloroquine for three days, ITNs Administration supervised: no
Outcomes	1. Haemoglobin 2. Birthweight
Notes	Location: Uganda

Ndyomugyenyi 2000 UGA *(Continued)*

	Urban/rural: rural (Hoima District) Malaria transmission: hyperendemic area Drug resistance: unknown Funding: The Danish Bilharziasis Laboratory, Denmark

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"After clinical and laboratory examination, women were randomly assigned to 1 of the 3 intervention group". Insufficient details.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo and active tablets of the same colour and shape.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided to make a judgement whether or not the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	A high attrition rate of 32.6% (268 out of 823 women were lost to follow-up).
Selective reporting (reporting bias)	Low risk	No apparent risk.
Other bias	Low risk	None identified.

Ndyomugyenyi 2011 UGA

Methods	Trial design: individually RCT Data collected: 2004 to 2008 Length of follow-up: from first antenatal visit to 28 days after delivery Frequency of follow-up: regularly through ANC clinics, and every seven days postnatally
Participants	Parity: all parities Number: 5775 randomized; 4715 singleton births followed up Inclusion criteria: pregnant women < 27 weeks at first clinic visit Excluded: > 26 weeks pregnant, non-residents and temporary residents
Interventions	1. ITNs + placebo 2. ITNS + IPT 3. IPT

Ndyomugyenyi 2011 UGA *(Continued)*

	Drugs given under direct observation. Two doses of SP.
Outcomes	Prevalence of maternal anaemia (Hb < 11.0 g/L) mean Hb at 36 to 40 weeks Clinical malaria Peripheral and placental parasitaemia Abortions, preterm births, stillbirths, perinatal deaths, neonatal deaths Low birthweight Mean birthweight
Notes	Location: Kabale Highlands, Uganda Urban/rural: rural Malaria transmission: low/unstable area Drug resistance: SP thought to be effective HIV: low Funding: Gates Partnership

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random number list".
Allocation concealment (selection bias)	Low risk	"individual sealed envelopes".
Blinding (performance bias and detection bias) All outcomes	Low risk	"Tablets of SP or placebo, identical in shape and colour".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All study participants, health staff and researchers were blind to drug assignment (SP or placebo)".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Delivery follow-up: 92%, 92%, and 93% to one month.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	None identified.

Njagi 2003i KEN

Methods	RCT

Njagi 2003i KEN *(Continued)*

Participants	Low parity (0-1) Number: 963 Inclusion criteria: gestational age of between 12 and 24 weeks Exclusion criteria: HIV/AIDS, severe systemic diseases
Interventions	1. ITN + IPT-SP (2 doses) 2. ITN + placebo (2 doses) Other: Folic acid and iron given to all women Administration supervised: yes
Outcomes	1. Maternal anaemia 2. Maternal mortality 3. Birth outcomes: abortions Length of follow-up: From 1st antenatal visit to 1 week after delivery Frequency of follow-up: monthly antenatal clinic visits
Notes	Location: Western Kenya Malaria transmission: intense Drug resistance: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random number sequences in blocks of 12.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Placebo and active drug tablets were of equal size, colour and shape. The investigators had no knowledge of the assigned groups until after data collection, editing and data analysis were completed."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rate 17.4% (168/963): 114 lost due to migration, 35 – home delivery, 19 – refused to continue. Attrition rate in ITN and SP group 35/242 (14.5%), in ITN and placebo group 32/238 (13.4%), in SP group 52/245 (21.2%), in placebo group 49/238 (20.6%). Together with the exclusions, 211/963 (21.9%) women with no treatment outcome.
Selective reporting (reporting bias)	Unclear risk	Mentioned that mode of delivery, birthweight and baby's Hb were recorded but they were never reported. The trial report fails to include results for a key outcome that would be expected to have been reported for such a trial.
Other bias	Low risk	None identified.

Njagi 2003ii KEN

Methods	As for Njagi 2003i KEN
Participants	As for Njagi 2003i KEN
Interventions	1. IPT-SP (2 doses) 2. Placebo (2 doses) Other: Folic acid and iron given to all women
Outcomes	As for Njagi 2003i KEN
Notes	As for Njagi 2003i KEN

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random number sequences in blocks of 12.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Placebo and active drug tablets were of equal size, colour and shape. The investigators had no knowledge of the assigned groups until after data collection, editing and data analysis were completed."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition rate 17.4% (168/963): 114 lost due to migration, 35 – home delivery, 19 – refused to continue. Attrition rate in ITN and SP group 35/242 (14.5%), in ITN and placebo group 32/238 (13.4%), in SP group 52/245 (21.2%), in placebo group 49/238 (20.6%). Together with the exclusions, 211/963 (21.9%) women with no treatment outcome.
Selective reporting (reporting bias)	Unclear risk	Mentioned that mode of delivery, birthweight and baby's Hb were recorded but they were never reported. The trial report fails to include results for a key outcome that would be expected to have been reported for such a trial.
Other bias	Low risk	None identified.

Nosten 1994 THA

Methods	Trial design: RCT Data collected: 1987 to 1990 Length of follow-up: from first antenatal visit at > 20 weeks of estimated gestation to 2 years after delivery Frequency of follow-up: weekly

Nosten 1994 THA *(Continued)*

Participants	Parity: all Number: 339 Inclusion criteria: antenatal attendees > 20 weeks of gestation Excluded: none stated
Interventions	1. Mefloquine: weekly 2. Nothing Other: treated antenatally if parasitaemic; given folic acid and iron if anaemic Administration supervised: yes
Outcomes	1. Antenatal episodes of parasitaemia 2. Anaemia 3. Preterm birth 4. Birthweight 5. Perinatal death
Notes	Location: Thailand Urban/rural: rural (camps Wangka, Shoklo, Bonoko) Malaria transmission: unstable malarious area (mesoendemic) Drug resistance: multiple drug resistance present Funding: United Nations Development Programme/World Bank/WHO Special Programme for Research and Training in Tropical Diseases; Wellcome Trust of Great Britain; Prevention Foundation, The Hague

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trial described as "a double-blind, placebo-controlled trial". No details provided of the sequence generation method used.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo tablets identical with treatments were used. "The investigators were unaware of the randomization".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessors not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate 8% (10/119) in Phase 1 and 8% (18/220) in Phase 2. Across groups: 7.1% (12/170) were excluded from the mefloquine group and 9.5% (16/169) were excluded from the placebo group. Explanation provided.
Selective reporting (reporting bias)	Low risk	No apparent risk.
Other bias	Low risk	None identified.

Parise 1998i KEN

Methods	Trial design: Quasi-RCT Data collected:1994 to 1996 Length of follow-up: from first antenatal visit to delivery; for infants: follow-up at 3-7 days of life and at 6 weeks of age Frequency of follow-up: at two and four weeks after enrolment and then monthly until delivery
Participants	Parity: para 0-1 Number: 2077 Inclusion criteria: antenatal clinic attendees; first or second pregnancy Excluded: prior ADRs to sulfa-containing or other antimalarial medications
Interventions	1. SP: treatment dose, repeated in late pregnancy (2 doses); not administered at intervals of less than 1 month 2. No intermittent preventive treatment, SP given with recent history of fever or parasitaemia Other: 200 mg ferrous sulphate and 5 mg folic acid daily Administration supervised: Yes
Outcomes	1. Maternal anaemia 2. Mean haemoglobin 3. Placental infection 4. Birthweight 5. Preterm birth 6. Stillbirth 7. Neonatal death
Notes	Location: Kenya Urban/rural: urban Malaria transmission: hyperendemic area Drug resistance: chloroquine HIV seroprevalence : 2SP - 26.9% (53/196); Case management - 26.9% (57/212) Funding: UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (ID No. 940060); the US Agency for International Development through the Health and Human Resources Analysis for Africa (HHRAA) Project through a Participating Agency Service Agreement (PASA number AOT-0483-P-HI-2171)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Women were systematically assigned to receive one of three regimens using a rotating assignment based on day of clinic visit." Comment: allocation was not random.

Parise 1998i KEN *(Continued)*

Allocation concealment (selection bias)	High risk	Allocation schedule not concealed.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding. Women were systematically assigned to receive either two-dose SP with treatment doses at enrolment and again early in the third trimester, or case management (CM).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	"Six hundred ninety-nine women (34%) were lost to follow-up during pregnancy because they moved out of the study area or failed to return for follow-up and the study team was unable to locate their houses." Data was not available for 36.5% (248/680) women in the 2 SP and 35.9% (264/736) women in the case management group.
Selective reporting (reporting bias)	Low risk	The trial protocol was available. No selective reporting observed.
Other bias	Low risk	No apparent risk.

Parise 1998ii KEN

Methods	As for Parise 1998i KEN
Participants	As for Parise 1998i KEN
Interventions	1. SP: monthly with treatment doses at enrolment and then monthly through 34 weeks of gestation 2. No intermittent preventive treatment, SP given with recent history of fever or parasitaemia
Outcomes	As for Parise 1998i KEN
Notes	As for Parise 1998i KEN HIV seroprevalence: Monthly SP - 23.7% (40/169); Case management - 26.9% (57/212)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Women were systematically assigned to receive one of three regimens using a rotating assignment based on day of clinic visit." Comment: allocation was not random.
Allocation concealment (selection bias)	High risk	Allocation schedule not concealed.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding.

Parise 1998ii KEN *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided as to whether the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Six hundred ninety-nine women (34%) were lost to follow-up. Data was not available for 34.8% (230/661) in the monthly SP and 35.9% (264/736) in the case management group.
Selective reporting (reporting bias)	Low risk	No selective reporting observed.
Other bias	Low risk	None identified.

Shulman 1999 KEN

Methods	Trial design: RCT Data collected: 1996 to 1997 Length of follow-up: from first antenatal visit to one month post delivery (neonatal period) Frequency of follow-up: unclear (drug administered as follows: three doses for women recruited at 16 to 19 weeks of gestation; two for those recruited at 20 to 26 weeks; and one for those recruited at 27 to 30 weeks, followed by a visit at 34 weeks and a visit 4 weeks after delivery).
Participants	Parity: 0 Number: 1264 Inclusion criteria: primigravidae attending antenatal clinics at a health centre (1) or hospital (1); singleton pregnancy; 16 to 30 weeks gestation Excluded: severely anaemic and sick patients excluded
Interventions	1. SP: 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 Administration supervised: yes
Outcomes	1. Antenatal: parasitaemia and haemoglobin at 34 weeks 2. Stillbirth 3. Neonatal death 4. Maternal death 5. Morbidity
Notes	Location: Kenya Urban/rural: rural (Kilifi) Malaria transmission: hyperendemic and mesoendemic areas Drug resistance: present Funding: UK Department for International Development and KEMRI

Risk of bias

Shulman 1999 KEN *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were assigned unique identification numbers sequentially… identification numbers had been randomly allocated to a number between zero and nine, in blocks of ten." Comment: randomization method, using permuted blocks
Allocation concealment (selection bias)	Low risk	Drugs supplied in bottles. "Questionnaires were premarked with this unique identification number and the bottle number. The code relating bottle numbers to their contents was retained by a statistician and clinician, not involved in the study." Comment: allocation concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	SP and placebo tablets, "identical in appearance and taste".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition rate 11.41% (73/640) in the SP group and 9.5 % (59/624) in the placebo group, signifying the number of women with no blood test during third trimester.
Selective reporting (reporting bias)	Low risk	Trial protocol available; no apparent risk of selective reporting identified.
Other bias	Unclear risk	Protocol violation: 6 women from SP group and 8 from placebo group reported taking extra doses of SP (unclear whether women from the placebo group took placebo tablets, or real SP). 69 women from SP group reported taking chloroquine. 61 women from placebo group reported taking chloroquine.

Villegas 2007 THA

Methods	Trial design: RCT Data collected: November 1998 to January 2000 (infant follow-up completed in December 2001) Length of follow-up: Mother: from the first antenatal visit to delivery; infant follow-up completed 1 year after delivery Frequency of follow-up: weekly
Participants	Parity: all Number: 951 Inclusion criteria: pregnant women of all parities, of any gestational age, with a negative malaria smear and able to comply with the trial protocol

Villegas 2007 THA *(Continued)*

	Excluded: allergy to chloroquine, inability to tolerate oral drugs, severe renal or hepatic impairment, tuberculosis treatment, a history of epilepsy or diabetes mellitus or both, or signs of labour
Interventions	1. Chloroquine: 4 tablets (250 mg chloroquine phosphate, 153 mg base) given on enrolment. Two tablets of the same type given on a weekly basis afterwards, until delivery. 2. Placebo Other: ferrous sulphate + folic acid Administration supervised: yes
Outcomes	1. Maternal mortality 2. *P. vivax* and *P. falciparum* parasitaemia 3. Anaemia 4. Birth outcomes (miscarriage, stillbirth) 5. Birthweight (mean and low birthweight) 6. Prematurity
Notes	Location: Thailand Urban/rural: rural (Maela Refugee Camp and the vicinity of Maw Ker Tai village) Malaria transmission: low, seasonal transmission Drug resistance: possible chloroquine resistance HIV prevalence: no information Funding: Wellcome Trust of Great Britain, Ministerio de Salud de Venezuela (Proyecto Control de Enfermedades), the UNDP/World Bank/WHO Special Programme for Research training in Tropical Diseases (Research Training Grant)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were assigned unique identification numbers sequentially. All identification numbers were allocated randomly by computer to a number between one and ten, in blocks of ten (five randomly allocated to CQ and five to placebo in each block)". Randomization method, using permuted blocks.
Allocation concealment (selection bias)	Low risk	"Each unique identification number was linked to a brown paper envelope which contained the study drugs in weekly allotments, sealed into zippered plastic bags… labelled with week number of the study. The preparation of the study drugs was done in Mae Sot by the SMRU pharmacist who was not involved with any other aspect of the study. The study codes and randomization list was retained by a clinician at SMRU..." Allocation was concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo and active tablets, "identical in appearance and taste".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The investigators and staff participating in the trial were unaware of the study codes until data collection was completed." Outcome assessors were probably blinded.

Villegas 2007 THA *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 49/1000 pregnant women (4.9%), out of which 28/500 (5.6%) in the chloroquine group and 21/500 (4.2%) in the placebo group were excluded from the final analysis of efficacy against *P. vivax*. Reasons for exclusion were provided.
Selective reporting (reporting bias)	Low risk	None identified.
Other bias	Low risk	No apparent risk.

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

Study	Reason for exclusion
Asa 2008 NGA	No placebo/no intervention group. Compares chloroquine with SP.
Briand 2009 BEN	No placebo/no intervention group. Compares SP with mefloquine.
Clerk 2008 GHA	No placebo/no intervention group. Compares SP with amodiaquine or amodiaquine plus SP.
Deen 2001	The study is a part of a double-blinded, placebo-controlled, village-randomized malaria transmission-reduction trial, comparing the efficacy of a single dose of artesunate and SP against placebo. However, target group is the general population (14,017 villagers). Women who were "thought that they might be pregnant", were advised not to take the study drugs. Some of them unknowingly took the drugs and their outcomes are reported. There is no specific method of randomization of the pregnant women who "accidentally" took the drugs, to ensure similarity of the groups. Also, distribution is uneven: N = 287 in the intervention group versus N =40 in the control group.
Diakite 2011 MLI	No placebo/no intervention group. Compares intermittent SP: 2 doses versus 3 doses.
Diallo 2007 MLI	No placebo/no intervention group. Compares weekly chloroquine with intermittent SP.
Dolan 1993	Trial of impregnated mosquito nets.
Filler 2006 MWI	No placebo/no intervention group. Compares intermittent SP: 2 doses versus 3 doses.
Gies 2009	Described as "a health centre randomized trial". This study evaluated the IPT-SP uptake in a community-based trial where health centres were randomized to one of three arms: IPT-SP with health promotion, IPT-SP without promotion and weekly CQ. The purpose was to assess the impact of a village-based promotional campaign to enhance antenatal clinic (ANC) attendance.
Hamer 2007 ZMB	No placebo/no intervention group. Compares intermittent SP: 2 doses versus 3 doses
Hamilton 1972 UGA	This previously included trial was excluded in the updated version because Hamilton and his team administered iron to one of the control groups and folic acid to the other, but nothing was mentioned of iron and folates being administered to women in the intervention group (chloroquine).
Helitzer 1994	4 clinics trying different methods to achieve adherence; not randomized.
Kayentao 2005 MLI	No placebo/no intervention group. Compares weekly chloroquine with intermittent SP.
Luntamo 2010 MWI	No placebo/no intervention group. Compares intermittent SP: 2 doses versus 3 doses.

Study	Reason for exclusion
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.
McDermott 1988	Started as a RCT, 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.
Menéndez 2011	Study done in the context of a randomized, double-blind, placebo-controlled trial of IPT- SP for malaria prevention (already included, Menendez 2008 MOZ).
Mutabingwa 1993 TZA	No placebo/no intervention group. Compares weekly chloroquine with daily proguanil.
Naniche 2008	Study done in the context of a randomized, double-blind, placebo-controlled trial of IPT- SP for malaria prevention (already included, Menendez 2008 MOZ).
Ouedraogo 2008 BFA	No placebo/no intervention group. Compares weekly chloroquine with intermittent SP.
Pertet 1994	Possible RCT; wrote to the authors in 1998; no response.
Randriam. 2011 MDG	No placebo/no intervention group. Compares weekly chloroquine with intermittent SP.
Schultz 1994 MWI	No placebo/no intervention group. Compares weekly chloroquine with intermittent SP.
Serra-Casas 2010	Study is done in the context of a randomized, double-blind, placebo-controlled trial of IPT- SP for malaria prevention during pregnancy (already included, Menendez 2008 MOZ), investigating the effect of IPT-SP on maternal and cord Immunoglobulin G (IgG) levels and comparing antibody levels between intervention groups. The study is mostly about the association between antibody levels and morbidity outcomes, and not focused on the specific outcomes included in the protocol for the review.
Shulman 1998	Study of impregnated mosquito nets.
Steketee 1996	Comparison between mefloquine and chloroquine.
Tagbor 2010	A randomized controlled non-inferiority trial conducted in Ghana, comparing the safety and efficacy of intermittent screening and treatment (IST), a new strategy for malaria control, and treatment with SP. There were two intervention groups: SP and IST; IST and treatment with amodiaquine+artesunate (AQ+AS), versus the control group - standard IPT-SP. We excluded this study because a different strategy (not chemoprevention but early screening and treatment) was used in the intervention arm.
Thaler 2006	Study, comparing riboflavin (not an active antimalarial drug) to placebo.
Tukur 2007 NGA	No placebo/no intervention group. Compares chloroquine once only followed by weekly pyrimethamine with intermittent SP.
Valea 2010 BFA	No placebo/no intervention group. Compares intermittent SP: 2 doses versus 3 doses.

DATA AND ANALYSES

Comparison 1. Preventive antimalarials versus placebo/no intervention

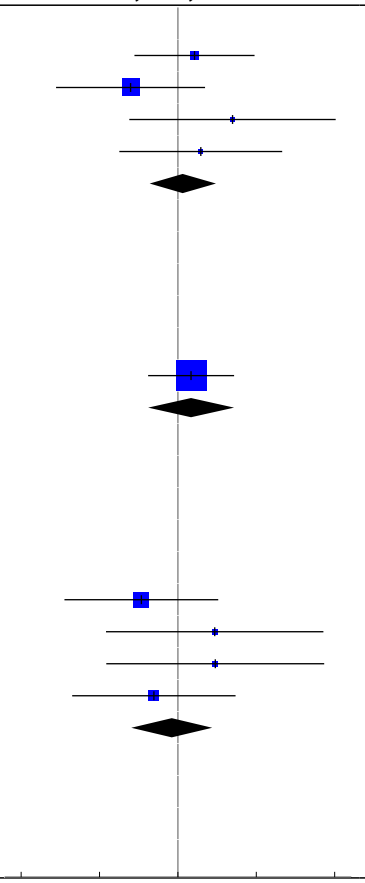
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (mother)	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Para 0-1	4	2097	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.44, 3.06]
1.2 Multigravidae	1	2239	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.42, 5.21]
1.3 All women	4	6026	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.25, 2.74]
2 Severe anaemia (mother)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Para 0-1	4	2503	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.47, 0.75]
2.2 Multigravidae	2	2682	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.41, 2.25]
2.3 All women	2	1327	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.05, 0.75]
3 Anaemia (mother)	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Para 0-1	7	3662	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.74, 0.93]
3.2 All women	3	3027	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.87, 1.23]
4 Mean haemoglobin (g/dL)	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Baseline Hb	5	3004	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.10, 0.17]
4.2 Para 0-1	7	3363	Mean Difference (IV, Fixed, 95% CI)	0.41 [0.29, 0.54]
4.3 Multigravidae	2	676	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.23, 0.24]
4.4 All women	3	2223	Mean Difference (IV, Fixed, 95% CI)	0.13 [0.00, 0.25]
5 Clinical malaria (mother)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Para 0-1	2	307	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.18, 0.74]
5.2 All women	4	3455	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.11, 1.23]
6 Parasitaemia (mother)	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Para 0-1	10	3663	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.26, 0.58]
6.2 Multigravidae	4	3022	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.28, 0.50]
6.3 All women	5	3961	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.44, 1.13]
7 Adverse effects with SP	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Skin reactions	2	1472	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.27, 2.65]
7.2 Nausea and vomiting	2	1472	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.22, 12.81]
7.3 Any other adverse effects	3	2599	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.38, 1.36]
8 Adverse effects with mefloquine	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Dizziness	1	107	Risk Ratio (M-H, Fixed, 95% CI)	1.6 [0.90, 2.83]
8.2 Vertigo	1	339	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.81, 1.28]
8.3 Vomiting	1	339	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.53, 1.10]
8.4 Itching	1	339	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.73, 1.38]
8.5 Visual abnormalities	1	339	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.72, 1.39]
9 Spontaneous abortion	10	8643	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.56, 1.05]
9.1 Para 0-1	7	2876	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.41, 1.02]
9.2 All women	3	5767	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.58, 1.36]
10 Stillbirth	9	9833	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.79, 1.28]
10.1 Para 0-1	4	2703	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.63, 1.49]
10.2 All women	5	7130	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.76, 1.36]
11 Perinatal deaths	6	6836	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.81, 1.22]
11.1 Para 0-1	2	1620	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.54, 1.00]
11.2 All women	4	5216	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.94, 1.63]
12 Neonatal and infant mortality	9	10486	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.76, 1.14]
12.1 Para 0-1 (neonatal death: day 0-28)	3	2156	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.37, 1.05]
12.2 Para 1+ (deaths up to six weeks)	1	2017	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.90, 2.38]
12.3 All women (neonatal and infant death: day 0-1 year)	5	6313	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.71, 1.16]
13 Preterm birth	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Para 0-1	3	1493	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.10]
13.2 All women	2	1174	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.65, 1.38]
14 Low birthweight	13		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Para 0-1	10	3619	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.87]
14.2 Multigravidae	3	2743	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.65, 1.15]
14.3 All women	4	3644	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.89, 1.27]
15 Mean birthweight (baby)	15		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
15.1 Para 0-1	11	3936	Mean Difference (IV, Fixed, 95% CI)	92.72 [62.05, 123.39]
15.2 All women	5	6007	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-24.66, 23.58]
16 Cord blood anaemia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Para 0-1	1	64	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [0.78, 11.05]
16.2 All women	1	870	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.30, 0.80]
17 Cord blood haemoglobin	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 Para 0-1	1	64	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-3.46, -0.14]
17.2 All women	1	990	Mean Difference (IV, Fixed, 95% CI)	1.01 [0.05, 1.97]
18 Placental parasitemia (fetus)	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 Para 0-1	9	2830	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.43, 0.69]
18.2 All women	4	3200	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.15, 1.29]
19 Cord blood parasitaemia	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Para 0-1	2	1335	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.22, 1.01]
19.2 All women	1	2629	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.47, 1.14]
20 Adverse effects (baby)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 Neonatal icterus	3	2233	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.63, 1.13]
20.2 Congenital anomalies	2	1328	Risk Ratio (M-H, Fixed, 95% CI)	3.53 [0.58, 21.33]

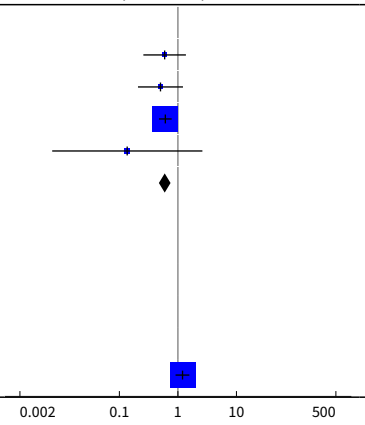
Analysis 1.1. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 1 Death (mother).

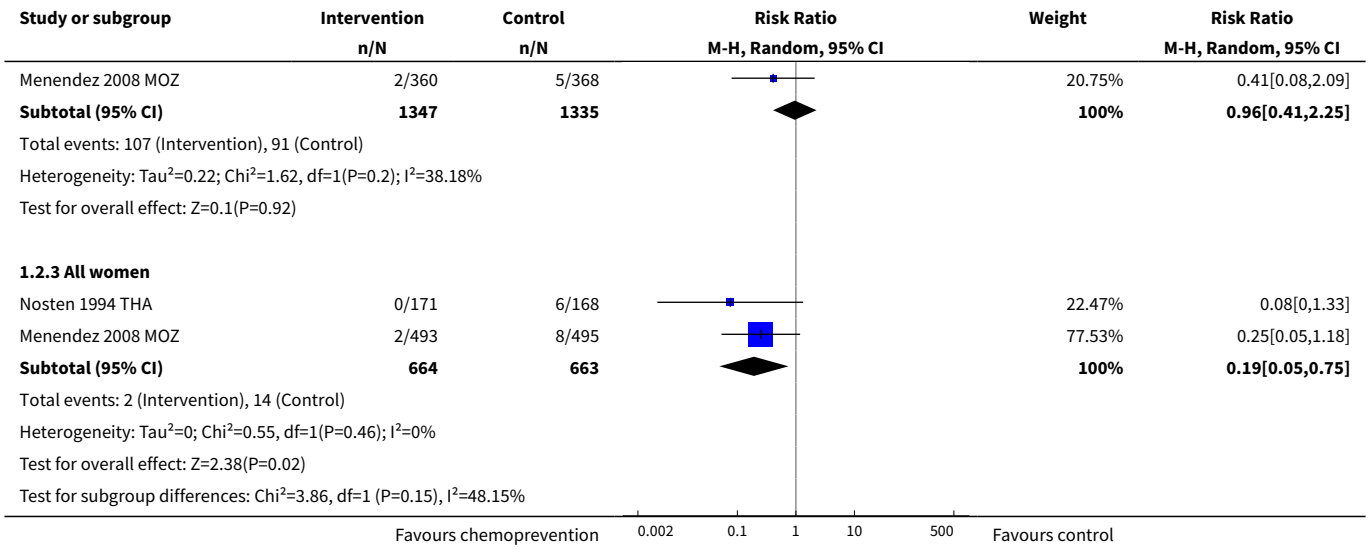
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Para 0-1					
Menendez 1994 GMB	3/82	2/89		25.78%	1.63[0.28,9.5]
Shulman 1999 KEN	1/567	4/564		53.9%	0.25[0.03,2.22]
Njagi 2003i KEN	2/207	0/206		6.74%	4.98[0.24,103.02]
Njagi 2003ii KEN	2/193	1/189		13.58%	1.96[0.18,21.42]
Subtotal (95% CI)	**1049**	**1048**		**100%**	**1.15[0.44,3.06]**
Total events: 8 (Intervention), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.12, df=3(P=0.37); I^2=3.76%					
Test for overall effect: Z=0.29(P=0.77)					
1.1.2 Multigravidae					
Mbaye 2006 GMB	6/1129	4/1110		100%	1.47[0.42,5.21]
Subtotal (95% CI)	**1129**	**1110**		**100%**	**1.47[0.42,5.21]**
Total events: 6 (Intervention), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.6(P=0.55)					
1.1.3 All women					
Greenwood 1989 GMB	1/518	3/531		49.55%	0.34[0.04,3.27]
Nosten 1994 THA	1/171	0/168		8.44%	2.95[0.12,71.85]
Menendez 2008 MOZ	1/515	0/515		8.36%	3[0.12,73.47]
Ndyomugyenyi 2011 UGA	1/1815	2/1793		33.65%	0.49[0.04,5.44]
Subtotal (95% CI)	**3019**	**3007**		**100%**	**0.84[0.25,2.74]**
Total events: 4 (Intervention), 5 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2, df=3(P=0.57); I^2=0%					
Test for overall effect: Z=0.3(P=0.77)					
Test for subgroup differences: Chi^2=0.42, df=1 (P=0.81), I^2=0%					



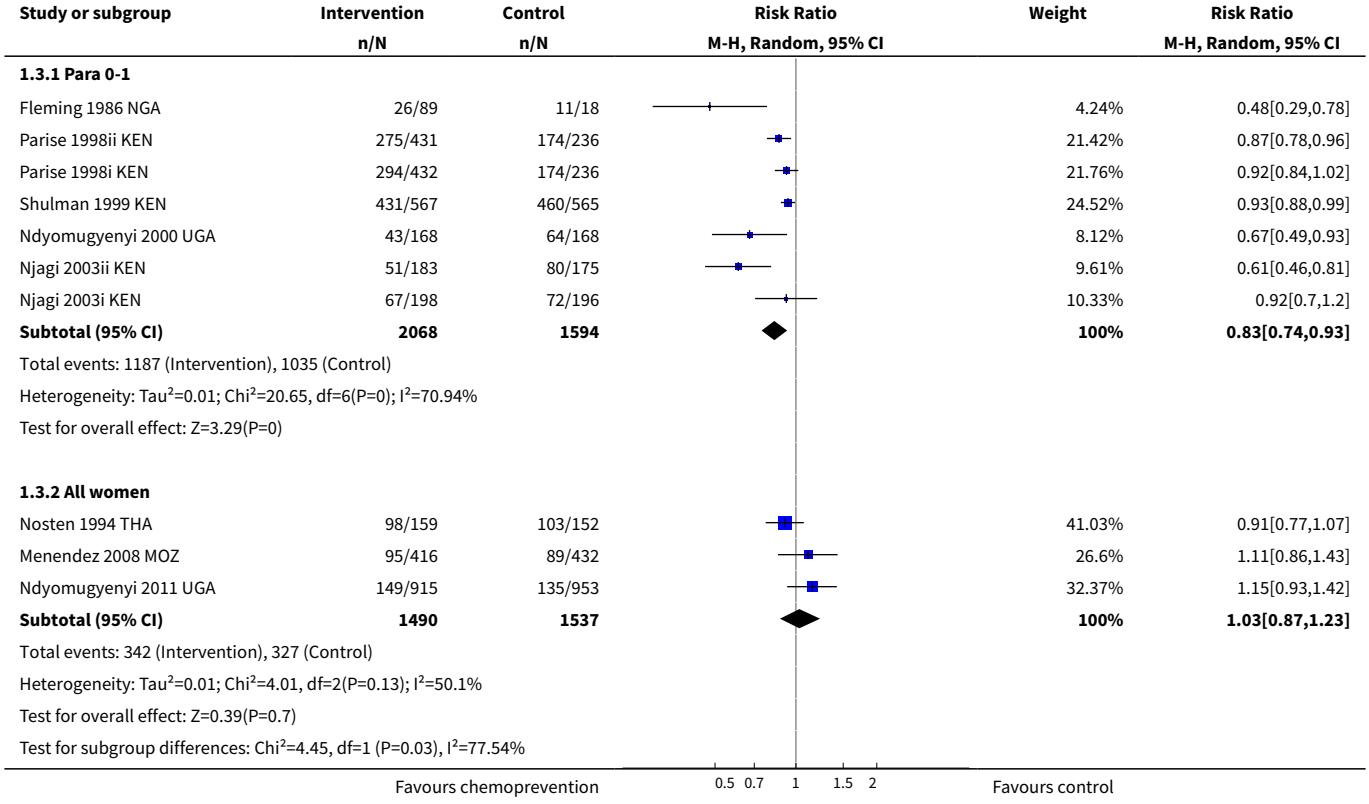
Analysis 1.2. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 2 Severe anaemia (mother).

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Para 0-1					
Parise 1998i KEN	11/365	10/197		7.5%	0.59[0.26,1.37]
Parise 1998ii KEN	9/352	10/197		6.76%	0.5[0.21,1.22]
Shulman 1999 KEN	82/567	134/565		85.14%	0.61[0.48,0.78]
Menendez 2008 MOZ	0/133	3/127		0.6%	0.14[0.01,2.62]
Subtotal (95% CI)	**1417**	**1086**		**100%**	**0.6[0.47,0.75]**
Total events: 102 (Intervention), 157 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.14, df=3(P=0.77); I^2=0%					
Test for overall effect: Z=4.43(P<0.0001)					
1.2.2 Multigravidae					
Mbaye 2006 GMB	105/987	86/967		79.25%	1.2[0.91,1.57]



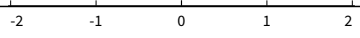


Analysis 1.3. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 3 Anaemia (mother).



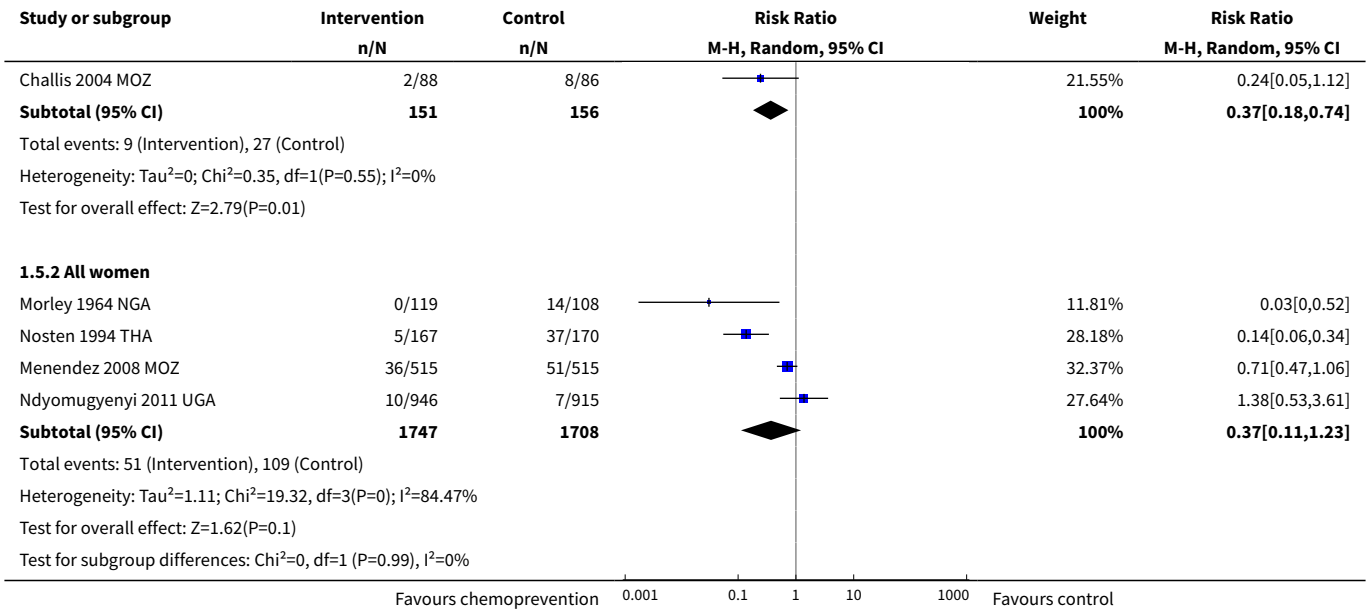
Analysis 1.4. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 4 Mean haemoglobin (g/dL).

Study or subgroup	Intervention N	Intervention Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.4.1 Baseline Hb							
Parise 1998i KEN	680	9.6 (1.9)	368	9.6 (1.9)		31.92%	0[-0.24,0.24]
Parise 1998ii KEN	661	9.7 (1.9)	368	9.6 (1.9)		31.6%	0.1[-0.14,0.34]
Ndyomugyenyi 2000 UGA	85	9.6 (1.5)	90	10.2 (1.7)		8.55%	-0.58[-1.05,-0.11]
Njagi 2003i KEN	198	10.5 (1.8)	196	10.5 (1.9)		13.87%	0[-0.37,0.37]
Njagi 2003ii KEN	183	10.7 (1.7)	175	10.3 (1.8)		14.06%	0.4[0.04,0.76]
Subtotal ***	**1807**		**1197**			**100%**	**0.04[-0.1,0.17]**
Heterogeneity: Tau^2=0; Chi^2=10.98, df=4(P=0.03); I^2=63.56%							
Test for overall effect: Z=0.55(P=0.58)							
1.4.2 Para 0-1							
Greenwood 1989 GMB	21	10 (1.6)	11	9.5 (1.1)		1.74%	0.5[-0.43,1.43]
Parise 1998i KEN	365	10.2 (1.7)	197	9.9 (1.7)		17.39%	0.3[0.01,0.59]
Parise 1998ii KEN	352	10.4 (1.8)	197	9.9 (1.7)		16.45%	0.5[0.2,0.8]
Shulman 1999 KEN	567	9.7 (1.8)	565	9.3 (1.9)		34.09%	0.4[0.19,0.61]
Ndyomugyenyi 2000 UGA	168	11 (1.7)	168	10.5 (1.5)		12.84%	0.45[0.11,0.79]
Njagi 2003ii KEN	183	11 (1.9)	175	10.3 (2.2)		8.29%	0.7[0.27,1.13]
Njagi 2003i KEN	198	10.8 (2)	196	10.6 (2.1)		9.2%	0.2[-0.21,0.61]
Subtotal ***	**1854**		**1509**			**100%**	**0.41[0.29,0.54]**
Heterogeneity: Tau^2=0; Chi^2=3.78, df=6(P=0.71); I^2=0%							
Test for overall effect: Z=6.6(P<0.0001)							
1.4.3 Multigravidae							
Greenwood 1989 GMB	126	10.2 (1.3)	118	10.1 (1.3)		52.79%	0.1[-0.23,0.43]
Mbaye 2006 GMB	213	8.9 (1.8)	219	9 (1.8)		47.21%	-0.1[-0.45,0.25]
Subtotal ***	**339**		**337**			**100%**	**0.01[-0.23,0.24]**
Heterogeneity: Tau^2=0; Chi^2=0.68, df=1(P=0.41); I^2=0%							
Test for overall effect: Z=0.05(P=0.96)							
1.4.4 All women							
Greenwood 1989 GMB	126	10.2 (1.3)	118	10.1 (1.3)		14.5%	0.1[-0.23,0.43]
Greenwood 1989 GMB	21	10 (1.6)	11	9.5 (1.1)		1.78%	0.5[-0.43,1.43]
Nosten 1994 THA	43	11.5 (1.2)	43	10.6 (1)		6.88%	0.86[0.39,1.33]
Ndyomugyenyi 2011 UGA	946	12.5 (1.6)	915	12.4 (1.6)		76.84%	0.06[-0.08,0.2]
Subtotal ***	**1136**		**1087**			**100%**	**0.13[0,0.25]**
Heterogeneity: Tau^2=0; Chi^2=10.69, df=3(P=0.01); I^2=71.95%							
Test for overall effect: Z=2.03(P=0.04)							
Test for subgroup differences: Chi^2=20.76, df=1 (P=0), I^2=85.55%							

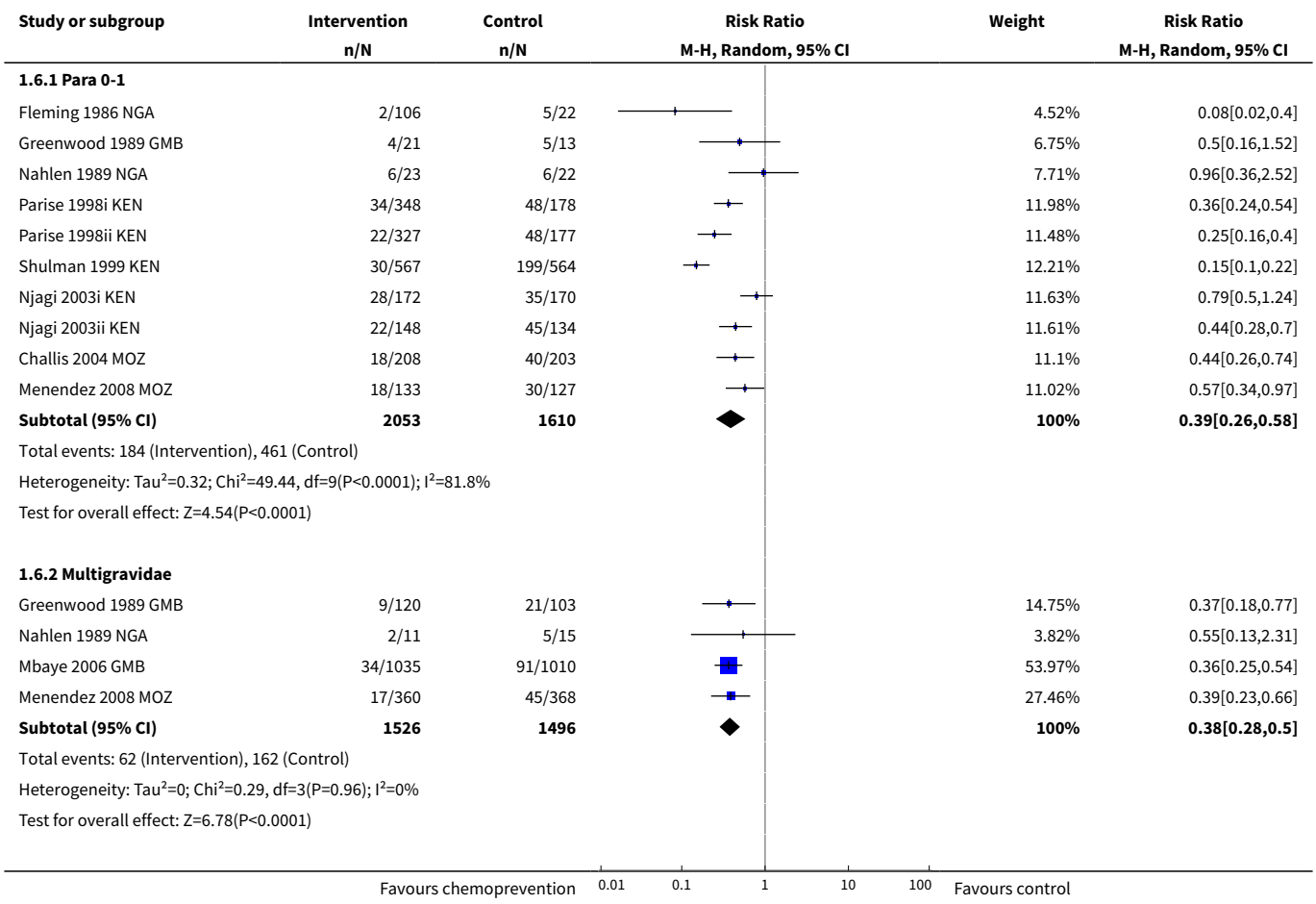


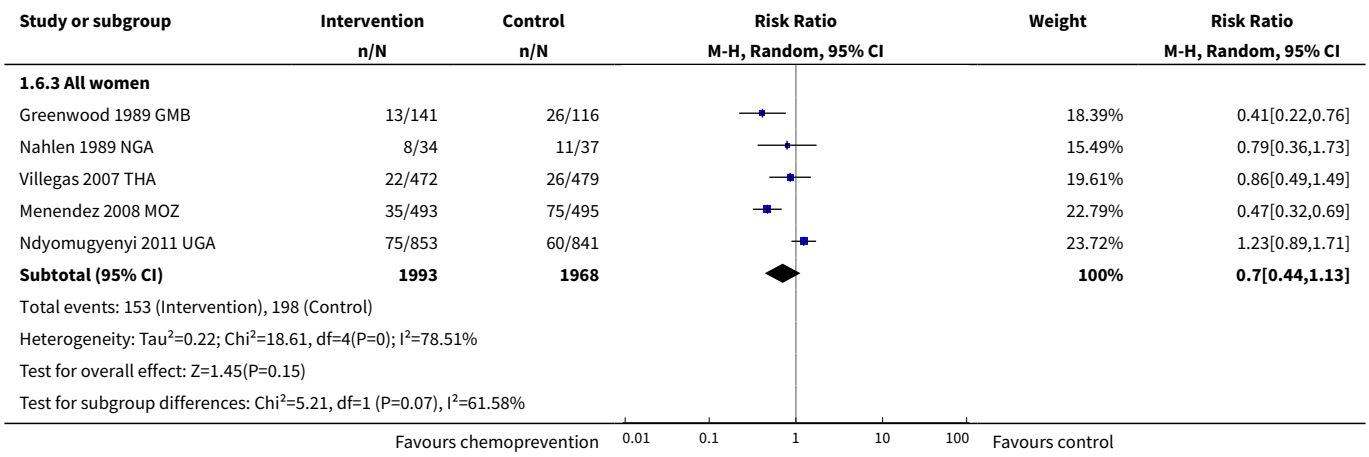
Analysis 1.5. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 5 Clinical malaria (mother).

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Para 0-1					
Cot 1995 CMR	7/63	19/70		78.45%	0.41[0.18,0.91]

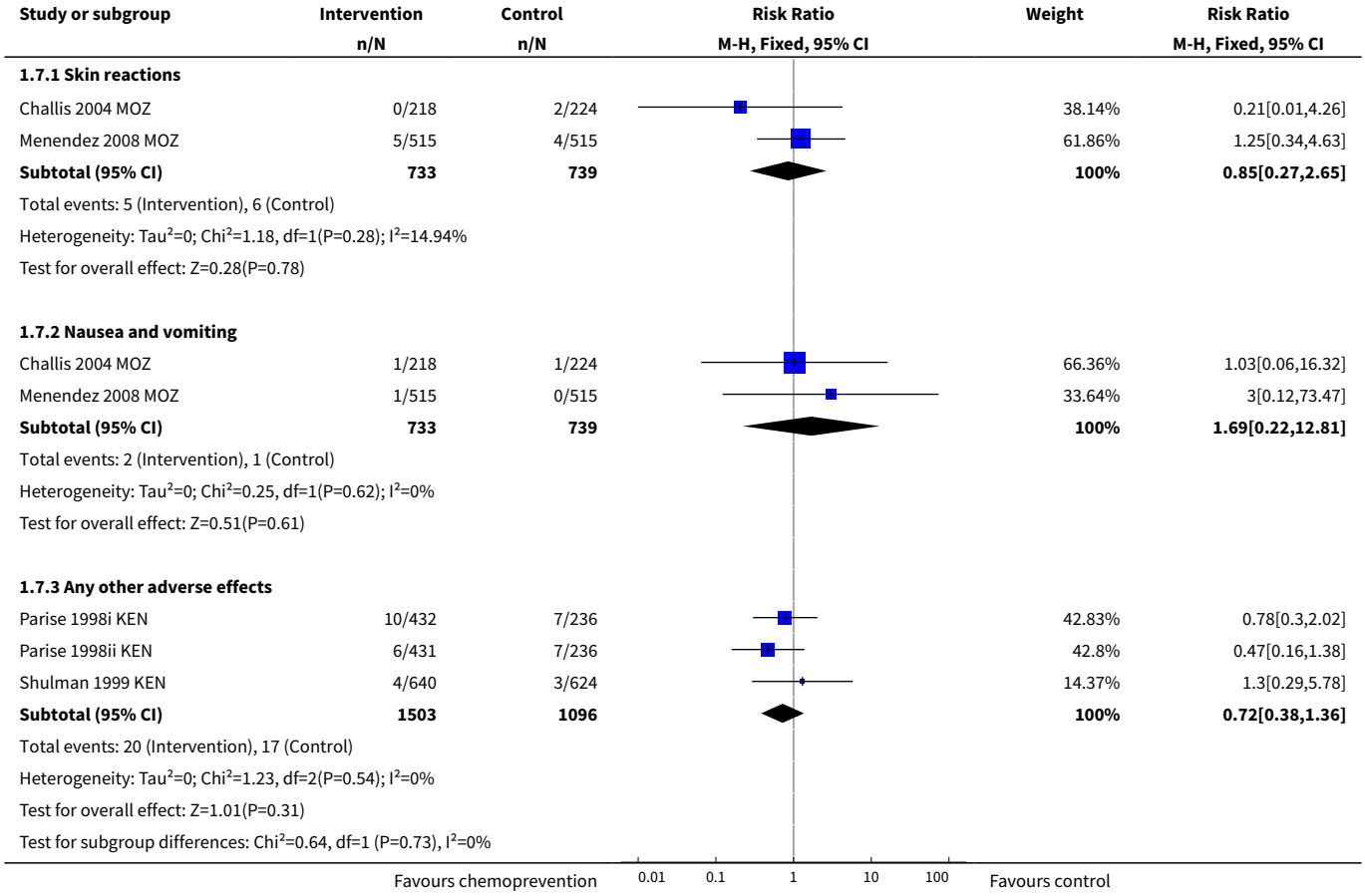


Analysis 1.6. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 6 Parasitaemia (mother).





Analysis 1.7. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 7 Adverse effects with SP.



Analysis 1.8. Comparison 1 Preventive antimalarials versus placebo/ no intervention, Outcome 8 Adverse effects with mefloquine.

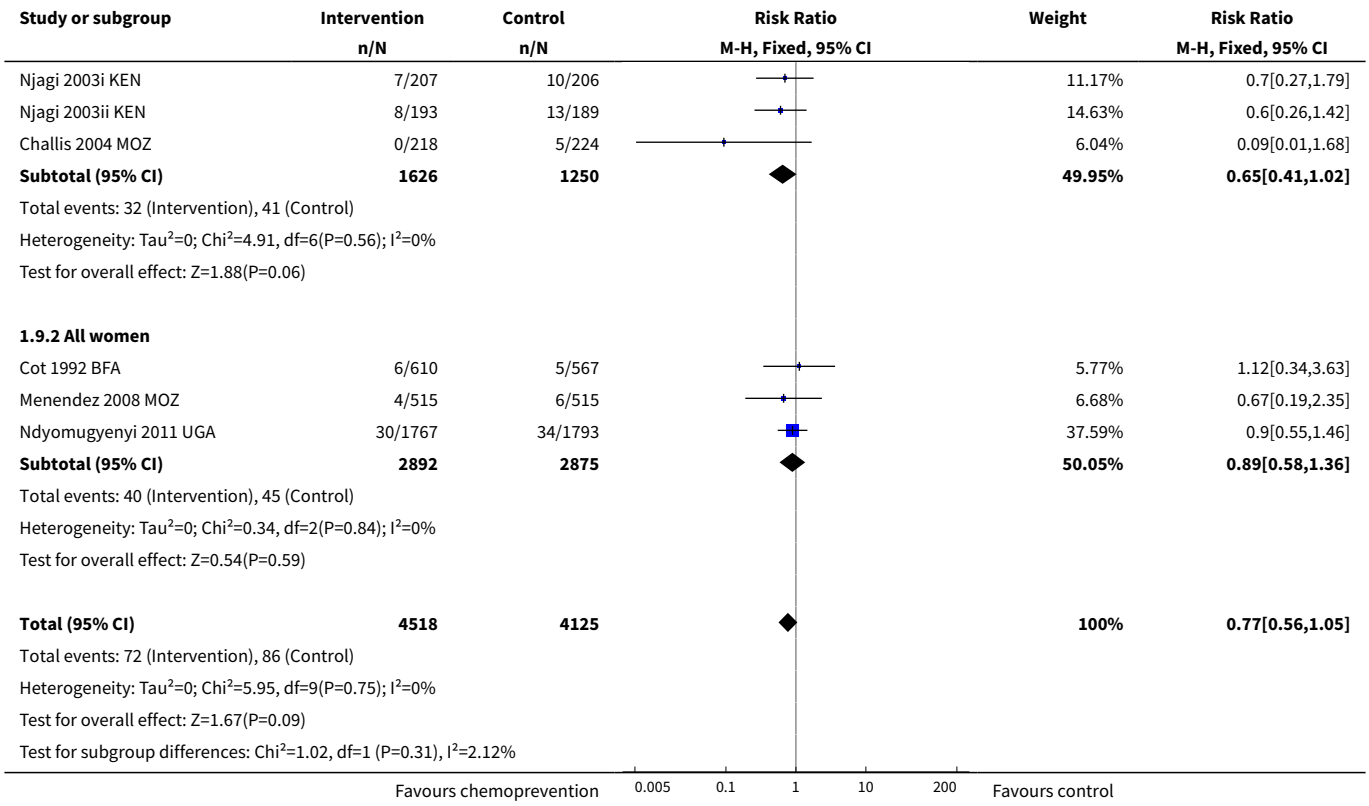
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Dizziness					
Nosten 1994 THA	22/55	13/52		100%	1.6[0.9,2.83]
Subtotal (95% CI)	**55**	**52**		**100%**	**1.6[0.9,2.83]**
Total events: 22 (Intervention), 13 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.61(P=0.11)					
1.8.2 Vertigo					
Nosten 1994 THA	80/171	77/168		100%	1.02[0.81,1.28]
Subtotal (95% CI)	**171**	**168**		**100%**	**1.02[0.81,1.28]**
Total events: 80 (Intervention), 77 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.18(P=0.86)					
1.8.3 Vomiting					
Nosten 1994 THA	39/171	50/168		100%	0.77[0.53,1.1]
Subtotal (95% CI)	**171**	**168**		**100%**	**0.77[0.53,1.1]**
Total events: 39 (Intervention), 50 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.45(P=0.15)					
1.8.4 Itching					
Nosten 1994 THA	53/171	52/168		100%	1[0.73,1.38]
Subtotal (95% CI)	**171**	**168**		**100%**	**1[0.73,1.38]**
Total events: 53 (Intervention), 52 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
1.8.5 Visual abnormalities					
Nosten 1994 THA	51/171	50/168		100%	1[0.72,1.39]
Subtotal (95% CI)	**171**	**168**		**100%**	**1[0.72,1.39]**
Total events: 51 (Intervention), 50 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
Test for subgroup differences: Chi^2=4.72, df=1 (P=0.32), I^2=15.28%					

Favours chemoprevention — Favours control

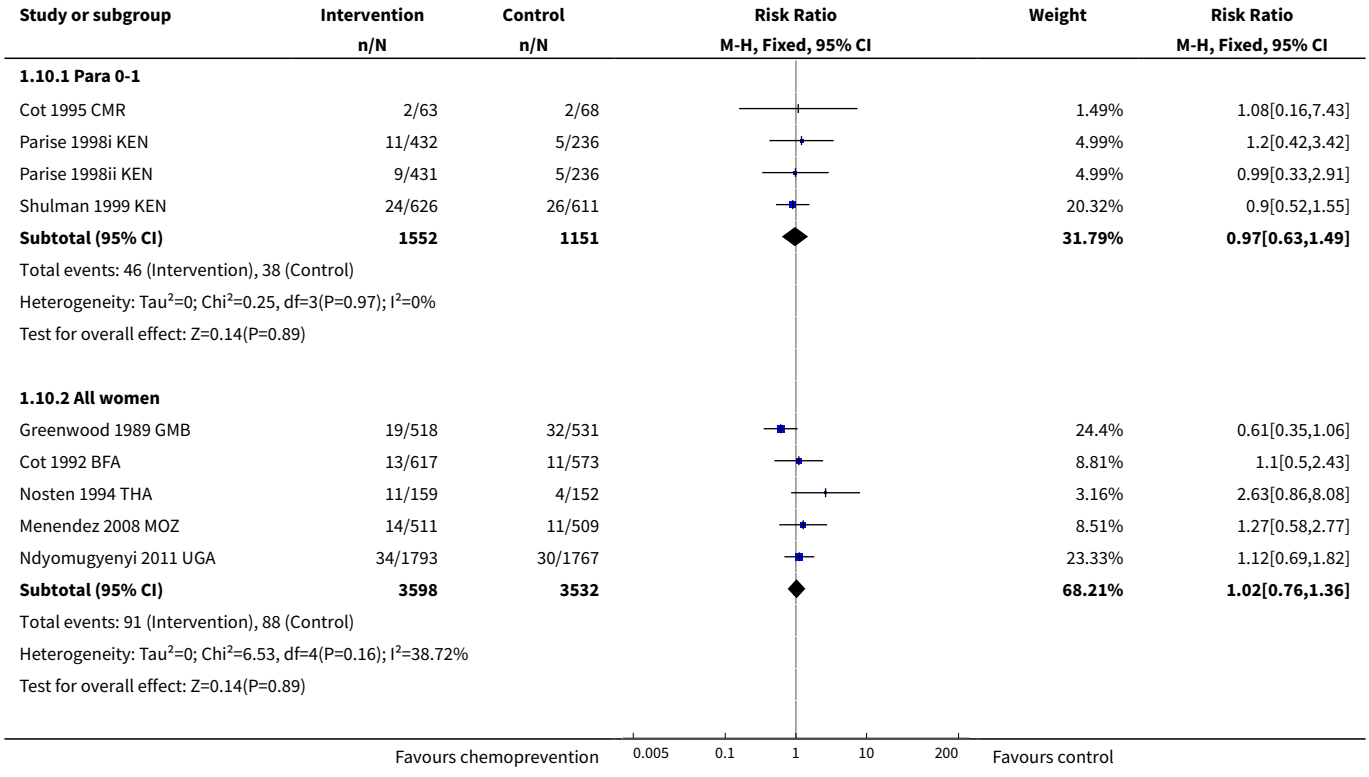
Analysis 1.9. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 9 Spontaneous abortion.

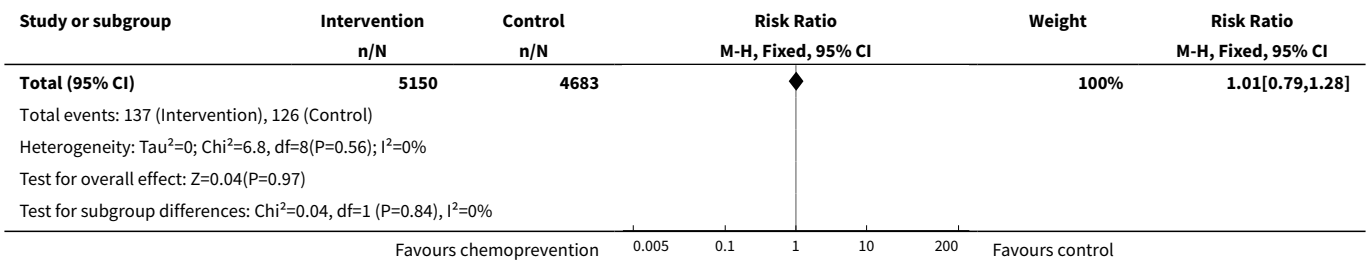
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 Para 0-1					
Menendez 1994 GMB	3/82	1/89		1.07%	3.26[0.35,30.68]
Cot 1995 CMR	0/63	2/70		2.64%	0.22[0.01,4.54]
Parise 1998ii KEN	9/431	5/236		7.2%	0.99[0.33,2.91]
Parise 1998i KEN	5/432	5/236		7.2%	0.55[0.16,1.87]

Favours chemoprevention — Favours control

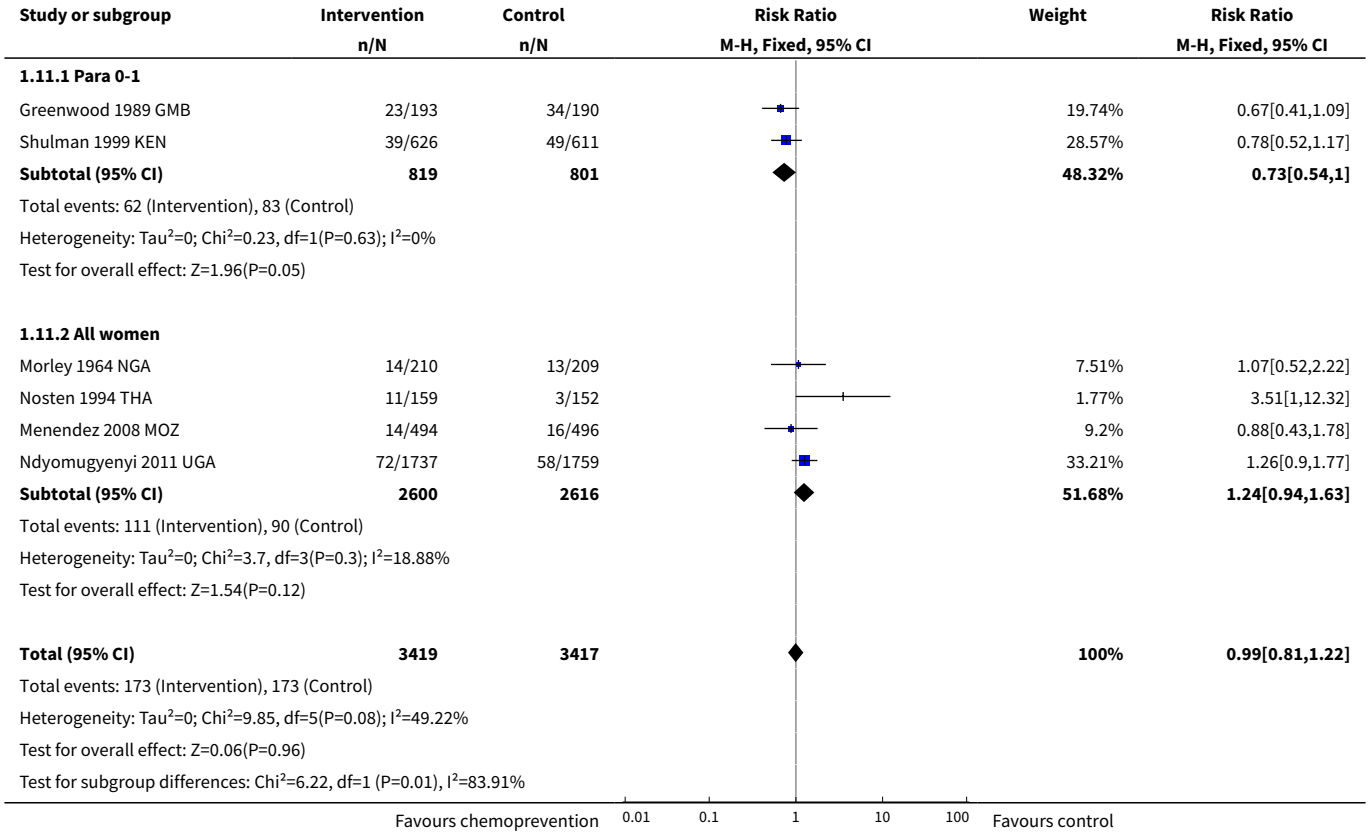


Analysis 1.10. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 10 Stillbirth.

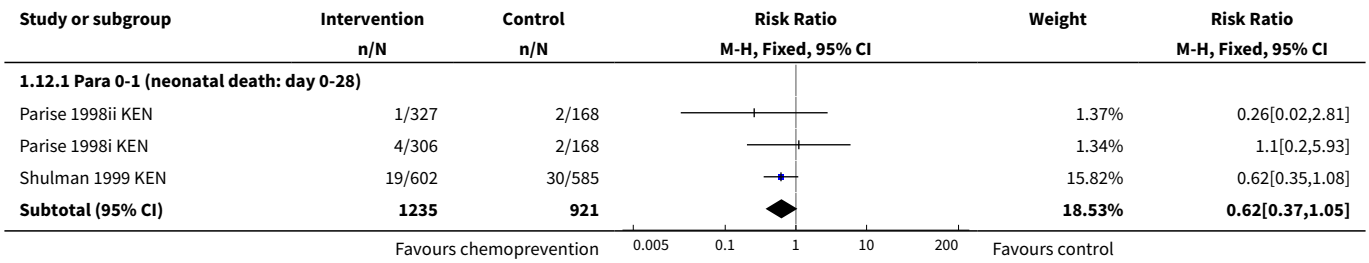


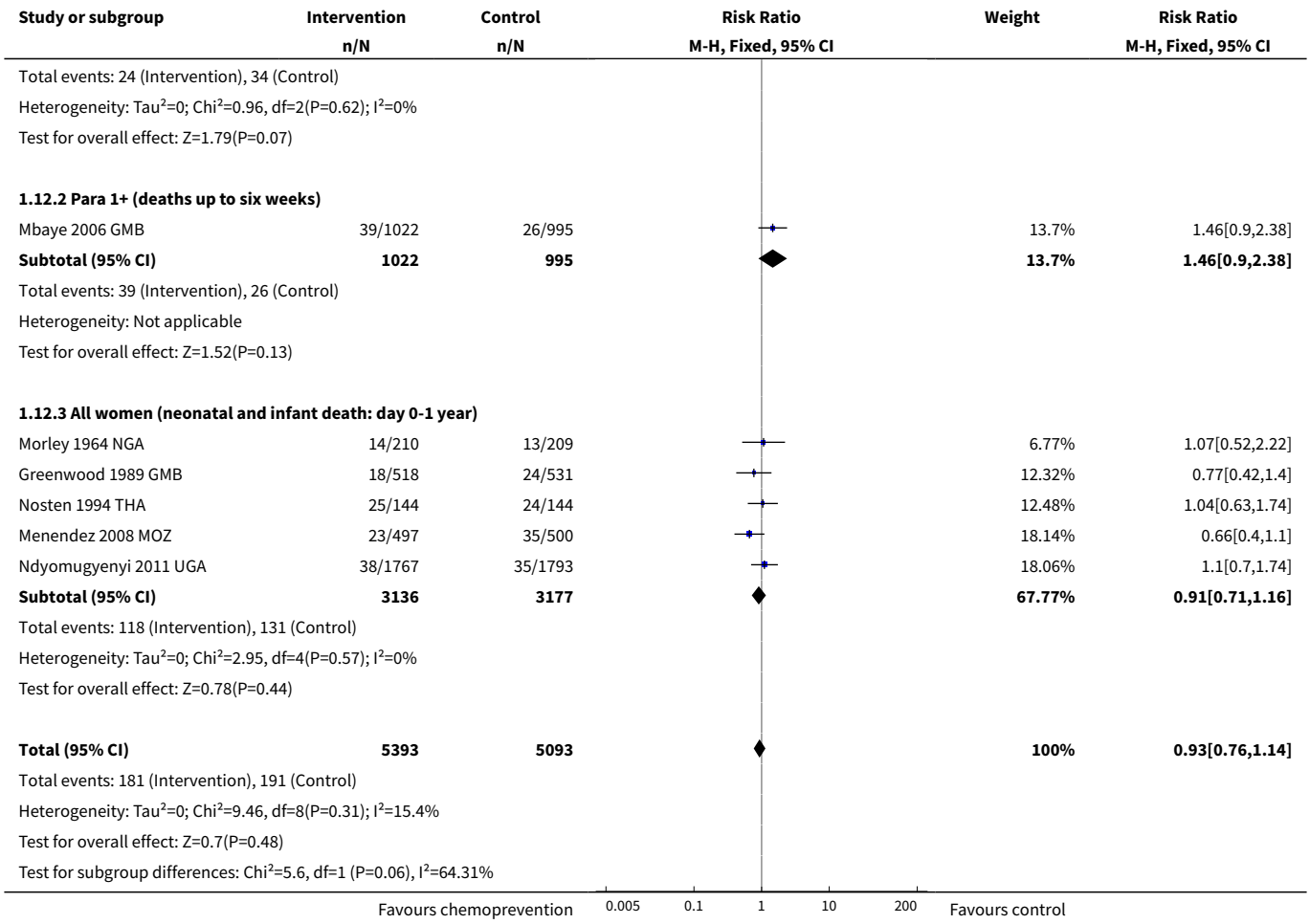


Analysis 1.11. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 11 Perinatal deaths.

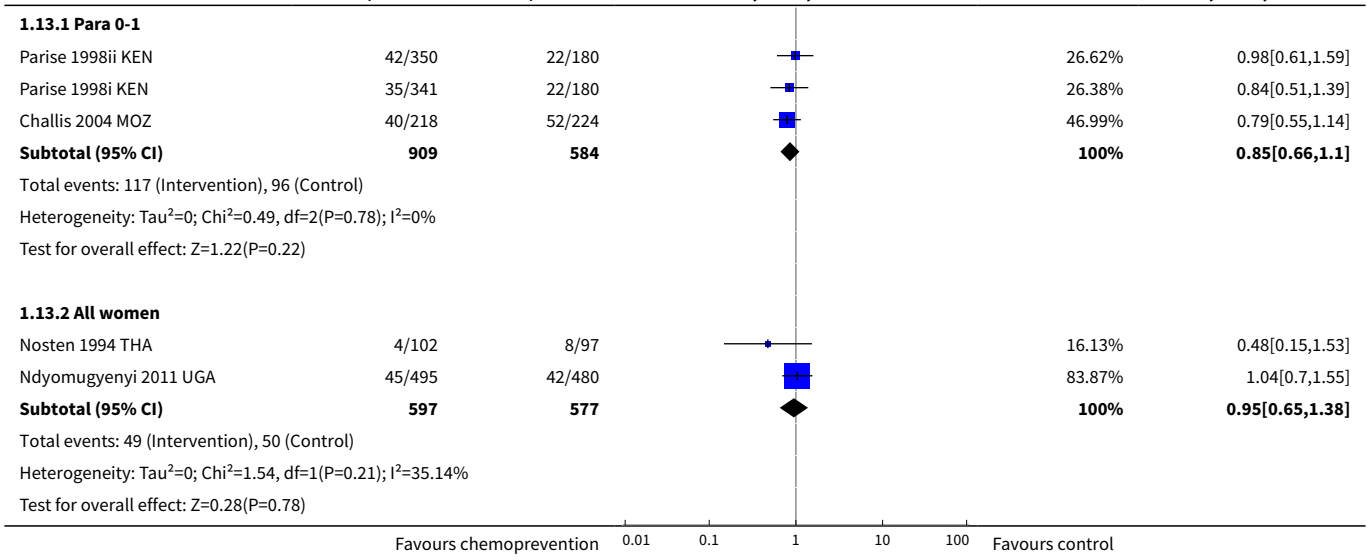


Analysis 1.12. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 12 Neonatal and infant mortality.





Analysis 1.13. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 13 Preterm birth.



Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for subgroup differences: Chi²=0.2, df=1 (P=0.65), I²=0%					

Favours chemoprevention 0.01 0.1 1 10 100 Favours control

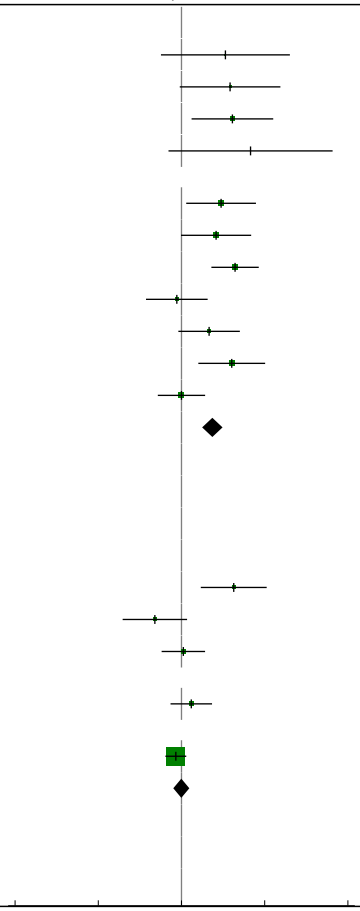
Analysis 1.14. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 14 Low birthweight.

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 Para 0-1					
Greenwood 1989 GMB	4/67	11/50		5.34%	0.27[0.09,0.8]
Cot 1995 CMR	6/57	18/65		7.13%	0.38[0.16,0.89]
Parise 1998ii KEN	26/331	26/170		14.57%	0.51[0.31,0.86]
Parise 1998i KEN	27/325	26/170		14.48%	0.54[0.33,0.9]
Ndyomugyenyi 2000 UGA	7/169	15/168		6.38%	0.46[0.19,1.11]
Njagi 2003i KEN	25/193	22/189		9.43%	1.11[0.65,1.9]
Njagi 2003ii KEN	21/176	29/170		12.51%	0.7[0.42,1.18]
Challis 2004 MOZ	19/200	27/203		11.37%	0.71[0.41,1.24]
Menendez 2008 MOZ	29/133	25/121		11.1%	1.06[0.66,1.7]
Ndyomugyenyi 2011 UGA	27/333	18/329		7.68%	1.48[0.83,2.64]
Subtotal (95% CI)	**1984**	**1635**		**100%**	**0.73[0.61,0.87]**
Total events: 191 (Intervention), 217 (Control)					
Heterogeneity: Tau²=0; Chi²=20.13, df=9(P=0.02); I²=55.29%					
Test for overall effect: Z=3.41(P=0)					
1.14.2 Multigravidae					
Mbaye 2006 GMB	40/738	46/716		48.63%	0.84[0.56,1.27]
Menendez 2008 MOZ	29/361	34/375		34.74%	0.89[0.55,1.42]
Ndyomugyenyi 2011 UGA	14/276	16/277		16.63%	0.88[0.44,1.76]
Subtotal (95% CI)	**1375**	**1368**		**100%**	**0.86[0.65,1.15]**
Total events: 83 (Intervention), 96 (Control)					
Heterogeneity: Tau²=0; Chi²=0.03, df=2(P=0.99); I²=0%					
Test for overall effect: Z=1.01(P=0.31)					
1.14.3 All women					
Cot 1992 BFA	97/595	91/554		46.13%	0.99[0.76,1.29]
Nosten 1994 THA	24/146	17/144		8.38%	1.39[0.78,2.48]
Menendez 2008 MOZ	58/494	59/496		28.82%	0.99[0.7,1.39]
Ndyomugyenyi 2011 UGA	41/609	34/606		16.68%	1.2[0.77,1.86]
Subtotal (95% CI)	**1844**	**1800**		**100%**	**1.06[0.89,1.27]**
Total events: 220 (Intervention), 201 (Control)					
Heterogeneity: Tau²=0; Chi²=1.57, df=3(P=0.67); I²=0%					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Chi²=8.28, df=1 (P=0.02), I²=75.83%					

Favours chemoprevention 0.01 0.1 1 10 100 Favours control

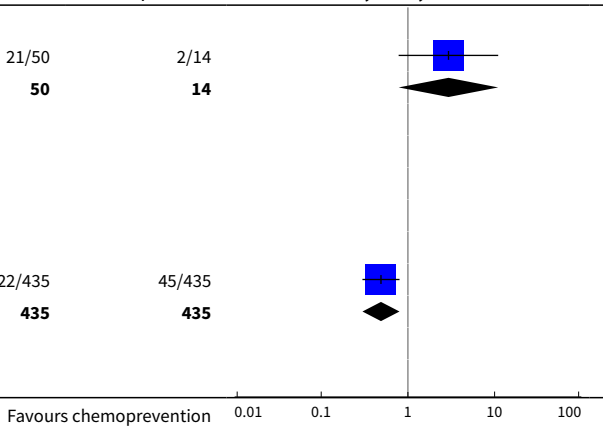
Analysis 1.15. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 15 Mean birthweight (baby).

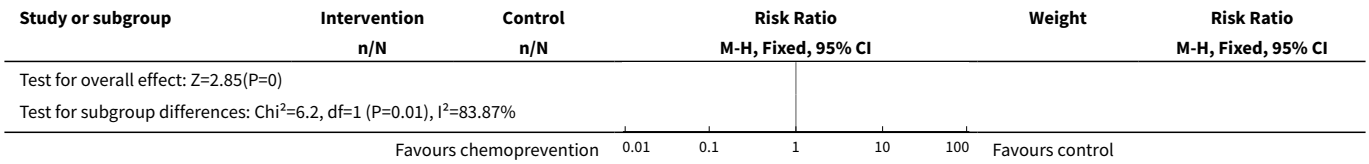
Study or subgroup	Intervention N	Intervention Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.15.1 Para 0-1							
Fleming 1986 NGA	128	2855 (500)	32	2723 (500)		2.51%	132[-61.69,325.69]
Greenwood 1989 GMB	67	2872 (330)	50	2726 (465)		4.12%	146[-5.18,297.18]
Menendez 1994 GMB	87	3028 (414)	95	2875 (430)		6.25%	153[30.34,275.66]
Cot 1995 CMR	57	3069.8 (669.9)	65	2862.3 (718.7)		1.55%	207.5[-39.02,454.02]
Parise 1998ii KEN	331	3198 (528)	170	3079 (585)		8.58%	119[14.27,223.73]
Parise 1998i KEN	325	3183 (534)	170	3079 (585)		8.47%	104[-1.37,209.37]
Ndyomugyenyi 2000 UGA	284	3009 (350)	282	2848 (500)		18.58%	161[89.85,232.15]
Njagi 2003i KEN	193	2961 (477)	189	2975 (446)		10.97%	-14[-106.58,78.58]
Njagi 2003ii KEN	176	2991 (418)	170	2908 (457)		11.02%	83[-9.37,175.37]
Challis 2004 MOZ	200	3077 (533)	203	2926 (494)		9.34%	151[50.63,251.37]
Ndyomugyenyi 2011 UGA	333	3.1 (471)	329	3.2 (462)		18.62%	-0.05[-71.12,71.02]
Subtotal ***	**2181**		**1755**			**100%**	**92.72[62.05,123.39]**
Heterogeneity: Tau^2=0; Chi^2=19.21, df=10(P=0.04); I^2=47.93%							
Test for overall effect: Z=5.93(P<0.0001)							
1.15.2 All women							
Morley 1964 NGA	196	2954 (500)	196	2797 (500)		5.94%	157[58.01,255.99]
Nosten 1994 THA	170	2877 (433)	169	2957 (475)		6.21%	-80[-176.77,16.77]
Cot 1992 BFA	594	2937.8 (651.5)	554	2932.2 (467.4)		13.66%	5.6[-59.67,70.87]
Menendez 2008 MOZ	494	3033 (477.1)	496	3003.6 (522.7)		14.97%	29.45[-32.89,91.79]
Ndyomugyenyi 2011 UGA	1561	3144 (444)	1577	3161 (452)		59.21%	-17[-48.35,14.35]
Subtotal ***	**3015**		**2992**			**100%**	**-0.54[-24.66,23.58]**
Heterogeneity: Tau^2=0; Chi^2=14.3, df=4(P=0.01); I^2=72.03%							
Test for overall effect: Z=0.04(P=0.97)							
Test for subgroup differences: Chi^2=21.95, df=1 (P<0.0001), I^2=95.44%							



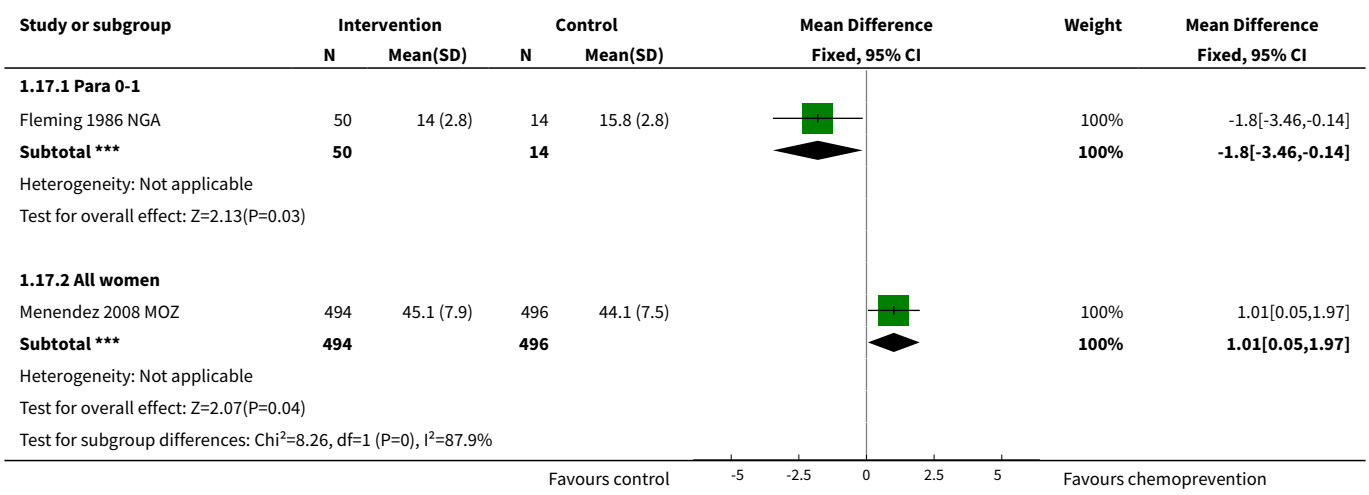
Analysis 1.16. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 16 Cord blood anaemia.

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.16.1 Para 0-1					
Fleming 1986 NGA	21/50	2/14		100%	2.94[0.78,11.05]
Subtotal (95% CI)	**50**	**14**		**100%**	**2.94[0.78,11.05]**
Total events: 21 (Intervention), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.6(P=0.11)					
1.16.2 All women					
Menendez 2008 MOZ	22/435	45/435		100%	0.49[0.3,0.8]
Subtotal (95% CI)	**435**	**435**		**100%**	**0.49[0.3,0.8]**
Total events: 22 (Intervention), 45 (Control)					
Heterogeneity: Not applicable					

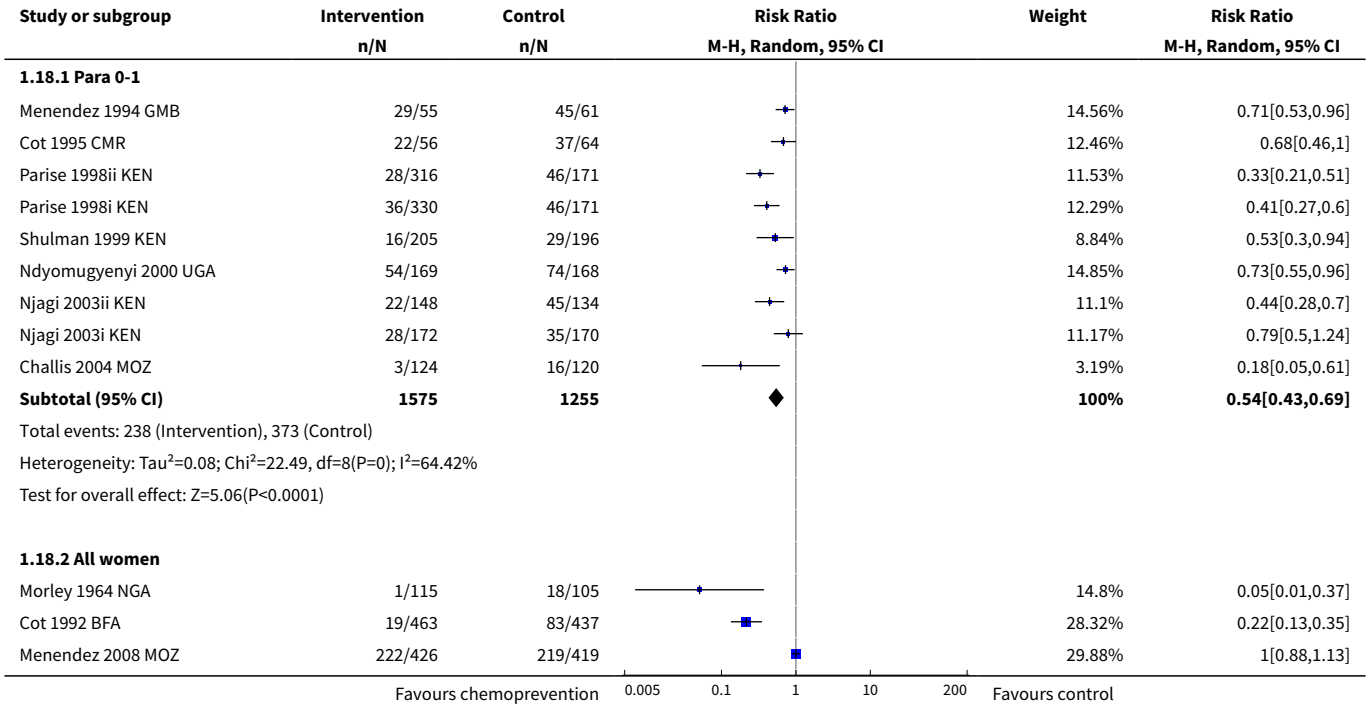


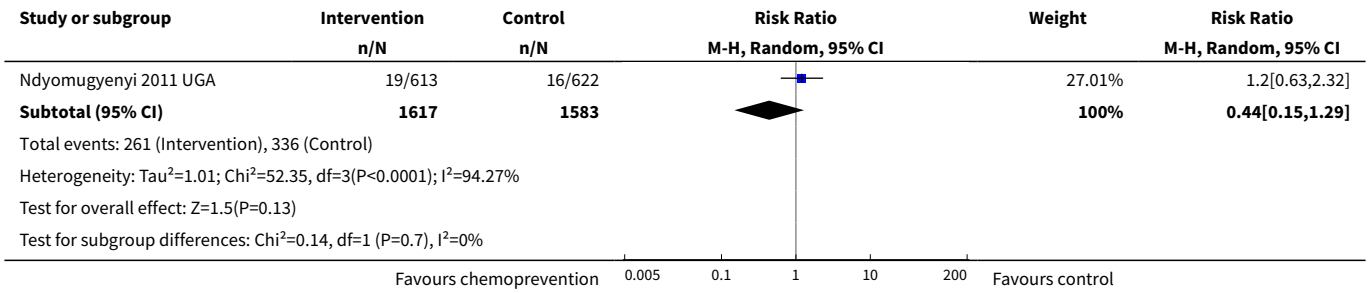


Analysis 1.17. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 17 Cord blood haemoglobin.

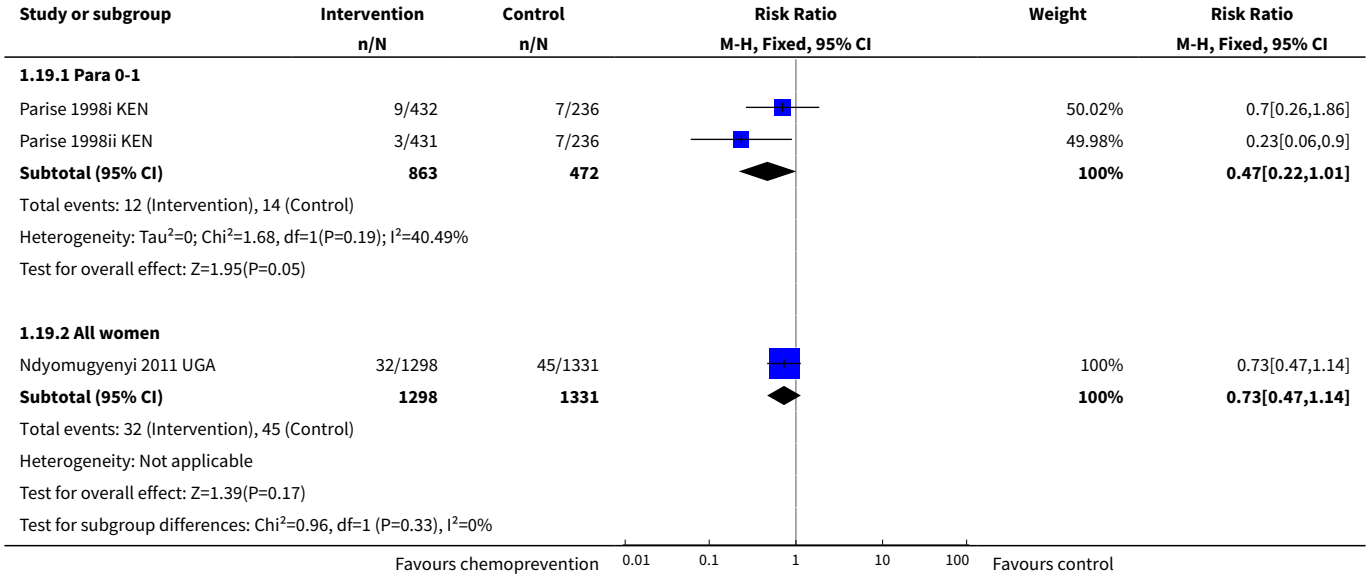


Analysis 1.18. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 18 Placental parasitemia (fetus).

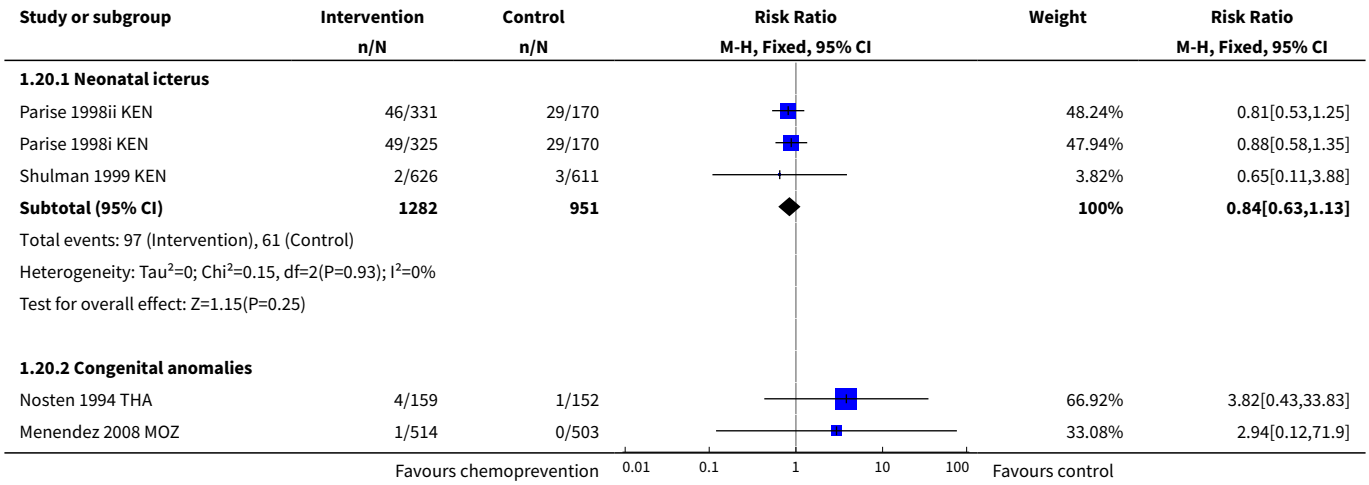


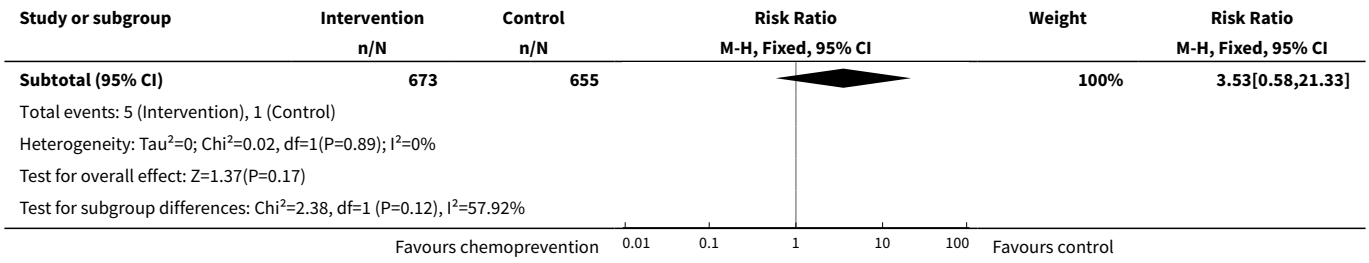


Analysis 1.19. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 19 Cord blood parasitaemia.



Analysis 1.20. Comparison 1 Preventive antimalarials versus placebo/no intervention, Outcome 20 Adverse effects (baby).



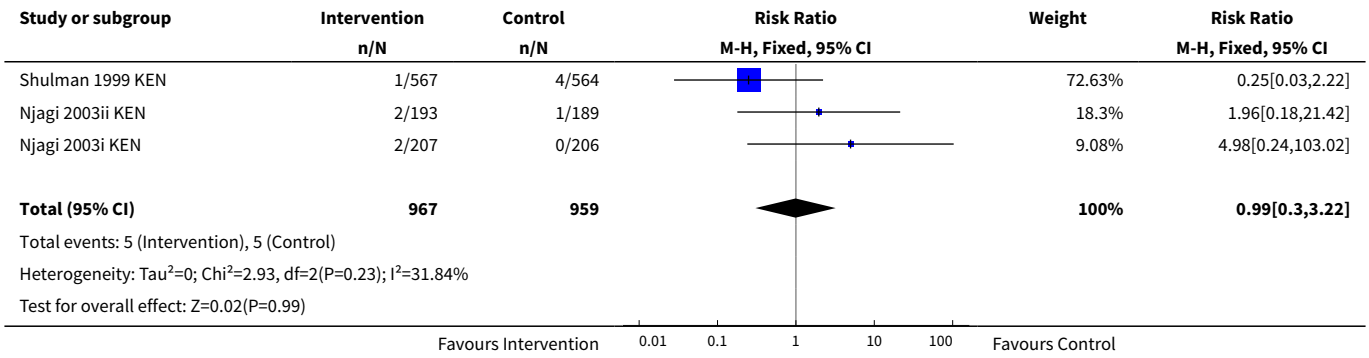


Comparison 2. IPT with SP versus placebo/no intervention

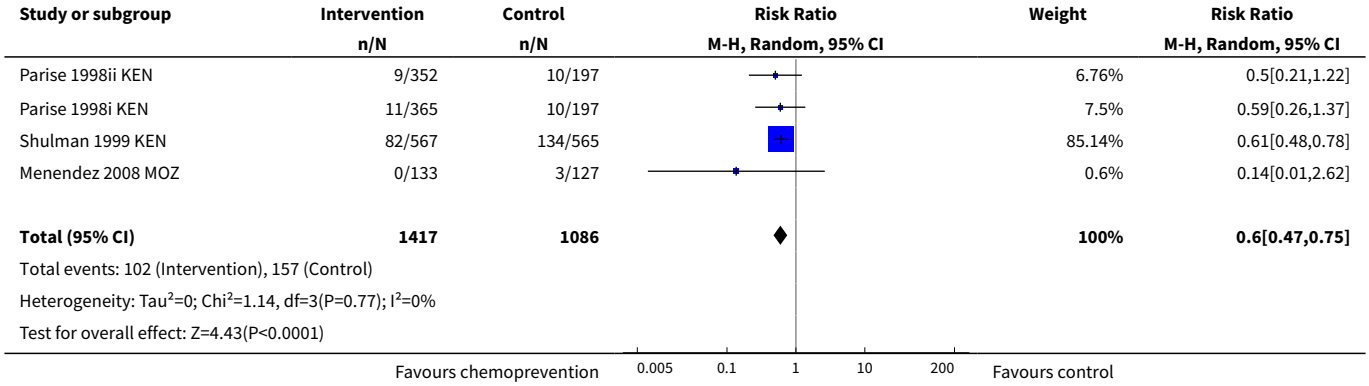
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (mother)	3	1926	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.30, 3.22]
2 Severe anaemia (mother)	4	2503	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.47, 0.75]
3 Anaemia (mother)	5	3219	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.81, 0.96]
4 Mean haemoglobin (g/dL)	5	2995	Mean Difference (IV, Fixed, 95% CI)	0.41 [0.27, 0.54]
5 Parasitaemia (mother)	7	3456	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.24, 0.59]
6 Clinical malaria (mother)	1	174	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.05, 1.12]
7 Spontaneous abortion	5	2572	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.38, 0.99]
8 Stillbirth	3	2572	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.62, 1.50]
9 Perinatal deaths	1	1237	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.52, 1.17]
10 Neonatal and infant mortality	3	2156	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.37, 1.05]
11 Preterm birth	3	1493	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.10]
12 Low birthweight	7	3043	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.67, 0.99]
13 Mean birthweight (baby)	6	2693	Mean Difference (IV, Fixed, 95% CI)	105.50 [68.02, 142.98]
14 Placental parasitemia (fetus)	6	2257	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.33, 0.61]
15 Cord blood parasitaemia	2	1335	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.22, 1.01]
16 Adverse effects (baby)	4	3250	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.64, 1.15]
16.1 Neonatal icterus	3	2233	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.63, 1.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.2 Congenital anomalies	1	1017	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [0.12, 71.90]

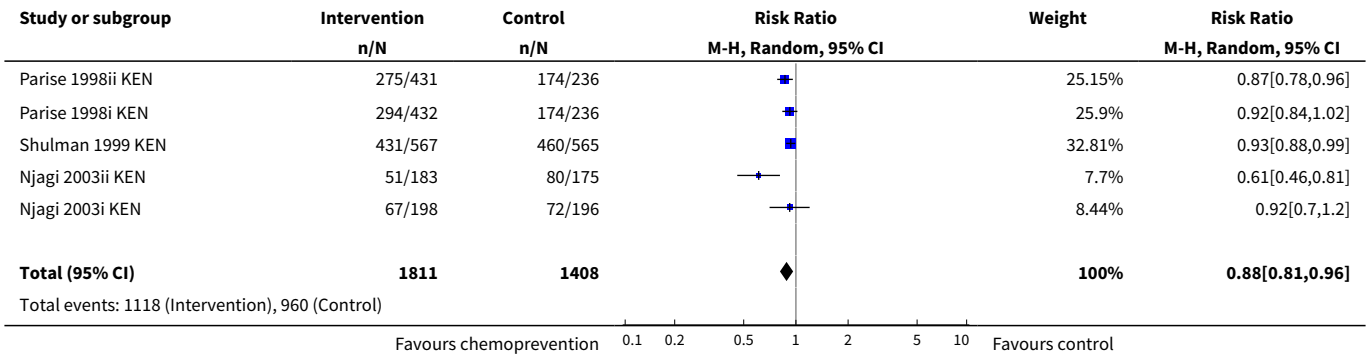
Analysis 2.1. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 1 Death (mother).

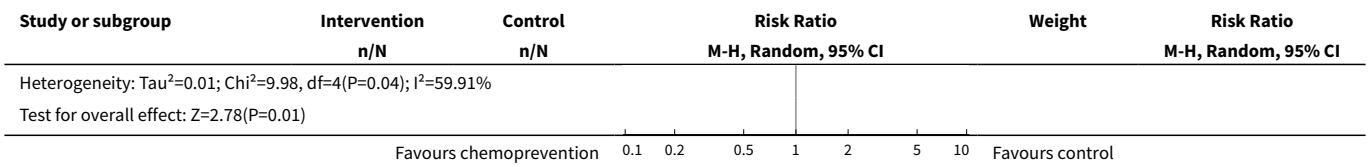


Analysis 2.2. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 2 Severe anaemia (mother).

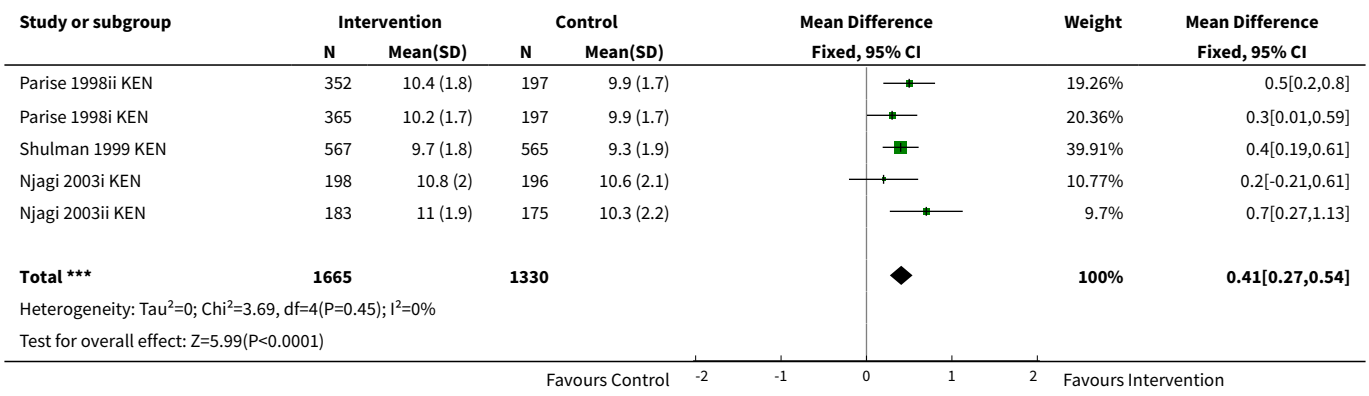


Analysis 2.3. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 3 Anaemia (mother).

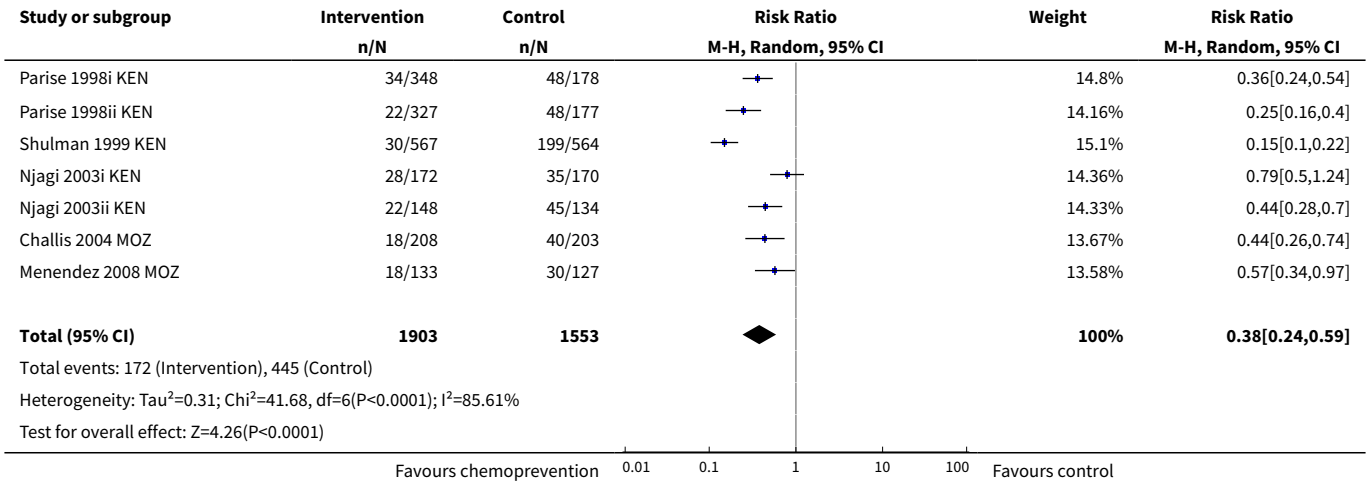




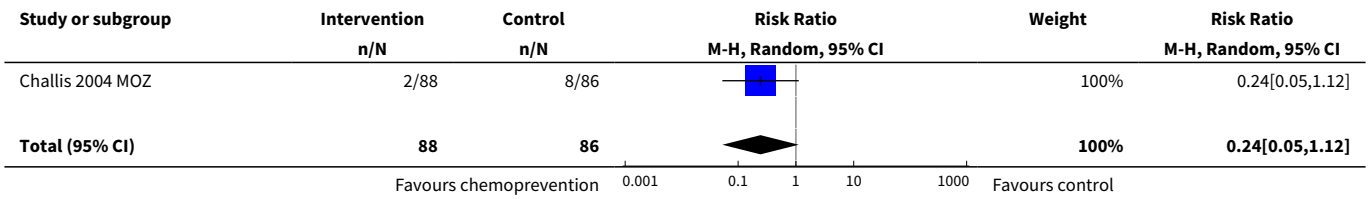
Analysis 2.4. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 4 Mean haemoglobin (g/dL).

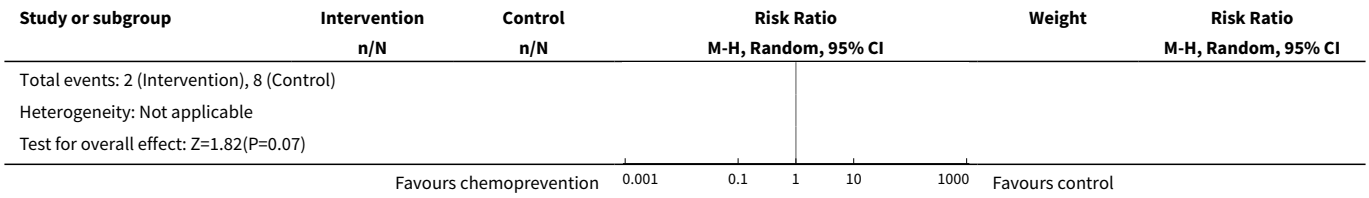


Analysis 2.5. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 5 Parasitaemia (mother).

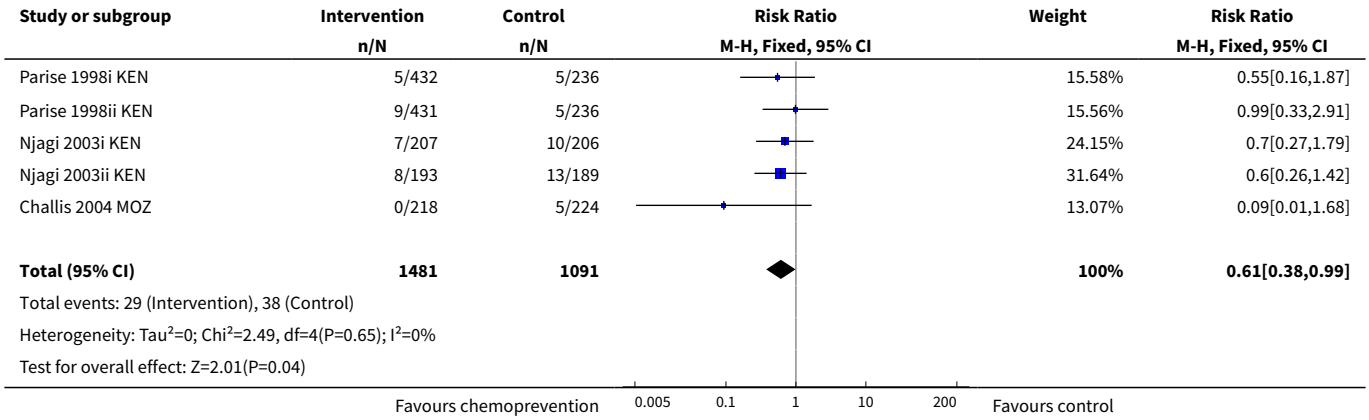


Analysis 2.6. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 6 Clinical malaria (mother).

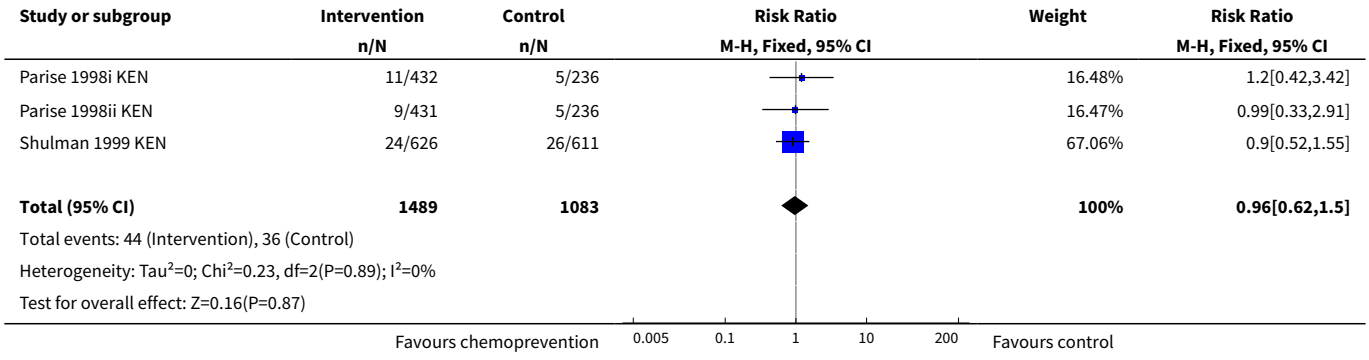




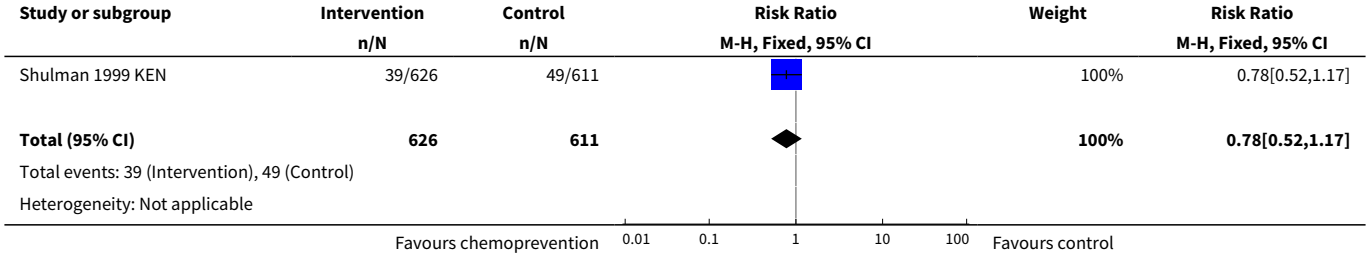
Analysis 2.7. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 7 Spontaneous abortion.



Analysis 2.8. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 8 Stillbirth.



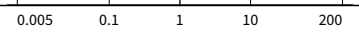
Analysis 2.9. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 9 Perinatal deaths.



Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.22(P=0.22)					

Analysis 2.10. Comparison 2 IPT with SP versus placebo/ no intervention, Outcome 10 Neonatal and infant mortality.

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Parise 1998i KEN	4/306	2/168		7.24%	1.1[0.2,5.93]
Parise 1998ii KEN	1/327	2/168		7.41%	0.26[0.02,2.81]
Shulman 1999 KEN	19/602	30/585		85.35%	0.62[0.35,1.08]
Total (95% CI)	**1235**	**921**		**100%**	**0.62[0.37,1.05]**
Total events: 24 (Intervention), 34 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.96, df=2(P=0.62); I^2=0%					
Test for overall effect: Z=1.79(P=0.07)					

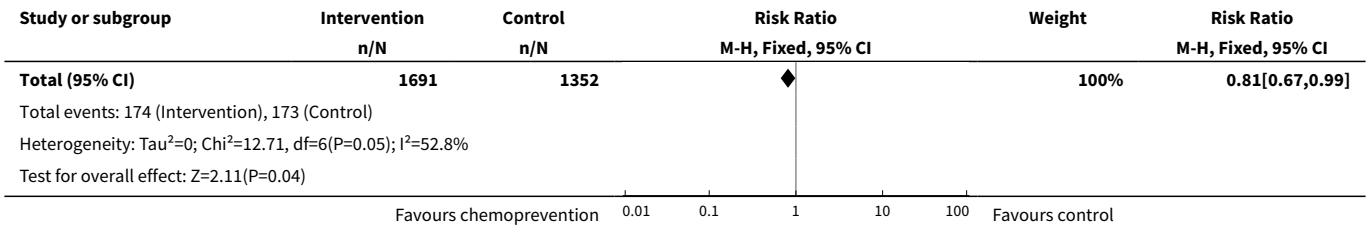


Analysis 2.11. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 11 Preterm birth.

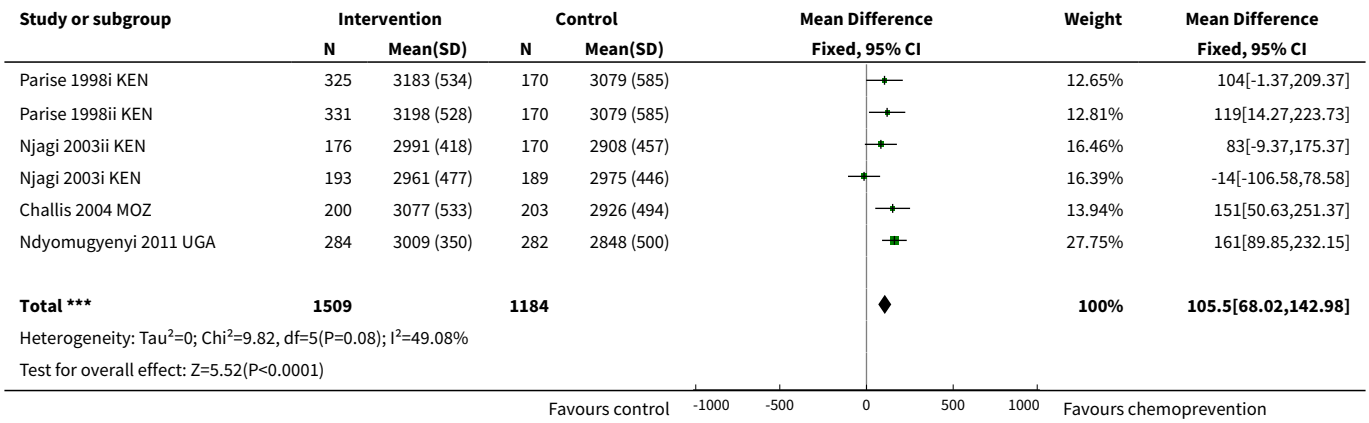
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Parise 1998ii KEN	42/350	22/180		26.62%	0.98[0.61,1.59]
Parise 1998i KEN	35/341	22/180		26.38%	0.84[0.51,1.39]
Challis 2004 MOZ	40/218	52/224		46.99%	0.79[0.55,1.14]
Total (95% CI)	**909**	**584**		**100%**	**0.85[0.66,1.1]**
Total events: 117 (Intervention), 96 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.49, df=2(P=0.78); I^2=0%					
Test for overall effect: Z=1.22(P=0.22)					

Analysis 2.12. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 12 Low birthweight.

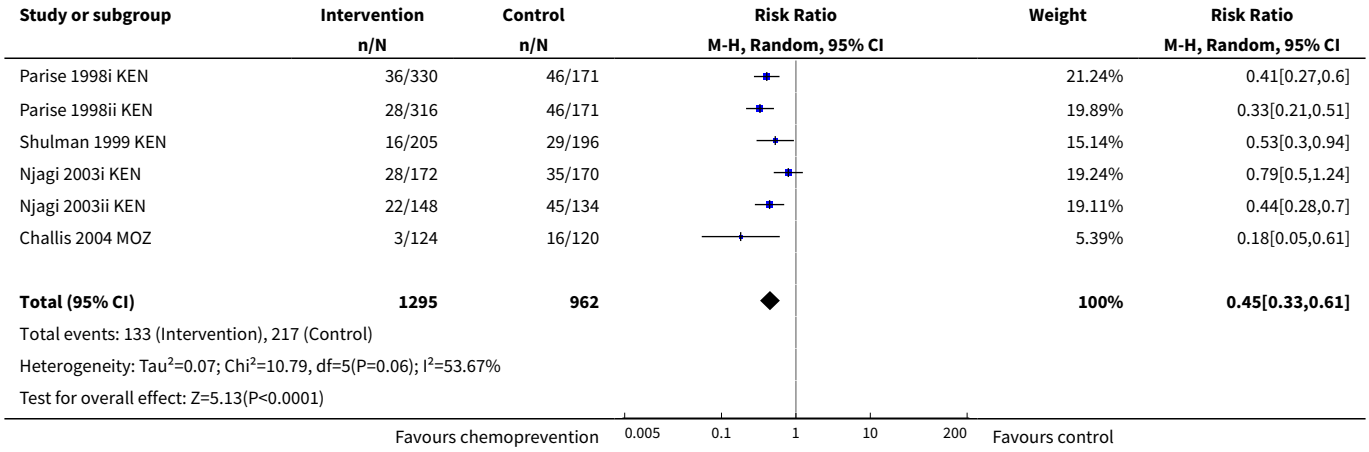
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Parise 1998ii KEN	26/331	26/170		17.96%	0.51[0.31,0.86]
Parise 1998i KEN	27/325	26/170		17.85%	0.54[0.33,0.9]
Njagi 2003i KEN	25/193	22/189		11.62%	1.11[0.65,1.9]
Njagi 2003ii KEN	21/176	29/170		15.42%	0.7[0.42,1.18]
Challis 2004 MOZ	19/200	27/203		14.01%	0.71[0.41,1.24]
Menendez 2008 MOZ	29/133	25/121		13.68%	1.06[0.66,1.7]
Ndyomugyenyi 2011 UGA	27/333	18/329		9.47%	1.48[0.83,2.64]



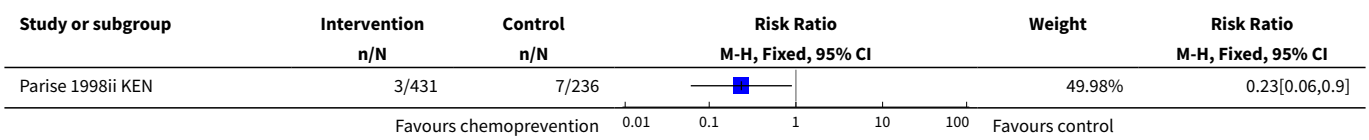
Analysis 2.13. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 13 Mean birthweight (baby).

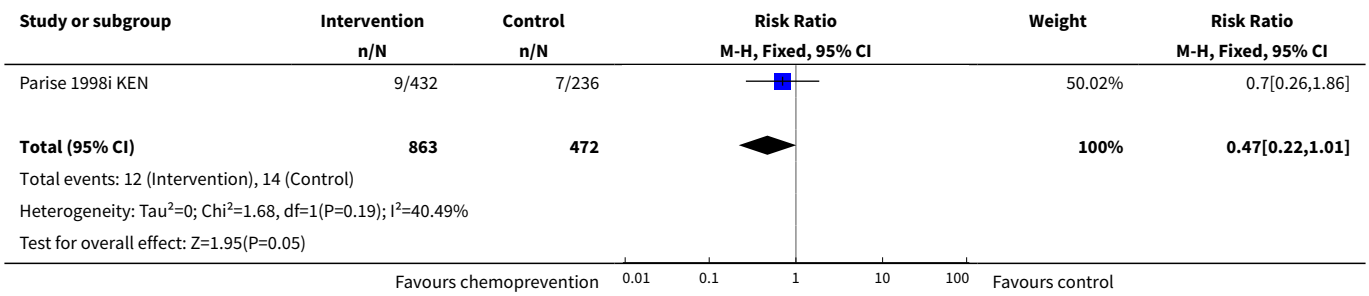


Analysis 2.14. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 14 Placental parasitemia (fetus).

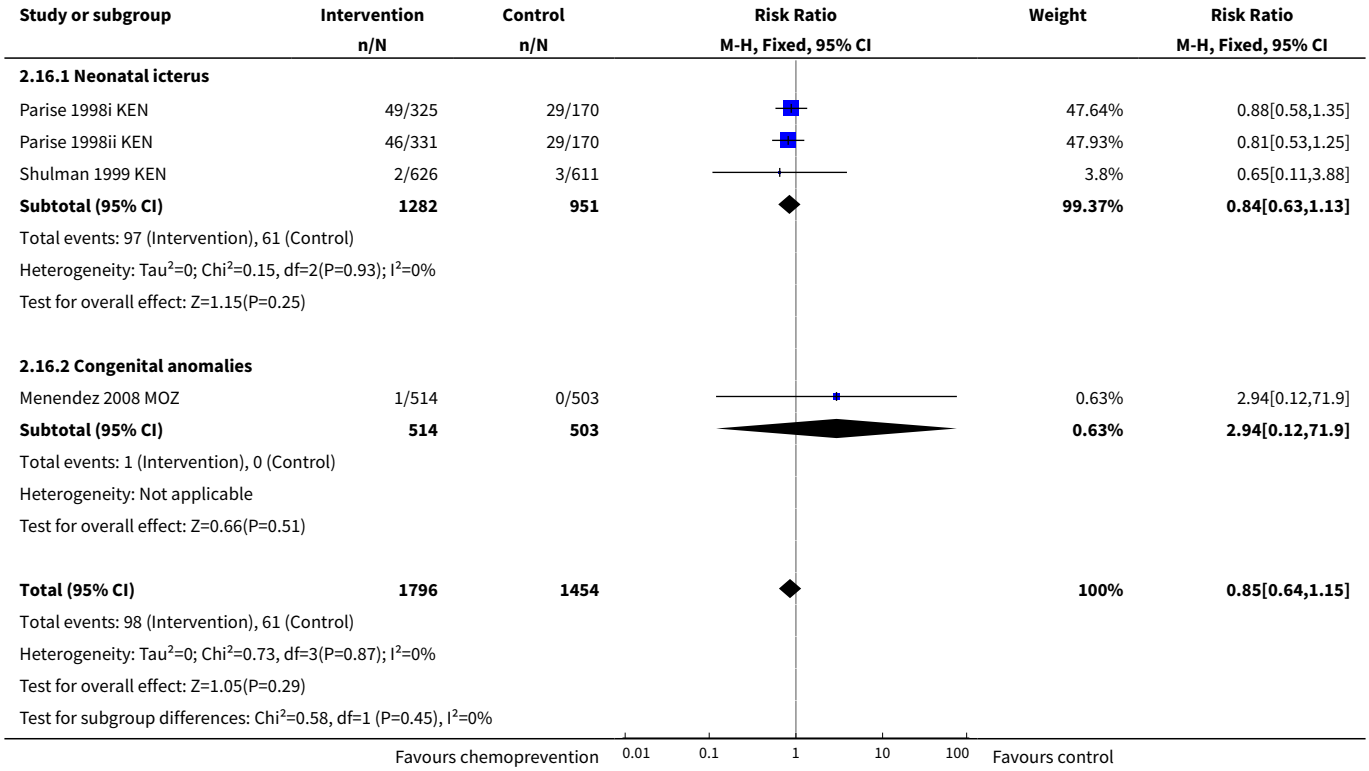


Analysis 2.15. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 15 Cord blood parasitaemia.





Analysis 2.16. Comparison 2 IPT with SP versus placebo/no intervention, Outcome 16 Adverse effects (baby).



ADDITIONAL TABLES

Table 1. Optimal information size calculations: Chemoprevention versus placebo

Outcome	Assumed risk	Source	Clinically important relative reduction	Sample size required[1,2]
Maternal mortality	350/100,000	Analysis 1.1	25%	125228
Severe anaemia	150/1000	Analysis 1.2	25%	2540
Anaemia	650/1000	Analysis 1.3	25%	284

Table 1. Optimal information size calculations: Chemoprevention versus placebo *(Continued)*

Malaria	170/1000	Analysis 1.5	25%	2194
Parasitaemia	290/1000	Analysis 1.6	25%	1124
Spontaneous abortions	32/1000	Analysis 1.9	25%	13348
Still births	33/1000	Analysis 1.10	25%	12932
Neonatal deaths	37/1000	Analysis 1.12	25%	11492
Preterm birth	160/1000	Analysis 1.13	25%	2356
Low birthweight	150/1000	Analysis 1.14	25%	2540
Placental parasitaemia	300/1000	Analysis 1.18	25%	1074

[1] All calculations are based on: 2-sided tests, with a ratio of 1:1, power of 0.8, and confidence level of 0.05.
[2] All calculations were performed using: http://www.sealedenvelope.com/power/binary-superiority

Table 2. Chloroquine versus placebo (effect on *P. vivax* malaria)

Outcomes	Trials	Participants	Effect estimate	Comment
Death (mother)	1	951	Risk ratio 0.34 (0.01, 8.28)	-
Severe anaemia	1	-	-	Not reported
Anaemia	1	951	Risk ratio 1.00 (0.92, 1.08)	Defined as PCV < 30%
Clinical malaria	1	-	-	Not reported
P. vivax parasitaemia	1	942	Risk ratio 0.01 (0.00, 0.20)	History of antenatal parasitaemia. Nine women censored (they had *P. falciparum* infection prior to their first *P. vivax* episode)
Adverse effects with chloroquine	1	951	Risk ratio 2.03 (0.18, 22.31)	The 5 most commonly reported adverse events were headache, anorexia, sleep disorder, dizziness and weakness. CQ group: drug suspended in two cases (1 - constipation,1- nausea) One woman in the placebo group was complaining of visual problems
Spontaneous abortion	1	951	Risk ratio 0.71 (0.36, 1.39)	-
Stillbirth	1	865	Risk ratio 0.24 (0.03, 2.17)	-
Perinatal deaths	1	-	-	Not reported

Table 2. Chloroquine versus placebo (effect on *P. vivax* malaria) *(Continued)*

Neonatal and infant mortality	1	-	-	Not reported
Preterm birth (All)	1	733	Risk ratio 0.93 (0.46, 1.85)	-
Preterm birth (Para 0)	1	141	Risk ratio 2.41 (0.63, 9.24)	-
Preterm birth (Para 2+)	1	592	Risk ratio 0.62 (0.26, 1.46)	-
Low birthweight (All)	1	733	Risk ratio 1.02 (0.71, 1.46)	-
Low birthweight (Para 0)	1	141	Risk ratio 1.20 (0.65, 2.21)	-
Low birthweight (Para 2+)	1	592	Risk ratio 0.94 (0.60, 1.47)	-
Mean birthweight (All)	1	733	Mean difference -8.20 (-73.41, 57.02)	-
Mean birthweight (Para 0)	1	141	Mean difference -36.00 (-188.73, 116.73)	Mean (SD) 2741 ± 481 versus 2777 ± 435 in the CQ versus placebo group
Mean birthweight (Para 2+)	1	592	Mean difference -2.00 (-74.12, 70.12)	Mean (SD) 2954 ± 423 versus 2956 ± 471 in the CQ versus placebo group
Placental malaria	1	-	-	Not reported
Cord blood haemoglobin	1	-	-	Not reported
Cord blood parasitaemia	1	-	-	Not reported
Adverse effects (baby)	1	864	Risk ratio 1.22 (0.33, 4.50)	Congenital anomalies: Amniotic banding, brachydactyly; anophthalmia, Down's syndrome,; amniotic banding, absent digit toes; two cleft lip, one cleft palate in the placebo group.

APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	malaria	MALARIA	MALARIA	MALARIA	malaria

(Continued)

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$	—
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	—

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search 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. Chemoprophylaxis regimens evaluated in the trials

Chemoprevention regimen			Trials
Drug	**Dose**	**Frequency**	
Chloroquine	300 mg	Weekly	Cot 1992 BFA; Cot 1995 CMR; Ndyomugyenyi 2000 UGA; Villegas 2007 THA
Pyrimethamine	100 mg	Monthly	Morley 1964 NGA
	25 mg	Weekly	Nahlen 1989 NGA
Proguanil	100 mg	Daily	Fleming 1986 NGA
Pyrimethamine-dapsone	25 mg/100 mg	Every two weeks	Greenwood 1989 GMB
	12.5 mg/100 mg	Weekly	Menendez 1994 GMB
Sulfadoxine-pyrimethamine	1500 mg/75 mg	One to two doses	Shulman 1999 KEN
		Two doses	Challis 2004 MOZ; Menendez 2008 MOZ; Njagi 2003i KEN; Parise 1998i KEN
		Up to four doses	Mbaye 2006 GMB
		Monthly	Parise 1998ii KEN
Mefloquine	500 mg loading dose, 250 mg weekly for 4 weeks, 125 mg weekly until delivery	Weekly	Nosten 1994 THA

Appendix 3. Trial participants: number of previous pregnancies

No. of pregnancies	Trials	number of trials
All women	Morley 1964 NGA; Nahlen 1989 NGA; Cot 1992 BFA; Nosten 1994 THA; Greenwood 1989 GMB; Villegas 2007 THA; Menendez 2008 MOZ; Ndyomugyenyi 2011 UGA;	8
First pregnancy	Fleming 1986 NGA; Menendez 1994 GMB; Cot 1995 CMR; Shulman 1999 KEN; Ndyomugyenyi 2000 UGA; Challis 2004 MOZ	6
First or second pregnancy	Parise 1998i KEN; Njagi 2003ii KEN	2
Only multiparous women	Mbaye 2006 GMB	1

Nahlen 1989 NGA; Greenwood 1989 GMB; Menendez 2008 MOZ all provided data disaggregated by parity.

Appendix 4. 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 MOZ	Parasitaemia	411/600	69	Low birthweight	403/600	67
Cot 1992 BFA	Placental malaria	904/1464	62	Birthweight	1148/1148	100
Cot 1995 CMR	Placental malaria	120/266	57	Birthweight	209/266	79
Fleming 1986 NGA	Haemoglobin	107/200	45	Perinatal death	152/200	76
Greenwood 1989 GMB	Parasitaemia	257/1049	24	Birthweight	877/1034	85
Menendez 1994 GMB	Placental malaria	116/230	50	Birthweight	182/203	90
Morley 1964 NGA	Antenatal parasitaemia	227/429	53	Birthweight	429/429	100
Nahlen 1989 NGA	Parasitaemia	71/71	100	—	—	—
Ndyomugyenyi 2000 UGA	Anaemia	510/860	59	Congenital malaria	337/510	66
Nosten 1994 THA	Parasitaemia	399/399	100	Birthweight	290/290	100
Parise 1998i KEN, Parise 1998ii KEN	Haemoglobin	1378/2077	66	—	—	—
Shulman 1999 KEN	Severe anaemia	1132/1264	90	—	—	—

[a]Number analysed/number randomized.

WHAT'S NEW

Date	Event	Description
29 September 2014	New citation required but conclusions have not changed	We repeated all searches. Trial inclusion criteria, data extraction, risk of bias assessment, and data entry were all done afresh. We additionally carried out GRADE analysis and a sensitivity analysis of IPT. Contributions of individuals are outlined in section 'Contributions of authors'.
29 September 2014	New search has been performed	Review updated.

HISTORY

Protocol first published: Issue 1, 1995
Review first published: Issue 1, 1995

Date	Event	Description
16 September 2008	Amended	Converted to new review format with minor editing.
20 August 2006	Amended	2006, Issue 4: added Challis 2004 MOZ and Kayentao 2005 MLIa; 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

DR-P re-ran the searches, re-extracted data with PG, updated the risk of bias tables, created GRADE tables, and rewrote the results. PG assisted with the update, provided advice on the structure and analysis, completed the conceptual framework, checked the GRADE assessments and revised the results, and wrote the discussion. DS contributed to the GRADE assessment, rewriting the results, and restructuring the review. KK and FK helped with conceptualising the questions and interpreting the results in context. KK and FK carefully considered all the included trials and checked for accuracy and completeness. All authors contributed to the final agreed version of the review.

DECLARATIONS OF INTEREST

PG is Director of Evidence Building and Synthesis Research Consortium that receives money to increase the number of evidence-informed decisions by intermediary organizations, including WHO and national decision-makers that benefit the poor in middle- and low-income countries. DS is employed as part of this Consortium. PG is the coordinator of a WHO Collaborating Centre for Evidence Synthesis for Infectious and Tropical Diseases (http://apps.who.int/whocc/Detail.aspx?cc_ref=UNK-234&cc_code=unk&cc_contact=garner&): one of the

Centre's aims is to help WHO in its role as an infomediary in communicating reliable summaries of research evidence to policy makers, clinicians, teachers, and the public in developing countries.

Feiko ter Kuile is Chief Executive Officer of the Malaria in Pregnancy Consortium, a network of 47 research institutions worldwide conducting research on the treatment and prevention of malaria in pregnancy, funded by the Bill and Melinda Gates Foundation. He is principal investigator on several trials investigating intermittent preventive treatment and intermittent screening and treatment in pregnancy.

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

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy