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Intermittent preventive treatment for malaria in infants (Review)

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[Intervention Review]

Intermittent preventive treatment for malaria in infants

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ABSTRACT

Background

Intermittent preventive treatment could help prevent malaria in infants (IPTi) living in areas of moderate to high malaria transmission in sub-Saharan Africa. The World Health Organization (WHO) policy recommended IPTi in 2010, but its adoption in countries has been limited.

Objectives

To evaluate the effects of intermittent preventive treatment (IPT) with antimalarial drugs to prevent malaria in infants living in malaria-endemic areas.

Search methods

We searched the following sources up to 3 December 2018: the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (the Cochrane Library), MEDLINE (PubMed), Embase (OVID), LILACS (Bireme), and reference lists of articles. We also searched the metaRegister of Controlled Trials (mRCT) and the WHO International Clinical Trials Registry Platform (ICTRP) portal for ongoing trials up to 3 December 2018.

Selection criteria

We included randomized controlled trials (RCTs) that compared IPT to placebo or no intervention in infants (defined as young children aged between 1 to 12 months) in malaria-endemic areas.

Data collection and analysis

The primary outcome was clinical malaria (fever plus asexual parasitaemia). Two review authors independently assessed trials for inclusion, evaluated the risk of bias, and extracted data. We summarized dichotomous outcomes and count data using risk ratios (RR) and rate ratios respectively, and presented all measures with 95% confidence intervals (CIs). We extracted protective efficacy values and their 95% CIs; when an included trial did not report this data, we calculated these values from the RR or rate ratio with its 95% CI. Where appropriate, we combined data in meta-analyses and assessed the certainty of the evidence using the GRADE approach.

Main results

We included 12 trials that enrolled 19,098 infants; all were conducted in sub-Saharan Africa. Three trials were cluster-RCTs. IPTi with sulfadoxine-pyrimethamine (SP) was evaluated in 10 trials from 1999 to 2013 (n = 15,256). Trials evaluating ACTs included dihydroartemisinin-piperaquine (1 trial, 147 participants; year 2013), amodiaquine-artesunate (1 study, 684 participants; year 2008), and SP-artesunate (1 trial, 676 participants; year 2008). The earlier studies evaluated IPTi with SP, and were conducted in Tanzania (in 1999 and

2006), Mozambique (2004), Ghana (2004 to 2005), Gabon (2005), Kenya (2008), and Mali (2009). One trial evaluated IPTi with amodiaquine in Tanzania (2000). Later studies included three conducted in Kenya (2008), Tanzania (2008), and Uganda (2013), evaluating IPTi in multiple trial arms that included artemisinin-based combination therapy (ACT).

Although the effect size varied over time and between drugs, overall IPTi impacts on the incidence of clinical malaria overall, with a 30% reduction (rate ratio 0.70, 0.62 to 0.80; 10 studies, 10,602 participants). The effect of SP appeared to attenuate over time, with trials conducted after 2009 showing little or no effect of the intervention. IPTi with SP probably resulted in fewer episodes of clinical malaria (rate ratio 0.78, 0.69 to 0.88; 8 trials, 8774 participants, moderate-certainty evidence), anaemia (rate ratio 0.82, 0.68 to 0.98; 6 trials, 7438 participants, moderate-certainty evidence), parasitaemia (rate ratio 0.66, 0.56 to 0.79; 1 trial, 1200 participants, moderate-certainty evidence), and fewer hospital admissions (rate ratio 0.85, 0.78 to 0.93; 7 trials, 7486 participants, moderate-certainty evidence). IPTi with SP probably made little or no difference to all-cause mortality (risk ratio 0.93, 0.74 to 1.15; 9 trials, 14,588 participants, moderate-certainty evidence).

Since 2009, IPTi trials have evaluated ACTs and indicate impact on clinical malaria and parasitaemia. A small trial of DHAP in 2013 shows substantive effects on clinical malaria (RR 0.42, 0.33 to 0.54; 1 trial, 147 participants, moderate-certainty evidence) and parasitaemia (moderate-certainty evidence).

Authors' conclusions

In areas of sub-Saharan Africa, giving antimalarial drugs known to be effective against the malaria parasite at the time to infants as IPT probably reduces the risk of clinical malaria, anaemia, and hospital admission. Evidence from SP studies over a 19-year period shows declining efficacy, which may be due to increasing drug resistance. Combinations with ACTs appear promising as suitable alternatives for IPTi.

PLAIN LANGUAGE SUMMARY

Administering antimalarial drugs to prevent malaria in infants

What is the aim of the review?

This Cochrane Review aimed to find out if administering repeated doses of antimalarial treatment to infants living in sub-Saharan Africa can prevent malaria. We found and analysed results from 12 relevant studies conducted between 1999 and 2013 that addressed this question in infants (defined as young children aged between 1 to 12 months).

Key messages

Intermittent preventive treatment with sulfadoxine-pyrimethamine (SP)

Giving SP as preventive antimalarial treatment to infants probably reduced the risk of clinical malaria, anaemia, and hospital admissions in the African countries it was evaluated. However, this effect was attenuated in more recent studies.

Intermittent preventive treatment with artemisinin-based combination therapy (ACT)

Giving ACT as preventive antimalarial treatment to infants may reduce the risk of clinical malaria. It may also reduce the proportion of infants with malaria parasites in their blood.

What was studied in the review?

In areas where malaria is common, infants often suffer repeated episodes of malarial illness. In areas where malaria transmission occurs all-year, some authorities recommend intermittent preventive treatment, which requires giving drugs at regular intervals (at child vaccination visits) regardless of whether the child has malaria symptoms or not to prevent malarial illness.

We studied the effects of IPTi with SP and other medicines (including ACTs) on malaria-related outcomes. Review outcomes included clinical malaria, severe malaria, death, hospital admission, parasitaemia, anaemia, change in haemoglobin level, and side effects.

What are the main results of the review?

We included 12 studies that enrolled 19,098 infants. All studies were done in sub-Saharan Africa (Gabon, Ghana, Kenya, Mali, Mozambique, Tanzania, and Uganda). These studies compared infants who received IPTi to those who received placebo pills or nothing. The infants in the IPTi group were given different medicines, in different doses, and for different lengths of time.

Ten studies evaluated IPTi with SP from 1999 to 2013. The effect of SP appear to wane over time, with trials conducted after 2009 showing little or no effect of the intervention. The studies show that IPTi with SP probably resulted in fewer episodes of clinical malaria, anaemia, hospital admission, and blood parasites without symptoms (moderate-certainty evidence). IPTi with SP probably made little or no difference to the risk of death (moderate-certainty evidence).

Since 2009, IPTi some small studies have evaluated artemisinin-based combination medicines and indicate impact on clinical malaria and blood parasites. A small study of IPTi with dihydroartemisinin-piperaquine in 2013 showed up to 58% reduction in episodes of clinical malaria (moderate-certainty evidence) and reductions in proportion of infants with blood parasites (moderate-certainty evidence).

How up-to-date is this review?

The review authors searched for studies published up to 3 December 2018.

SUMMARY OF FINDINGS

Summary of findings 1. 'Summary of findings' table 1

Intermittent preventive treatment in infants (IPTi) with sulfadoxine-pyrimethamine (SP) versus placebo or no IPTi

Participant or population: children under 12 months of age
Settings: areas with moderate to high malaria transmission (August 1999 to September 2013; Gabon, Ghana, Mali, Mozambique,Tanzania, and Uganda)
Intervention: intermittent preventive treatment (IPT) with SP

Comparison: placebo or no IPTi

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no IPTi	Risk with IPTi-SP				
Clinical malaria	74 episodes per 100 infants per year[a]	58 episodes per 100 infants per year (51 to 65)	Rate ratio 0.78 (0.69 to 0.88)	8774 (8 trials)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-SP probably reduced the risk of clinical malaria compared to placebo or no IPTi
Severe malaria	20 episodes per 1000 infants per year[c]	19 episodes per 1000 infants per year (11 to 31)	Rate ratio 0.92 (0.47 to 1.81)	1347 (2 trials)	⊕⊕⊖⊖ LOW[d,e] *due to inconsistency and imprecision*	IPTi-SP may have made little or no difference to the risk of severe malaria compared to placebo or no IPTi
All-cause mortality	23 per 1000 per year	21 per 1000 per year (17 to 26)	Risk ratio 0.93 (0.74 to 1.15)	14,588 (9 trials)	⊕⊕⊕⊖ MODERATE[f] *due to inconsistency*	IPTi-SP may have made little or no difference to the risk of death compared to placebo or no IPTi
Hospital admission for any reason	37 episodes per 100 infants per year[g]	32 episodes per 100 infants per year (29 to 36)	Rate ratio 0.85 (0.78 to 0.93)	7486 (7 trials)	⊕⊕⊕⊖ MODERATE[h] *due to imprecision*	IPTi-SP probably slightly reduced hospital admission compared to placebo or no IPTi
Parasitaemia	60 episodes per 100 infants per year[i]	40 episodes per 100 infants per year (34 to 47)	Rate ratio 0.66 (0.56 to 0.79)	1200 (1 trial)	⊕⊕⊕⊖ MODERATE[j] *due to imprecision*	IPTi-SP probably reduced the risk of parasitaemia compared to placebo or no IPTi

Anaemia	32 episodes per 100 infants per year[k]	26 episodes per 100 infants per year (22 to 31)	Rate ratio 0.82 (0.68 to 0.98)	7438 (6 trials)	⊕⊕⊕⊖ MODERATE[l] *due to inconsistency*	IPTi-SP probably reduced the risk of anaemia compared to placebo or no IPTi

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

Abbreviations: CI: confidence interval; IPT: intermittent preventive treatment: IPTi: intermittent preventive treatment in infants; sulfadoxine-pyrimethamine: SP.

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

[a]The incidence of malaria in the control groups was between 0.16 and 6.41 episodes per child per year.
[b]Downgraded by 1 due to imprecision: these trials and the overall meta-analysis are underpowered to detect a difference or to prove equivalence.
[c]The incidence of severe malaria in the control groups was between 0.02 and 0.03 episodes per child per year.
[d]Downgraded by 1 due to inconsistency: there was considerable variation in the size of effect.
[e]Downgraded by 1 for serious imprecision: these trials and the overall meta-analysis are underpowered to detect a difference or to prove equivalence. Also the 95% CI overlaps and had no effect.
[f]Downgraded by 1 due to inconsistency: wide variance of point estimates observed among the 9 trials in this meta-analysis.
[g]The incidence of hospital admissions for any cause in the control groups was between 0.06 and 0.63 episodes per child per year.
[h]Downgraded by 1 due to imprecision: these trials and the overall meta-analysis are underpowered to detect a difference or to prove equivalence.
[i]The incidence of parasitaemia in the control group of one trial from Ghana was 0.6 episodes per child per year.
[j]Downgraded by 1 due to imprecision: very small sample included in this analysis and is unlikely to detect differences or prove equivalence.
[k]The incidence of anaemia in the control groups was between 0.07 and 0.67 episodes per child per year.
[l]Downgraded by 1 due to inconsistency: significant statistical heterogeneity observed in this meta-analysis (I^2 statistic = 67%, P = 0.01).

Summary of findings 2. 'Summary of findings' table 2

Intermittent preventive treatment in infants (IPTi) with AQ-AS compared to placebo or no IPTi for malaria in infants

Patient or population: malaria in infants
Setting: areas with moderate to high malaria transmission (March 2004 to March 2008; Kenya)
Intervention: IPTi-AQ-AS
Comparison: placebo or no IPTi

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

	Risk with placebo or no IPTi	Risk with IPTi-AQ-AS				
Clinical malaria	133 episodes per 100 infants per year[a]	100 episodes per 100 infants per year (81 to 125)	Rate ratio 0.75 (0.61 to 0.94)	547 (1 trial)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-AQ-AS probably reduces the risk of clinical malaria compared to placebo or no IPTi
Severe malaria	-	-	-	-	-	Not reported
All-cause mortality	36 per 1000	43 per 1000 (21 to 91)	Risk ratio 1.21 (0.58 to 2.55)	684 (1 trial)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-AQ-AS probably makes little or no difference to the risk of death compared to placebo or no IPTi
Hospital admission for any reason	65 episodes per 100 infants per year[c]	64 episodes per 100 infants per year (49 to 83)	Rate ratio 0.98 (0.76 to 1.27)	684 (1 trial)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-AQ-AS probably makes little or no difference to the risk of hospital admission compared to placebo or no IPTi
Parasitaemia	-	-	-	-	-	Not reported
Anaemia	30 infants per 1000 infants[d]	23 per 100 infants (159 to 336)	Rate ratio 0.77 (0.53 to 1.12)	684 (1 trial)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-AQ-AS probably makes little or no difference to the risk of anaemia compared to placebo or no IPTi

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Abbreviations: CI: confidence interval; IPT: intermittent preventive treatment: IPTi: intermittent preventive treatment in infants; AQ-AS: amodiaquine-artesunate

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

[a]The incidence of malaria in the control group was 1.33 episodes per child per year (Odhiambo 2010 KEN).
[b]Downgraded by 1 due to imprecision: CIs include potential for important harm and benefit.
[c]The incidence of hospital admissions for any cause in the control group was 0.65 episodes per child per year (Odhiambo 2010 KEN).
[d]The incidence of anaemia in the control group 0.3 episodes per child per year (Odhiambo 2010 KEN).

Summary of findings 3. 'Summary of findings' table 3

Intermittent preventive treatment in infants (IPTi) with DHAP compared to placebo or no IPTi for malaria in infants

Patient or population: malaria in infants
Setting: areas with moderate to high malaria transmission (June 2010 to September 2013; Uganda)
Intervention: IPTi-DHAP
Comparison: placebo or no IPTi

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no IPTi	Risk with IPTi-DHAP				
Clinical malaria	641 episodes per 100 infants per year[a]	269 episodes per 100 infants per year (211 to 346)	Rate ratio 0.42 (0.33 to 0.54)	147 (1 trial)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-DHAP probably reduces the risk of clinical malaria compared to placebo or no IPTi
Severe malaria	29 episodes per 1000 infants per year[c]	37 episodes per 1000 infants per year (8 to 173)	Rate ratio 1.29 (0.28 to 5.98)	147 (1 trial)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-DHAP probably makes little or no difference to the risk of severe malaria compared to placebo or no IPTi
All-cause mortality	20 per 1000	3 per 1000 (0 to 83)	Risk ratio 0.17 (0.01 to 4.06)	147 (1 trial)	⊕⊕⊖⊖ LOW[b,d] *due to imprecision*	IPTi-DHAP may make little or no difference to the risk of death compared to placebo or no IPTi
Hospital admission for any reason	58 episodes per 1000 infants per year[e]	92 episodes per 1000 infants per year (27 to 314)	Rate ratio 1.58 (0.46 to 5.42)	147 (1 trial)	⊕⊕⊖⊖ LOW[b,d] *due to imprecision*	IPTi-DHAP may make little or no difference to the risk of hospital admission compared to placebo or no IPTi
Parasitaemia	The prevalence in the IPTi-DHAP group was 3% compared to 11% in the control group (P < 0.001)			147 (1 trial)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-DHAP probably reduces the risk of parasitaemia compared to placebo or no IPTi

Anaemia	The prevalence in the IPTi-DHAP group was half the prevalence in the control group (3% versus 6%; P = 0.04)	147 (1 trial)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-DHAP probably reduces the risk of anaemia compared to placebo or no IPTi

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; IPT: intermittent preventive treatment: IPTi: intermittent preventive treatment in infants; DHAP: dihydroartemisinin-piperaquine

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

[a]The incidence of malaria in the control group was 6.41 episodes per child per year (Bigira 2014 UGA).
[b]Downgraded by 1 due to imprecision: very few infants contributed to this analysis.
[c]The incidence of severe malaria in the control group was 0.029 episodes per child per year (Bigira 2014 UGA).
[d]Downgraded by 1 due to imprecision: CIs include potential for important harm and benefit.
[e]The incidence of hospital admission in the control group was 0.058 episodes per child per year (Bigira 2014 UGA).

Summary of findings 4. 'Summary of findings' table 4

Intermittent preventive treatment in infants (IPTi) with SP-AS compared to placebo or no IPTi for malaria in infants

Patient or population: malaria in infants
Setting: areas with moderate to high malaria transmission (March 2004 to March 2008; Kenya)
Intervention: IPTi-SP-AS
Comparison: placebo or no IPTi

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no IPTi	Risk with IPTi-SP-AS				
Clinical malaria	133 episodes per 100 infants per year[a]	104 episodes per 100 infants per year (82 to 129)	Rate ratio 0.78 (0.62 to 0.97)	676 (1 trial)	⊕⊕⊕⊕ HIGH	IPTi-SP-AS reduces the risk of clinical malaria compared to placebo or no IPTi
Severe malaria	-	-	-	-	-	Not reported

All-cause mortality	36 per 1000	30 per 1000 (13 to 67)	Risk ratio 0.83 (0.36 to 1.89)	676 (1 trial)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-SP-AS probably makes little or no difference to the risk of death compared to placebo or no IPTi
Hospital admission for any reason	65 episodes per 100 infants per year[c]	60 episodes per 100 infants per year (462 to 780)	Rate ratio 0.92 (0.71 to 1.20)	676 (1 trial)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-SP-AS probably makes little or no difference to the risk of hospital admission compared to placebo or no IPTi
Parasitaemia	-	-	-	-	-	Not reported
Anaemia	30 infants per 100 infants[d]	22 per 100 infants per year (15 to 32)	Rate ratio 0.72 (0.49 to 1.07)	676 (1 trial)	⊕⊕⊕⊖ MODERATE[b] *due to imprecision*	IPTi-SP-AS probably makes little or no difference to the risk of anaemia compared to placebo or no IPTi

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; IPT: intermittent preventive treatment: IPTi: intermittent preventive treatment in infants; SP-AS: sulfadoxine-pyrimethamine-artesunate

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

[a]The incidence of malaria in the control group was 1.33 episodes per child per year (Odhiambo 2010 KEN).
[b]Downgraded by 1 for imprecision: CIs include potential for important harm and benefit.
[c]The incidence of hospital admissions for any cause in the control group was 0.65 episodes per child per year (Odhiambo 2010 KEN).
[d]The incidence of anaemia in the control group 0.3 episodes per child per year (Odhiambo 2010 KEN).

BACKGROUND

Description of the condition

Malaria is caused by infection with the *Plasmodium* parasite, which is transmitted to humans through the bite of infected female *Anopheles* mosquitoes. In the human body, the parasites multiply in the liver and then infect red blood cells. Malaria can also be transmitted from a mother to her unborn baby (congenitally) and through blood transfusions. Five *Plasmodium* species are known to cause this disease in humans. *Plasmodium falciparum* is the most common worldwide, and is responsible for almost all severe disease cases and deaths (WHO 2018). People visiting or living in areas where malaria transmission is prevalent are at risk of malaria infection; children and pregnant women living in malaria-endemic areas are particularly at risk. People who are infected with *Plasmodium* parasites may show no sign of illness (asymptomatic malaria), or may develop symptoms such as fever, chills, weakness, and headache (symptomatic malaria). The severity of malaria infection varies from mild (uncomplicated) to life-threatening (severe). People with severe malaria may experience severe anaemia, convulsions, unconsciousness, and in some cases can die. Severe malaria is more likely to occur in people with low or no immunity to malaria (Gilles 2000). Children living in malaria-endemic areas have relatively less acquired immunity to malaria. In 2017, 61% of global cases of malaria were in children under five years of age, most of whom were residing in sub-Saharan Africa (WHO 2018).

Description of the intervention

Malaria control efforts have been aimed towards reduction of illness and death from *Plasmodium* infection. The World Health Organization (WHO) global malaria control strategy combines preventive interventions (for example, use of long-lasting insecticide-treated nets (LLINs), and indoor residual spraying) with early diagnosis and appropriate treatment of symptomatic people with artemisinin-based combination therapy (ACT) (WHO 2018). Intermittent preventive treatment (IPT) is one of the interventions recommended for malaria prevention in vulnerable and at-risk groups (infants, children, and pregnant women) (WHO 2004; WHO 2010; WHO 2012).

IPT is defined as "the administration of a full therapeutic course of an antimalarial or antimalarial combination to a selected target population at specified times without determining whether or not the subject is infected" (Greenwood 2010). IPT in infants (IPTi) is a full therapeutic course of antimalarial medicine delivered to infants through routine immunization services, regardless of whether the child is infected with malaria or not. The WHO recommends IPTi with sulfadoxine-pyrimethamine (SP) in areas with moderate-to-high malaria transmission in sub-Saharan Africa where the prevalence of the pfdhps-540E allele of the *P falciparum* parasite is less than 50% (WHO 2010; WHO 2011). Administration of IPTi is aimed at reducing the risk of clinical malaria, anaemia, and severe malaria in the first year of life. Treatment is given three times during the first year of life at approximately 10 weeks, 14 weeks, and nine months of age, which corresponds to the routine vaccination schedule of the Expanded Programme on Immunization (EPI) (WHO 2011).

IPTi was proposed as an alternative to prophylaxis because of concerns that the latter may impair the acquisition of natural immunity to malaria in infants, making them more vulnerable to severe malaria after prophylaxis is discontinued when they are older (Greenwood 2004; Otoo 1988; WHO 1993). There are also concerns that the widespread use of antimalarial drugs for prophylaxis in infants could increase the resistance of the *Plasmodium* parasites to these drugs (Alexander 2007; WHO 1990; WHO 1993). Further concerns about chemoprophylaxis include the feasibility and sustainability of the intervention. While the mechanism of IPTi may not be clear, available data does suggest the post-treatment prophylaxis (longer-acting drugs) is an important component in areas of high transmission where reinfection is likely. Studies that have tried IPTi with shorter-acting drugs have not achieved as good a preventive effect. It is unclear whether it is by the intermittent clearance of existing *Plasmodium* infections or the post-treatment prophylactic effect of long-acting drugs (White 2005). There is also the 'leaky vaccine' hypothesis that a partially effective drug combined with high LLIN coverage may lead to attenuated blood-stage infections, enabling immunity to develop without leading to clinical disease. This may increase subclinical infection and promote protection in infants, as has been demonstrated in one study (Pombo 2002). The duration of protection from IPTi is limited to periods when the drug has not been eliminated from the body, typically about 1 to 2 months after drug administration (Cairns 2010).

Since 2009, when the policy recommendations were made, only Chad has adopted IPTi as national policy (WHO 2015). However, as of 2015 no countries have reported implementation of an IPTi policy (WHO 2018).This may be due to concerns about dosage and administration to young infants, a limited understanding of the baseline prevalence of molecular markers of anti-folate resistance. The research capacity to obtain and monitor relevant resistance data is often inadequate in endemic countries of sub-Saharan Africa. The complexity of the IPTi policy may have also affected the uptake. Moreover, an increase in *P falciparum* resistance to SP in sub-Saharan Africa may have also confounded the cost-effectiveness assessments upon which the policy recommendations for IPTi were based. This has raised concerns for policy makers at country level on the effectiveness of implementing IPTi on a public health scale. However, alternative drugs are being investigated for IPTi. Some of the alternatives studied include single-drug regimens (such as amodiaquine, mefloquine) and artemisinin-based combination drug regimens (such as amodiaquine-artesunate, SP-artesunate, SP-amodiaquine).

How the intervention might work

The effects of IPTi may be mediated through chemoprophylaxis (White 2005). The terminal elimination half-lives of sulfadoxine and pyrimethamine in infants has been shown to be about nine days and 16 days respectively (Salman 2011). The effects wane over time, hence the need for intermittent repeat doses. SP may be useful for IPTi because this drug combination is readily available, relatively affordable, and well-tolerated in both adults and children. Moreover, it is already recommended for IPT in pregnancy (WHO 2004). The long half-life of SP and alternative drugs used for IPTi produces a prolonged prophylactic effect. In addition, SP can be administered as a single dose, which is easier to directly observe at health facilities. Also, IPTi is associated with more limited drug exposure than in chemoprophylaxis. Thus the effect of IPTi on the spread of resistance and impairment

of immunity development might also be lower. Furthermore, logistical challenges of intervention delivery are almost eliminated by administering IPTi at time points that fit the schedule of routine vaccinations through the WHO EPI.

Why it is important to do this review

Earlier versions of this systematic review addressed the broader question of the effectiveness of chemoprevention (including prophylaxis and IPT) against malaria in preschool children living in malaria-endemic communities (Meremikwu 2002; Meremikwu 2005; Meremikwu 2008). A previous Cochrane Review documented the evidence for IPT in children (IPTc) (Meremikwu 2012). Although there is a meta-analysis on IPTi (Aponte 2009), there have been additional studies since its publication. Moreover, these additional studies have evaluated the protective efficacy of alternative drugs for use as IPTi. This Cochrane Review summarizes the updated evidence to inform public health practice and policy.

OBJECTIVES

To evaluate the effects of intermittent preventive treatment (IPT) with antimalarial drugs to prevent malaria in infants living in malaria-endemic areas.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs). The randomization unit could be the individual participant or a cluster, such as a household.

Types of participants

Children aged below 12 months living in an area where malaria was endemic with moderate-to-high perennial transmission. Children with unknown infection status (that is, it is unknown whether each child was infected or uninfected) or known infection status were eligible. We excluded trials that, at enrolment, included children aged ≥ 12 months and only anaemic participants.

Types of interventions

Intervention

- IPTi

Control

- Placebo or no treatment

We included trials that allocated an additional intervention (such as insecticide-treated nets or iron supplementation) to both the intervention and control group provided the additional intervention was the same for each group. We included trials that compared one drug with another under the IPTi platform.

Types of outcome measures

Primary outcomes

- Clinical malaria (fever plus asexual parasitaemia)

Secondary outcomes

- Severe malaria (as defined by WHO 2000)
- All-cause mortality
- Hospital admission for any reason
- Parasitaemia
- Anaemia (< 8 g/dL)
- Change in haemoglobin (or haematocrit)

Adverse events

- Serious adverse effects
- Other adverse events, that occur within the follow-up time of the trial

Search methods for identification of studies

Electronic searches

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

Databases

We searched the following databases using the search terms and strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library, Issue 12, 2018; MEDLINE (PubMed; 1966 to 3 December 2018); Embase (OVID; 1980 to 3 December 2018); and LILACS (Bireme; 1982 to 3 December 2018). We also searched the metaRegister of Controlled Trials (mRCT; www.isrctn.com/) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) portal (www.who.int/ictrp/en/) using 'malaria', 'infant*', 'intermittent', 'prevent*' and 'IPT' as search terms.

Searching other resources

Reference lists

We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

Review author EE and researcher Obiamaka Okafo (OO) independently screened the results of the literature search for potentially relevant trials by title and abstract. We coded articles as either 'retrieve' if articles potentially fulfilled the inclusion criteria or if it was unclear whether the article fulfilled the inclusion criteria or not; or 'do not retrieve' for articles that did not fulfil the inclusion criteria. We obtained the full-text reports of potentially relevant trials. We independently applied the inclusion criteria to the full reports using an eligibility form and scrutinized publications to ensure we included each trial in the review only once. Any disagreements were resolved through discussion with either MM or CO, and when necessary by consulting a member of the Cochrane Infectious Diseases Group (CIDG) editorial team. We listed the excluded studies and the reasons for their exclusion in the 'Characteristics of excluded studies' table. We illustrated the study selection process in a PRISMA study flow diagram.

Data extraction and management

Two review authors (CO and EE) independently extracted data using a specifically developed piloted data extraction form. We resolved disagreements through discussion among all review

authors. We contacted the corresponding publication author in the case of unclear information or missing data.

For each outcome, we aimed to extract the number of participants randomized and the number analysed in each treatment group. 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 arithmetic means and standard deviations for each treatment group, together with the numbers assessed in each group. For outcomes reported as count data, we extracted the total number of episodes as well as the total time at risk.

For trials that randomized clusters, we recorded the number of clusters in the trial, the average size of clusters, and the randomization unit (for example, household or institution). We attempted to document details about adjustment for clustering or other covariates. When reported, we recorded the estimates of the intracluster correlation (ICC) coefficient for each outcome. If the trials' analyses adjusted for clustering, we extracted the treatment effect and a corresponding measure of variability.

Assessment of risk of bias in included studies

Two review authors (EE and CO) independently assessed the risk of bias in each included trial using a 'Risk of bias' form. We resolved any disagreements by discussion between the review authors.

For trials that randomized individuals, we assessed six components: generation of the randomization sequence, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases (such as early termination of the trial). For trials that randomized clusters, we assessed additional components, namely, recruitment bias, baseline imbalances, loss of clusters, incorrect analysis, and comparability with trials that randomized individuals.

We made judgements of either 'yes', 'no', or 'unclear' to indicate a low, high, or unclear risk of bias. We presented the results of the assessment in a 'Risk of bias' graph, 'Risk of bias' tables, and a 'Risk of bias' summary.

Measures of treatment effect

We used the risk ratio (RR) to summarize 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 (CIs). For time-to-event data presented as Kaplan-Meier curves in trial reports, we calculated Peto hazard ratios. We extracted protective efficacy values and their 95% CIs and when an included trial did not report this data, we calculated these values from the RR or rate ratio with its 95% CI.

Unit of analysis issues

If the original trial analyses did not adjust for clustering, we adjusted the results for clustering by multiplying the standard errors of the treatment effect by the square root of the design effect. We calculated the design effect as 1+(m-1)*ICC where 'm' is the average cluster size and ICC is the ICC coefficient.

Dealing with missing data

We aimed to perform the analysis according to the intention-to-treat (ITT) principle (all randomized participants analysed in the groups to which they were originally assigned). However, when there was loss to follow-up, we employed a complete-case analysis, such that, we excluded from the analysis participants for whom no outcome was reported. This analysis assumed that the participants for whom an outcome was available were representative of the originally randomized participants.

Assessment of heterogeneity

We assessed statistical heterogeneity between subgroups by visually inspecting the forest plots for overlapping CIs, applying the Chi^2 test (where a P value < 0.10 is considered statistically significant), and by using the I^2 statistic (with values > 40% representing moderate heterogeneity, > 60% substantial heterogeneity, and > 80% considerable heterogeneity).

Assessment of reporting biases

We planned to construct funnel plots to look for evidence of publication bias. However, the number of trials in each meta-analysis were insufficient to make this informative.

Data synthesis

We analysed the data using Review Manager 5 (RevMan 5) (Review Manager 2014). In the first instance, we applied a fixed-effect meta-analysis. However, if we detected moderate heterogeneity but still considered it appropriate to combine the trials, we used a random-effects approach. Where heterogeneity was very high such that meta-analysis was inappropriate, we displayed the results in forest plots or tables but did not combine the results.

We stratified the analyses by when the outcome was measured (during intervention and post-intervention follow-up). We placed cluster-RCTs that adjusted effects for clustering in the same forest plots as trials that randomized individual participants. Also, we included footnotes in forest plots to identify cluster-RCTs. We tabulated the results from non-adjusted cluster-RCTs. We used generic inverse variance meta-analysis.

Certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach (Guyatt 2008). We presented the main results of the review alongside the certainty of the evidence in the 'Summary of findings' tables. We appraised the certainty of evidence for each outcome against five criteria: risk of bias (an appraisal of the overall risk of bias for trials contributing to the outcome), consistency (an evaluation of explained and unexplained heterogeneity), directness (an appraisal of how directly the included trials address the review question), precision (an assessment of the statistical precision of the result), and publication bias (an assessment of the risk of publication bias). Where we identified deficiencies that were sufficient to decrease our confidence in the estimates of effect, we downgraded the certainty of evidence for RCTs from 'high' to either 'moderate', 'low', or 'very low' and explained our reasons for doing so. We used the GRADEpro GDT software, GRADEpro 2014, to import data from RevMan 5 (Review Manager 2014). We have presented 'Summary of findings' tables only for SP and the three drug combinations that are feasible for use as IPTi, given WHO recommendations regarding the use of monotherapy.

Subgroup analysis and investigation of heterogeneity

It was not feasible to undertake subgroup analyses by the length of follow-up as data were insufficient. There was still insufficient information available on the levels of parasite resistance to SP in the included trials.

Sensitivity analysis

We conducted a sensitivity analysis to investigate the robustness of the results to the risk of bias components by including only trials that concealed the allocation adequately and had low incomplete outcome data (less than 10%). We also excluded cluster-randomized trials that were at high or unclear risk of bias for one of the additional cluster-specific risk of bias components.

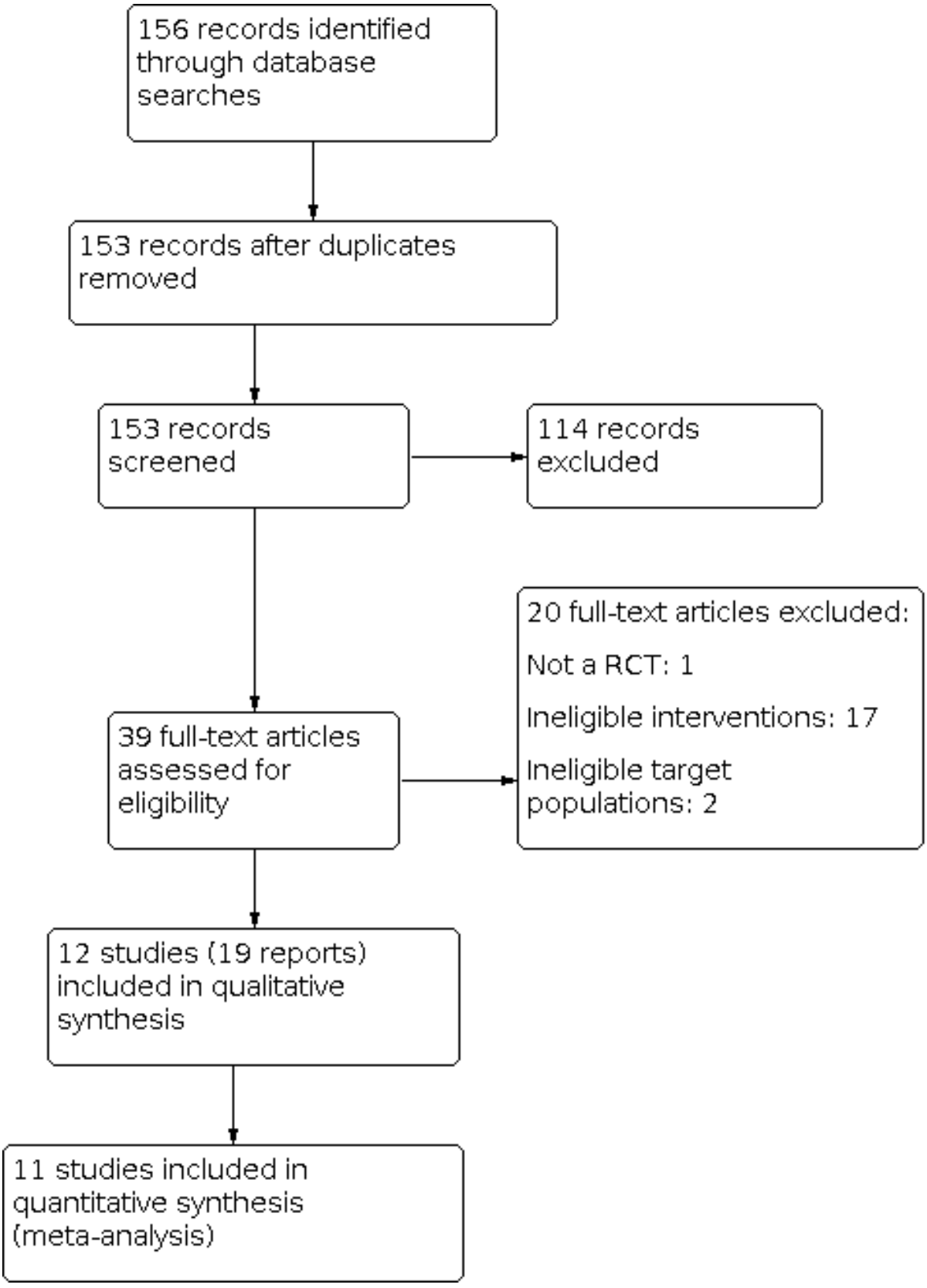
RESULTS

Description of studies

Results of the search

We conducted the literature search up to 3 December 2018. Searches of various databases yielded 153 records to be screened, after we deleted duplicates. Of these, we found that 114 were irrelevant to the review after screening by title/abstract. We obtained full texts of the remaining 39 studies. Of these, 12 studies (three cluster-RCTs and nine RCTs) described in 19 articles met our inclusion criteria (Figure 1). We reported reasons for excluding studies in the 'Characteristics of excluded studies' table.

Figure 1. Study flow diagram



Included studies

See the 'Characteristics of included studies' section for details of the included trials. We included 12 RCTs that enrolled 17,530 infants. Three of the included RCTs had a cluster-randomized trial design (Armstrong Schellenberg 2010 TZA; Chandramohan 2005 GHA; Dicko 2012 MLI), and the remaining nine RCTs randomized individuals.

Location

The included trials were all conducted in Africa where *P falciparum* is predominant: four in Tanzania, three in Ghana, and one trial each in Gabon, Kenya, Mali, Mozambique, and Uganda. We have attached a three letter country code to each trial ID to aid forest plot interpretation.

Trial design

Nine trials randomized individuals, while three trials randomized clusters (household units of families living in a compound or villages in subdistricts). All three cluster-RCTs adjusted for design effect and reported the average cluster size. Armstrong Schellenberg 2010 TZA adjusted for clustering in the analysis but did not provide the intra-cluster correlation coefficient (ICC) value. Chandramohan 2005 GHA adjusted for design effect using a random-effects model (REM) to allow for intra-cluster correlation and other covariates (sex and urban-rural residence). We obtained ICC values for Chandramohan 2005 GHA as follows: clinical malaria (ICC = 0.075), all-cause hospital admissions (ICC = 0.000), haematocrit less than 24% (that is, severe anaemia; ICC = 0.006), and all-cause death (ICC = 0.000).

Interventions

All included trials were conducted between 1999 and 2013. Nine trials compared IPT to placebo, while the remaining three trials had no IPT as the control arm (Armstrong Schellenberg 2010 TZA; Bigira 2014 UGA; Dicko 2012 MLI). Ten trials co-administered IPT with routine EPI vaccinations (Armstrong Schellenberg 2010 TZA; Chandramohan 2005 GHA; Dicko 2012 MLI; Gosling 2009 TZA; Kobbe 2007 GHA; Macete 2006 MOZ; Massaga 2003 TZA; Mockenhaupt 2007 GHA; Odhiambo 2010 KEN; Schellenberg 2001 TZA). Two trials administered iron to all enrolled infants (Chandramohan 2005 GHA; Schellenberg 2001 TZA). Nine trials administered IPT with sulfadoxine-pyrimethamine (SP) (Armstrong Schellenberg 2010 TZA; Chandramohan 2005 GHA; Dicko 2012 MLI; Gosling 2009 TZA; Grobusch 2007 GAB; Kobbe 2007 GHA; Macete 2006 MOZ; Mockenhaupt 2007 GHA; Schellenberg 2001 TZA). Alternative drug combinations to SP evaluated in the included trials were amodiaquine (AQ) (Massaga 2003 TZA), chlorproguanil-dapsone (CD) (Gosling 2009 TZA; Odhiambo 2010 KEN), dihydroartemisinin-piperaquine (DHAP) (Bigira 2014 UGA), and mefloquine (MQ) (Gosling 2009 TZA). One trial evaluated drug combinations that included SP; SP+ artesunate (AS) (Odhiambo 2010 KEN). Another drug combination evaluated was AQ+AS (Odhiambo 2010 KEN).

The length of follow-up was until 24 months of age in eight trials (Bigira 2014 UGA; Chandramohan 2005 GHA; Gosling 2009 TZA; Grobusch 2007 GAB; Kobbe 2007 GHA; Mockenhaupt 2007 GHA; Odhiambo 2010 KEN; Schellenberg 2001 TZA). In the remaining four trials infants were followed-up after the discontinuation of the intervention up to a maximum of 18 months of age (Armstrong Schellenberg 2010 TZA; Dicko 2012 MLI; Macete 2006 MOZ; Massaga 2003 TZA).

Outcome measures

Eleven trials reported on the outcome all-cause mortality death (Bigira 2014 UGA; Chandramohan 2005 GHA; Dicko 2012 MLI; Gosling 2009 TZA; Grobusch 2007 GAB; Kobbe 2007 GHA; Macete 2006 MOZ; Massaga 2003 TZA; Mockenhaupt 2007 GHA; Odhiambo 2010 KEN; Schellenberg 2001 TZA). Dicko 2012 MLI and Armstrong Schellenberg 2010 TZA were the only trials that did not report anaemia and clinical malaria respectively. Only two trials reported severe malaria (Bigira 2014 UGA; Macete 2006 MOZ). Ten trials reported hospital admissions during the intervention period (Armstrong Schellenberg 2010 TZA; Bigira 2014 UGA; Chandramohan 2005 GHA; Gosling 2009 TZA; Kobbe 2007 GHA; Macete 2006 MOZ; Massaga 2003 TZA; Mockenhaupt 2007 GHA; Odhiambo 2010 KEN; Schellenberg 2001 TZA). Three trials reported changes in haemoglobin (Armstrong Schellenberg 2010 TZA; Chandramohan 2005 GHA; Grobusch 2007 GAB). Four trials reported asymptomatic parasitaemia (Armstrong Schellenberg 2010 TZA; Bigira 2014 UGA; Macete 2006 MOZ; Mockenhaupt 2007 GHA). Nine trials reported on adverse events (Armstrong Schellenberg 2010 TZA; Bigira 2014 UGA; Chandramohan 2005 GHA; Grobusch 2007 GAB; Kobbe 2007 GHA; Macete 2006 MOZ; Massaga 2003 TZA; Odhiambo 2010 KEN; Schellenberg 2001 TZA).

We have listed the outcome definitions that the included trials used in Table 1. Other outcomes reported by trials that we did not include in this Cochrane Review were all-cause hospital attendance (Armstrong Schellenberg 2010 TZA; Schellenberg 2001 TZA); serological responses to EPI vaccines (Macete 2006 MOZ; Schellenberg 2001 TZA); and aspartate transaminase (AST), creatinine, and white blood cell counts (Grobusch 2007 GAB).

Excluded studies

The 'Characteristics of excluded studies' summarizes the reasons why we excluded studies. We excluded the 20 studies (20 reported papers) for the following reasons:

- the intervention was intermittent preventive treatment in children (IPTc) (13 studies: Bojang 2010; Cissé 2006; Dicko 2008; Dicko 2011a; Dicko 2011b; Glinz 2015; Konaté 2011a; Konaté 2011b; Kweku 2008; Liljander 2010; Sesay 2011; Tagbor 2011; Tine 2011);
- the intervention studied was chemoprophylaxis and not IPTi (4 studies: Greenwood 1988; Lemnge 1997; Menendez 1997; Wolde 1994);
- the study was conducted outside sub-Saharan Africa where IPTi is recommended (Senn 2012);
- IPT was given to participants post-discharge following recovery from malarial anaemia (Phiri 2012);
- the study was a meta-analysis (Aponte 2009).

Risk of bias in included studies

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

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included trial

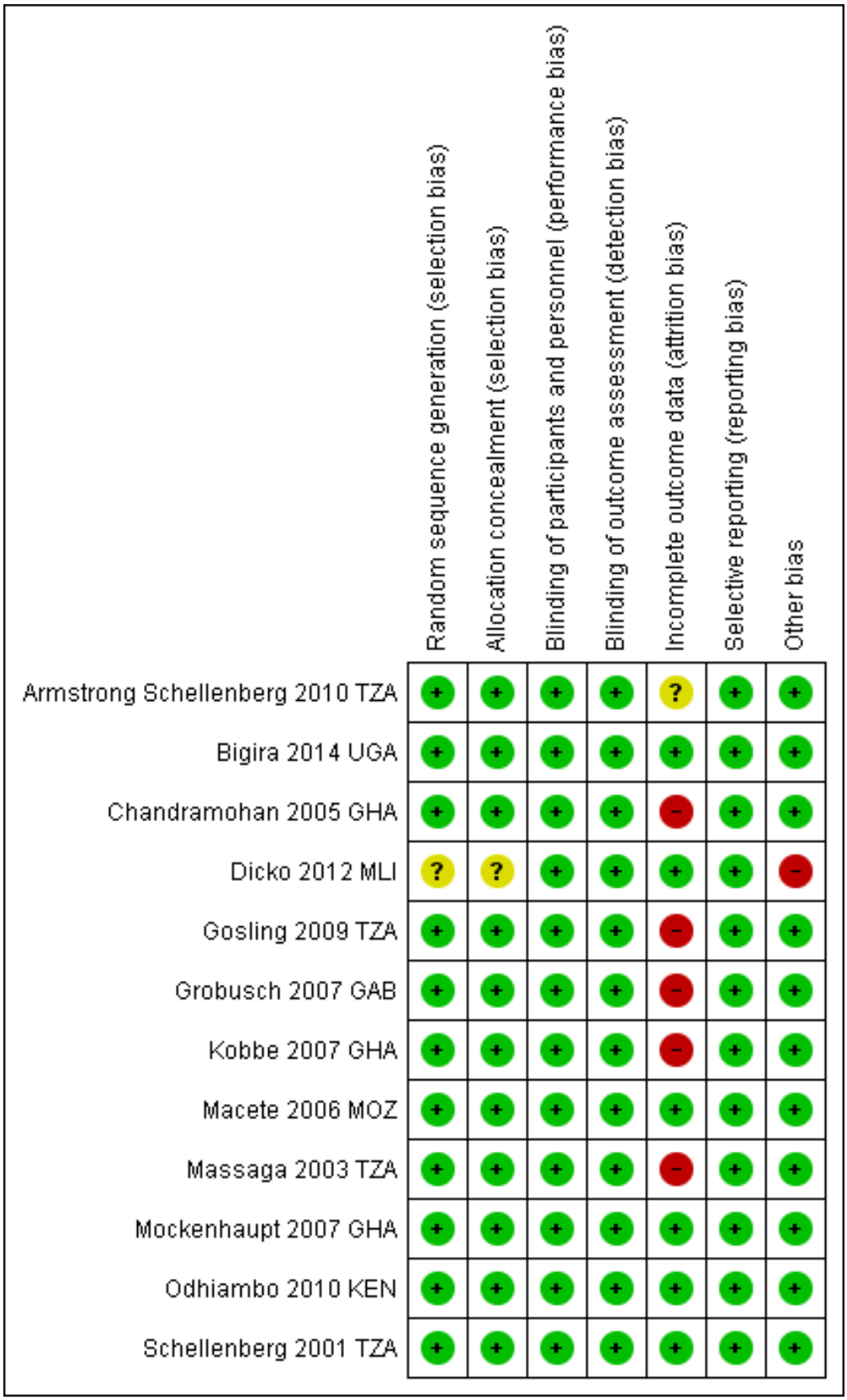
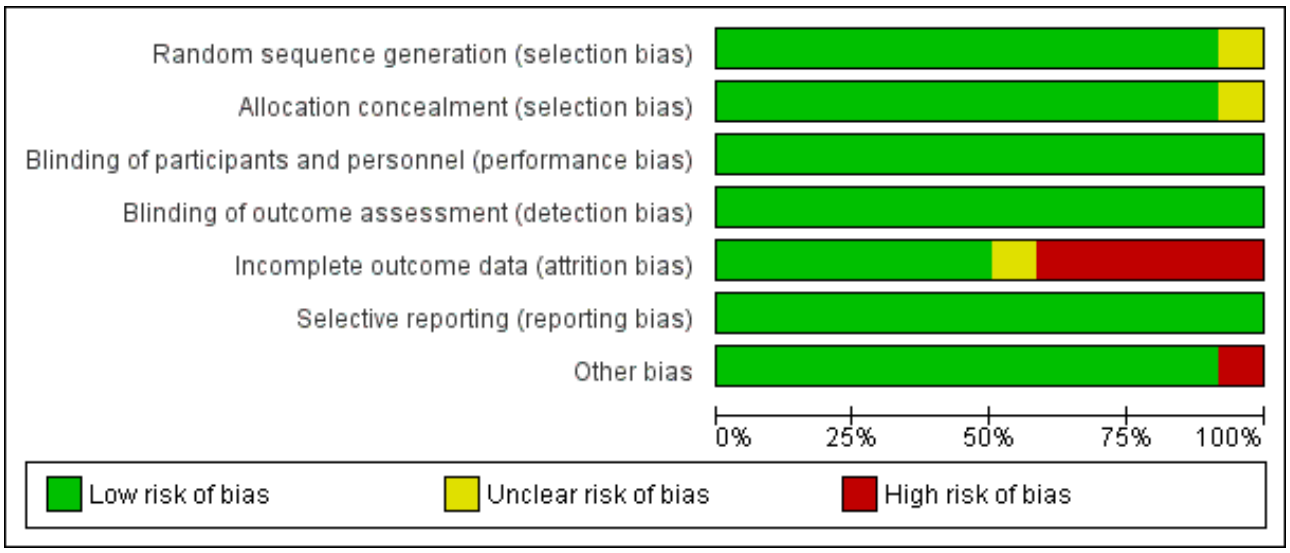


Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included trials



Allocation

Eleven trials were at low risk of bias regarding the generation of allocation sequence. One trial, Dicko 2012 MLI, was at unclear risk of bias because the trial authors did not provide enough information to permit us to make a judgement. Eleven trials were at low risk of bias regarding allocation concealment and the remaining trial, Dicko 2012 MLI, was at unclear risk of bias as the trial authors provided insufficient information to make a judgement.

Blinding

In all included trials, investigators and participants were unaware of treatment allocation. This was achieved by the use of clusters, the use of personnel not involved in patient care to perform treatment allocation, and the use of centrally coded drugs and placebos.

Incomplete outcome data

Six trials reported outcome data for at least 90% of randomized participants and were at low risk of bias regarding incomplete outcome data (Bigira 2014 UGA; Dicko 2012 MLI; Macete 2006 MOZ; Mockenhaupt 2007 GHA; Odhiambo 2010 KEN; Schellenberg 2001 TZA). Another five trials reported over 10% attrition in either one or both trial arms (Chandramohan 2005 GHA; Gosling 2009 TZA; Grobusch 2007 GAB; Kobbe 2007 GHA; Massaga 2003 TZA). One trial, Armstrong Schellenberg 2010 TZA, was at unclear risk of bias because different participants were surveyed at baseline and follow-up.

Selective reporting

We did not detect any evidence of selective outcome reporting in any of the included trials.

Other potential sources of bias

We did not identify any other sources of bias for the individually RCTs. However, for the cluster-RCTs, we considered recruitment bias, baseline imbalances, incorrect analyses, their comparability with individually RCTs, and the loss of clusters. We considered Armstrong Schellenberg 2010 TZA and Chandramohan 2005 GHA to be at low risk of bias for all of these additional sources of bias. However, we rated Dicko 2012 MLI as at high risk because of the high risk of recruitment bias, baseline imbalances, and incorrect analyses. Also, the trial authors did not provide any information on the loss of clusters.

Effects of interventions

See: **Summary of findings 1** '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

IPTi versus placebo or no IPTi

Clinical malaria

Sulfadoxine-pyrimethamine

IPTi with SP at that time probably reduced the risk of clinical malaria (rate ratio 0.78, 95% CI 0.69 to 0.88; 8 trials, 8774 participants; Analysis 1.1). There was substantial statistical heterogeneity as indicated by an I^2 statistic value of 64%. Sensitivity analysis, which excluded cluster-randomized trials and studies at high risk of selection bias, did not considerably change the summary effect estimate (rate ratio 0.71, 95% CI 0.55 to 0.92; 4 trials, 3551 participants; Analysis 2.1).

Artemisinin-combination therapy

IPTi with AQ-AS probably reduces the risk of clinical malaria (rate ratio 0.75, 95% CI 0.61 to 0.94; 1 trial, 547 participants; Analysis 1.1). IPTi with DHAP probably reduces the risk of clinical malaria (rate ratio 0.42, 95% CI 0.33 to 0.54; 1 trial, 147 participants; Analysis 1.1). We downgraded the certainty of the evidence by one level due to imprecision (very few infants contributed to the analysis).

IPTi with SP-AS reduces the risk of clinical malaria (rate ratio 0.78, 95% CI 0.62 to 0.97; 1 trial, 676 participants; Analysis 1.1).

Monotherapy

IPTi with amodiaquine may have reduced the risk of clinical malaria episodes at the time (rate ratio 0.35, 95% CI 0.22 to 0.56; 1 trial, 146 participants; Analysis 1.1).

IPTi with mefloquine resulted in a large reduction in the risk of clinical malaria (rate ratio 0.62, 95% CI 0.44 to 0.88; 1 trial, 480 participants; Analysis 1.1).

Severe malaria

Sulfadoxine-pyrimethamine

IPTi with SP may have made little or no difference on the risk of severe malaria (rate ratio 0.92, 95% CI 0.47 to 1.81; 2 trials, 1347 participants; Analysis 1.2). Another trial also found no difference in the risk of severe malaria (Macete 2006 MOZ; see Table 2). However, overall the sample size was too small to detect or exclude clinically important differences.

Artemisinin-combination therapy

IPTi with DHAP probably has little or no effect on the risk of severe malaria (rate ratio 1.29, 95% CI 0.28 to 5.98; 1 trial, 147 participants; Analysis 1.2). We downgraded the certainty of evidence by one level due to imprecision (very few infants contributed to the analysis). No studies that evaluated IPTI with SP-AS or AQ-AS reported on this outcome.

Monotherapy

No studies that evaluated IPTI with AQ or MQ reported on this outcome.

All-cause mortality

Sulfadoxine-pyrimethamine

IPTi with SP probably made little or no difference to the risk of all-cause mortality (risk ratio (RR) 0.93, 0.74 to 1.15; 9 trials, 14,588 participants; Analysis 1.3). Sensitivity analysis did not considerably change the summary effect estimate (RR 0.91, 95% CI 0.60 to 1.37; 4 trials, 3551 participants; Analysis 2.3).

Artemisinin-combination therapy

IPTi with AQ-AS probably does not reduce the risk of all-cause mortality (RR 1.21, 95% CI 0.58 to 2.55; 1 trial, 684 participants; Analysis 1.3). We downgraded the certainty of the evidence by one level due to imprecision (the CI included potential for important harm and benefit).

IPTi with DHAP may not reduce the risk of all-cause mortality (RR 0.17, 95% CI 0.01 to 4.06; 1 trial, 147 participants; Analysis 1.3). We downgraded the certainty of evidence by two levels due to imprecision (very few infants contributed to the analysis and the CI included potential for important harm and benefit).

IPTi with SP-AS probably has little or no effect on all-cause mortality (risk ratio 0.83, 95% CI 0.36 to 1.89; 1 trial, 676 participants; Analysis 1.3). We downgraded the certainty of the evidence by one level due to imprecision (the CI included potential for important harm and benefit).

Monotherapy

The evidence suggests IPTi with mefloquine may have resulted in little to no difference in all-cause mortality (risk ratio 0.33, 95% CI 0.06 to 1.97; 1 trial, 480 participants; Analysis 1.3).

However, IPTi with amodiaquine may not have reduced the risk of all-cause mortality (risk ratio 1.30, 95% CI 0.30 to 5.59; 1 trial, 146 participants; Analysis 1.3).

Hospital admission for any reason

Sulfadoxine-pyrimethamine

IPTi probably reduced the risk of hospital admission for any reason (rate ratio 0.85, 95% CI 0.78 to 0.93; 7 trials, 7486 participants; Analysis 1.4). Moderate levels of statistical heterogeneity were observed (I^2 statistic = 53%). Sensitivity analysis did not significantly change the summary effect estimate (rate ratio 0.78, 95% CI 0.68 to 0.88; 4 trials, 3551 participants; Analysis 2.4).

Artemisinin-combination therapy

IPTi with AQ-AS probably does not reduce the risk of hospital admission for any reason (rate ratio 0.98, 95% CI 0.76 to 1.27; 1 trial, 684 participants; Analysis 1.4) .We downgraded the certainty of the evidence by one level due to imprecision (the CI included potential for important harm and benefit).

IPTi with DHAP may not reduce the risk of hospital admission for any reason (rate ratio 1.58, 95% CI 0.46 to 5.42; 1 trial, 147 participants; Analysis 1.4). We downgraded the certainty of evidence by two levels due to imprecision (very few infants contributed to the analysis and the CI included potential for important harm and benefit).

IPTi with SP-AS probably has little or no effect on hospital admission for any reason (rate ratio 0.92, 95% CI 0.71 to 1.20; 1 trial, 676 participants; Analysis 1.4). We downgraded the certainty of the evidence by one level due to imprecision (the CI included potential for important harm and benefit).

Monotherapy

IPTi with amodiaquine may have reduced the risk of hospital admission for any reason (rate ratio 0.40, 95% CI 0.21 to 0.77; 1 trial, 146 participants; Analysis 1.4).

IPTi with mefloquine may not have reduced the risk of hospital admission for any reason (rate ratio 0.98, 95% CI 0.73 to 1.31; 1 trial, 480 participants; Analysis 1.4).

Parasitaemia

Sulfadoxine-pyrimethamine

IPTi with SP probably reduced the risk of asymptomatic parasitaemia among infants (rate ratio 0.66, 95% CI 0.56 to 0.79; 1 trial, 1200 participants; Analysis 1.5).

Artemisinin-combination therapy

One study evaluated IPTi with DHAP but did not contribute data to the meta-analysis. This study showed that IPTi with DHAP probably reduces the risk of parasitaemia (prevalence of 3% compared to 11% in the control group P < 0.001; Table 2). We downgraded the certainty of evidence by one level due to imprecision (very few infants contributed to the analysis).

No studies that evaluated IPTi with AQ-AS or SP-AS reported on this outcome.

Monotherapy

No studies that evaluated IPTi with AQ or MQ reported this outcome.

Anaemia

Sulfadoxine-pyrimethamine

IPTi with SP probably reduced the risk of anaemia in infants (rate ratio 0.82, 95% CI 0.68 to 0.98; 6 trials, 7438 participants; Analysis 1.6). Sensitivity analysis did not considerably change the summary effect estimate (rate ratio 0.77, 95% CI 0.62 to 0.95; 3 trials, 3404 participants; Analysis 2.2). One trial, Armstrong Schellenberg 2010 TZA, reported mild (Hb < 11 g/dL) and severe (Hb < 8 g/dL) anaemia. The trial authors reported a significantly lower risk of mild anaemia in the IPTi group (277/346, 80%) compared to controls (241/274, 88%). The risk of severe anaemia was also lower in the IPTi group compared to controls (12% versus 16%) as shown in Table 2. There was no overall difference in mean haemoglobin levels between infants in the IPTi and control groups (mean difference −0.03, 95% CI −0.43 to 0.36; 3 trials, 4295 participants; Analysis 1.7).

Artemisinin-combination therapy

IPTi with AQ-AS probably does not reduce the risk of anaemia (rate ratio 0.77, 95% CI 0.53 to 1.12; 1 trial, 684 participants; Analysis 1.6). We downgraded the certainty of the evidence by one level due to imprecision (the CI included potential for important harm and benefit). Similarly, the risk of moderate to severe anaemia was lower in the IPTi with DHAP group compared to controls (3% versus 6%), as shown in Table 2. We downgraded the certainty of evidence by two levels due to imprecision (very few infants contributed to the analysis and the CI included potential for important harm and benefit).

We found that IPTi with SP-AS probably has little or no effect on anaemia (rate ratio 0.72, 95% CI 0.49 to 1.07; 1 trial, 676 participants; Analysis 1.6). We downgraded the certainty of the evidence by one level due to imprecision (the CI included potential for important harm and benefit).

Monotherapy

IPTi with amodiaquine may have reduced the risk of anaemia (rate ratio 0.29, 95% CI 0.13 to 0.63; 1 trial, 146 participants; Analysis 1.6).

IPTi with mefloquine may not have reduced the risk of anaemia (rate ratio 1.06, 95% CI 0.78 to 1.44; 1 trial, 480 participants; Analysis 1.6).

Change in haemoglobin (or haematocrit)

Sulfadoxine-pyrimethamine

There was no overall difference in mean haemoglobin levels between infants in the IPTi and control groups (mean difference −0.03, 95% CI −0.43 to 0.36; 3 trials, 4295 participants; Analysis 1.7). No other studies were found that reported this outcome.

Post-intervention follow-up effects

We evaluated post-intervention follow-up effects of IPTi to determine if the effects were sustained beyond the intervention period. We found no evidence of an effect of IPTi on the risk of clinical malaria (Analysis 3.1), risk of death from any cause (Analysis 3.2), in the period after the discontinuation of the intervention. Similarly, IPTi had no effect on the risk of hospital admission (Analysis 3.3) and the risk of anaemia (Analysis 3.4) in the period after the discontinuation of the intervention. This lack of a sustained effect of IPTi in the period after the discontinuation of the intervention was consistent across all medicines.

Adverse events

Adverse events reported by trial authors were Stevens-Johnson syndrome, fever, loss of appetite, weakness, skin reactions, gastrointestinal, and respiratory events. One trial, Bigira 2014 UGA, reported elevated enzyme levels and raised levels of platelets and white blood cells. These adverse events were associated with SP and DHAP. The adverse events reported are shown in Analysis 4.1, Analysis 4.2, and Table 3.

DISCUSSION

See 'Summary of findings' tables 1 to 4 (Summary of findings 1; Summary of findings 2, Summary of findings 3 and Summary of findings 4). We have presented results for the review outcomes under three headings: sulfadoxine-pyrimethamine (SP), artemisinin-combination therapy (ACT), and monotherapy.

Summary of main results

We included 12 trials (19,098 participants) that were conducted in Africa.

IPTi with sulfadoxine-pyrimethamine (SP) versus placebo or no IPTi

These trials suggest that at the time, IPTi with SP probably reduced the risk of clinical malaria episodes, hospital admissions, anaemia, and the risk of asymptomatic parasitaemia (moderate-certainty evidence). IPTi with SP probably made little or no difference to the risk of all-cause mortality (moderate-certainty evidence). Also IPTi with SP may have made little or no difference to the risk of severe malaria (low-certainty evidence).

IPTi with artemisinin combination treatments (ACTs) versus placebo or no IPTi

IPTi with amodiaquine plus artesunate probably reduces the risk of clinical malaria (moderate-certainty evidence). However, IPTi with amodiaquine plus artesunate probably does not reduce the risk of all-cause mortality, hospital admission for any reason, and anaemia (moderate-certainty evidence).

IPTi with dihydroartemisinin-piperaquine (DHAP) probably reduces the risk of clinical malaria, anaemia, and parasitaemia (moderate-certainty evidence). However, IPTi with DHAP probably makes little or no difference to the risk of severe malaria (moderate-certainty evidence) and may not reduce the risk of all-cause mortality and hospital admission for any reason (low-certainty evidence).

IPTi with SP plus artesunate reduces the risk of clinical malaria (high-certainty evidence). However, IPTi with SP plus artesunate probably does not reduce the risk of all-cause mortality, hospital admission for any reason, and anaemia (moderate-certainty evidence). Severe malaria and parasitaemia were not reported for IPTi with SP plus artesunate.

Post-intervention follow-up effects

IPTi did not have sustained effects in the post-intervention follow-up period. There was no apparent effect of IPTi on the risk of clinical malaria, all-cause mortality, hospital admission for any reason, and anaemia.

Overall completeness and applicability of evidence

This Cochrane Review included trials from several countries in East and West Africa where *P falciparum* malaria is predominant. IPTi is a policy recommendation for sub-Saharan Africa, and thus it would be reasonable to generalize these findings to all sub-Saharan countries of Africa with moderate-to-high malaria transmission. We included all published studies that evaluated IPTi in sub-Saharan Africa with the currently recommended drug SP and alternative medicines. We found no ongoing studies. However, most included trials were not adequately powered to detect clinical differences for several outcomes.

Levels of parasite drug resistance to SP across Africa have increased and have led most countries to abandon SP as a monotherapy in first-line treatment. This has raised questions regarding the efficacy of SP in the prevention of malaria given this increasing parasite resistance levels. However, SP has a proven safety profile, is low-cost. Moreover, studies in pregnant women have demonstrated that SP could still be effective even in the presence of high levels of SP resistance (Desai 2015; Likwela 2012).

IPTi with SP probably reduced the risk of clinical malaria episodes, anaemia, and hospital admissions for any reason in infants. The artemisinin-based combination medicines evaluated for use as IPTi appear to have demonstrated a better protective effect against clinical malaria. Albeit from a few trials that enrolled a small number of infants. However, although the review shows that IPTi with SP probably had a protective effect against clinical malaria, hospital admission, and anaemia; the finding is based on trials conducted over a 14-year period. A close look at the meta-analysis shows an attenuation of the effect of IPTi-SP over time with the most recent trials showing no effect.

Current levels of SP resistance in Africa, suggest that the period over which SP remains useful as the drug of choice for IPTi may be very limited. The current World Health Organization (WHO) recommendations on IPTi with SP recommend a ≥ 50% cut-off of dhps 540E gene mutation in the population as a benchmark for discouraging IPTi-SP use. From a programmatic perspective, this portends additional challenges and a constant need to monitor SP molecular markers of resistance. Some of the antimalarial drug combination options evaluated for use as IPTi include some artemisinin-combination therapy formulations currently included in national malaria treatment policies as first-line treatment for uncomplicated falciparum malaria.

The WHO recommendation advises against treating a patient who has malaria using the same drug they were using for prophylaxis. This is to minimize the risk of overdosing and also to prolong the usefulness of the drugs reserved for treatment of uncomplicated malaria. Now, most countries are on artemether-lumefantrine as first-line treatment of uncomplicated malaria. There are also many trials that have used DHAP for mass drug administration. Seasonal malaria chemoprevention (SMC) now uses artesunate-amodiaquine for children aged 3 to 59 months in the Sahel subregion. Thus, artemether-lumefantrine and DHAP may not be appropriate for use as IPTi in countries where their components are part of the first-line treatment of uncomplicated malaria. Also, in areas where malaria transmission is intense, it may be judicious to restrict ACTs for the treatment of cases, and not overexpose the drug for prophylactic purposes given the limited number of ACTs currently available. Also, Bigira 2014 UGA reported a low adherence to DHAP which may be related to the three-day course of treatment. There have also been reports of the emergence of piperaquine-resistant *P falciparum* infections in Southeast Asia (Amaratunga 2016). This calls to question the suitability of DHAP as a potential candidate for use as IPTi.

Certainty of the evidence

The included trials were generally well-conducted with adequate methods for random sequence generation, allocation concealment, and blinding. There was also no evidence of selective reporting in the included studies.

For IPTi with SP, we have moderate certainty that the intervention probably reduced the risk of clinical malaria, anaemia, and hospital admission for any reason. As described above, for anaemia we downgraded the certainty of the evidence for inconsistency due to statistically significant heterogeneity observed. For clinical malaria, asymptomatic parasitaemia, and hospital admission for any reason, we downgraded the certainty to moderate for 'imprecision', as the trials were underpowered to exclude the possibility of small but clinically important effects. For the finding of no effect on death from any cause, we downgraded the certainty to moderate as a result of inconsistency (wide variation in the size of the effect). For severe malaria, the finding of no effect was downgraded to low certainty for reasons also related to inconsistency and 'imprecision'.

Although it was not feasible to undertake a priori specified subgroup analyses, in post-hoc analyses we found that for clinical malaria (Analysis 1.1), excluding the earliest conducted trial (Schellenberg 2001 TZA) from the meta-analysis reduced the I^2 from 64% to 0%. This may be related to the time at which this trial was performed (August 1999 to April 2000). At this time in Tanazia, SP was not associated with any late treatment failures and was still first-line treatment for uncomplicated malaria. This can be contrasted with the other trials which were conducted afterwards when SP resistance was becoming more widespread across sub-Saharan Africa. Similarly, in post-hoc analyses excluding the most recently conducted trials (Bigira 2014 UGA; Gosling 2009 TZA) from the meta-analysis for hospital admission for any reason (Analysis 1.4), the I^2 reduced from 53% to 0%. These two studies are the only multi-arm randomized controlled trials in the meta-analysis.

Potential biases in the review process

We only included peer-reviewed and published clinical trials in this review. We also searched clinical trial registers and found no ongoing studies. It is very unlikely that we missed papers that were unpublished. We did not identify any potential biases in the review process. We included three cluster-RCTs. However, only two reported that they took account of the cluster randomization. Intraclass correlation coefficients (ICCs) were available for one trial (Chandramohan 2005 GHA), and the other trial reported adjusting for clustering in the sample size determination (Dicko 2012 MLI). However, we did not include the third cluster-RCT, which did not

provide details, in the meta-analyses (Armstrong Schellenberg 2010 TZA).

Agreements and disagreements with other studies or reviews

The conclusions of this Cochrane Review are consistent with a previously published meta-analysis of trials that evaluated IPT in African infants (Aponte 2009). This meta-analysis, like our review, found that IPTi had a substantial protective effect against clinical malaria, anaemia, and hospital admissions. Both reviews also did not find significant effects of IPTi on all-cause mortality.

The main difference between the previous meta-analysis (Aponte 2009), and this Cochrane Review is that we included clinical trials that evaluated other antimalarial drug combination options used as IPTi in this Cochrane Review. We found ACT options had substantial protective effect against clinical malaria.

AUTHORS' CONCLUSIONS

Implications for practice

On the basis of the more recently conducted trials that showed no effect of IPTi with SP, the prospects for the continued use of SP as IPTi are limited. This is likely due to widespread resistance to SP. Several antimalarial drug combination options have been evaluated and show high levels of effectiveness. IPTi with other antimalarial drug combination options may reduce the risk of clinical malaria and asymptomatic parasitaemia. However, as long as SP remains the drug of choice for IPTi, resistance monitoring should be integrated into relevant epidemiological studies and surveillance programmes within national malaria control programmes in sub-Saharan Africa.

Implications for research

The evidence for the benefit of IPTi with SP is mainly from trials conducted up to 10 years ago. Questions remain regarding the efficacy of SP in the prevention of malaria in the face of widespread parasite resistance especially with the emergence of mutant *P falciparum* isolates carrying sulfadoxine resistance associated A437G and K540E mutations in the *Pfdhps* gene across West Africa. Concerns also remain about the potential for IPTi to increase the carriage and spread of drug-resistant *P falciparum* parasites.

There are a few trials that evaluated other drug combination options for use as IPTi with some evidence of effectiveness (Bigira 2014 UGA; Gosling 2009 TZA; Massaga 2003 TZA; Odhiambo 2010 KEN). However, larger adequately powered trials are needed to provide more robust evidence for or against IPTi. Additional trials would most likely improve our confidence in the effect estimates for the effectiveness of IPTi. Also, as more trials evaluate alternative drug options for IPTi, subgroup analyses based on the type of antimalarial drug would become more robust and informative.

Future studies should investigate the efficacy, safety, operational feasibility, and cost-effectiveness of IPTi with multi-day antimalarial drugs in a programmatic setting.

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This Cochrane Review is dedicated to the memory of our wonderful colleague, Ms Obiamaka Okafo, who passed away in 2019.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Armstrong Schellenberg 2010 TZA

Study characteristics

Methods	**Trial design:** cluster-RCT
	Unit of randomization: administrative divisions
	Trial dates: April 2005 to August 2006

Armstrong Schellenberg 2010 TZA *(Continued)*

	Length of follow-up: 11 months of age Average cluster size = 30; intracluster correlation coefficient (ICC) not given
Participants	**Number of participants:** 600 infants from 24 health divisions **Inclusion criteria:** infants aged 2 to 11 months in the study area **Exclusion criteria**: none stated
Interventions	• Intervention: intermittent preventive treatment in infants (IPTi) with sulfadoxine-pyrimethamine (SP) delivered in intervention divisions through existing government health centres when children presented for their routine EPI vaccine doses of DPT2, DPT3, and measles (given at 2, 3, and 9 months of age, respectively • Control: children presenting at government health centres in comparison divisions received their routine EPI vaccine, but not IPTi
Outcomes	**Outcomes included in the review** • Anaemia • Adverse events **Outcomes not included in the review** • All-cause hospital attendance • Antigenaemia
Notes	**Location:** Lindi and Mtwara regions of southern Tanzania (192 clusters, 5760 households) **Malaria transmission:** perennial transmission **Funding:** Bill and Melinda Gates Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial authors used restricted randomization
Allocation concealment (selection bias)	Low risk	The trial authors performed randomization centrally with computer programmes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial used clusters, which minimized the risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial used clusters, which minimized the risk of performance bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial surveyed different participants at follow-up
Selective reporting (reporting bias)	Low risk	The published trial report included all expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias.

Armstrong Schellenberg 2010 TZA *(Continued)*

Recruitment bias: "We allocated the 24 divisions to the two study arms using restricted randomization to assure adequate balance in terms of baseline mortality, overall population size, and geographic area (and hence district health management team)."

Baseline imbalances: "We used a program in Stata version 8.0 (Stata Corp., College Station, TX) to test whether each of these possibilities satisfied balance criteria, including the following.

- A mortality ratio between the two study arms of 0.9 to 1.1
- A population ratio between the two study arms of 0.7 to 1.3; and 3) an even distribution of intervention communities over the five project districts"

Incorrect analysis: "Statistical testing of household survey data was based on the t test, using a summary measure of the data from each of the 12 intervention and 12 comparison divisions. This adjusts both for the survey design and for the study design, which was randomized by division"

Loss of clusters: all clusters included in final analysis

Bigira 2014 UGA

Study characteristics	
Methods	**Trial design:** RCT **Trial dates:** June 2010 to September 2013 **Length of follow-up:** 36 months of age
Participants	**Number of participants:** 393 infants at 6 months of age **Inclusion criteria:** (1) born to HIV uninfected mothers, (2) residency within 30 km of the study clinic with no intention of moving outside the study area, (3) agreement to come to the study clinic for any illness and to avoid medications outside the study protocol, (4) provision of informed consent by parent/guardian **Exclusion criteria:** (1) no history of allergy or sensitivity to any study drugs, (2) absence of active medical problem requiring inpatient evaluation or chronic medical conditions requiring frequent attention, and (3) absence of clinically significant electrocardiogram (ECG) abnormalities, family history of long QT syndrome, and current use of drugs that prolong the QTc interval.
Interventions	• Intervention: IPTi with SP (Kamsidar, Kampala Pharmaceutical Industries, Uganda), single dose each month from 6 months to 24 months of age • Intervention: IPTi with dihydroartemisinin-piperaquine (DHAP) (Duo-Cotexin, Beijing Holley-Cotec Pharmaceuticals, China), once daily for three consecutive days each month given monthly from 6 months to 24 months of age. Each drug was provided for administration at home according to weight-based guidelines. Participants did not receive routine immunization along with IPTi • Control: this group received no chemoprevention At the time of treatment allocation and during each visit to the study clinic, parents/guardians were given a 2-month supply of drugs and a diary with dates for dosing and check-offs to indicate administration.
Outcomes	**Outcomes included in the review** • Clinical malaria • All-cause mortality • Severe malaria

Bigira 2014 UGA *(Continued)*

- Hospital admissions
- Anaemia
- Change in haemoglobin
- Parasitaemia
- Adverse events

Outcomes not included in the review: none

Notes	**Location:** Tororo District, Uganda **Malaria transmission:** perennial transmission; entomological inoculation rate (EIR) = 562 infectious bites/person/year (2002) **Funding:** National Institutes of Health (HD059454). Holley-Cotec provided the DHAP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used permuted block randomization with computer to generate the randomization list
Allocation concealment (selection bias)	Low risk	"Study participants were randomised to their assigned treatment group at 6 mo of age using pre made, consecutively numbered, sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treatment allocation was performed by nurses not involved with patient care"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Treatment allocation was performed by nurses not involved with patient care"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial authors included 90% of infants in the analyses postintervention
Selective reporting (reporting bias)	Low risk	The published trial report included all expected outcomes
Other bias	Low risk	The trial appears to be free of other sources of bias

Chandramohan 2005 GHA

Study characteristics

Methods	**Trial design:** cluster-RCT **Unit of randomization:** households Average cluster size = 26, ICCs and additional data provided by trial authors **Trial dates:** September 2000 to June 2004 **Length of follow-up:** 24 months of age

Chandramohan 2005 GHA *(Continued)*

Participants	**Number of participants:** 96 clusters comprising a total of 2485 infants **Inclusion criteria:** infants living in selected clusters attending routine immunization clinics for second (DPT-2) and third doses of diphtheria-pertussis-tetanus (DPT) vaccine (DPT-3), measles vaccine (usually at age 9 months) and at age 12 months **Exclusion criteria:** allergy to SP
Interventions	• Intervention: SP (500 mg sulfadoxine and 25 mg pyrimethamine) first dose given at 2 months, second dose at 3 months, third at 9 months, and fourth dose at 12 months. 1/2 tablet at time of DPT-2 and DPT3 vaccines; 1 tablet at time of measles vaccine and at 12 months • Placebo: all participants concurrently received routine immunization with DPT and measles vaccines In addition, all infants received 1 month's supply of iron supplement (2.5 mL, 15 mg elemental iron, twice weekly for 4 weeks) when they received each vaccine.
Outcomes	**Outcomes included in the review** • Clinical malaria • Anaemia • Hospital admissions • All-cause mortality • Adverse events **Outcomes not included in the review:** none
Notes	**Location:** Kassena-Nankana District, Upper East Region, Ghana **Malaria transmission:** high/seasonal; EIR = 418 infective bites/person/year (almost all between June and November) **Funding:** Department for International Development (DFID) UK (grant No R7602).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial computer-generated random numbers
Allocation concealment (selection bias)	Low risk	The trial used identical and centrally coded drugs and placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study team and caretakers of study children were blinded to the drug codes."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The study team and caretakers of study children were blinded to the drug codes."
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow up in the per protocol population was 11.8%
Selective reporting (reporting bias)	Low risk	Published report includes most expected outcomes

Chandramohan 2005 GHA *(Continued)*

Other bias	Low risk	The trial appears to be free of other sources of bias Recruitment bias: "To increase blinding, we assigned clusters allocated to sulfadoxine-pyrimethamine or placebo to eight different drug codes (four sulfadoxine-pyrimethamine and four placebo)." Baseline imbalances: there was baseline comparability of clusters from the data presented Incorrect analysis: results adjusted for clustering Loss of clusters: no loss of clusters identified

Dicko 2012 MLI

Study characteristics	
Methods	**Trial design:** cluster-RCT **Unit of randomization:** sub districts Average cluster size = 13 villages; cluster effect = 1.5 **Trial dates:** December 2006 to March 2009 **Length of follow-up:** 18 months of age
Participants	**Number of participants:** 22 health sub districts comprising a total of 5882 infants **Inclusion criteria:** infants living in health sub district attending routine immunization clinics for second (DPT-2) and third doses of diphtheria-pertussis-tetanus (DPT) vaccine (DPT-3), at age 3 and 4 months respectively and measles vaccine at age 9 months **Exclusion criteria:** none stated
Interventions	• Intervention: SP (500 mg sulfadoxine and 25 mg pyrimethamine) first dose given at 3 months, second dose at 4 months, and third at 9 months of age. 1/2 tablet at time of DPT-2 and DPT3 vaccines and measles/yellow fever vaccine • Control: no implementation of IPTi in 11 health subdistricts used as control All participants concurrently received routine immunization with DPT, measles, and yellow fever vaccines
Outcomes	**Outcomes included in the review** • All-cause mortality **Outcomes not included in the review:** none
Notes	**Location:** Kolokani District, Mali **Malaria transmission:** hyperendemic; malaria prevalence in children under 5 years of age= 45 and > 70% (dry and rainy seasons respectively) **Funding:** Institut de Recherche Biomédicale des Armées IRBA - ex- IMTSSA & UMR6236-URMITE, Marseille, France. We only extracted and included data from Cohort 2 for this review
Risk of bias	

Dicko 2012 MLI *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The 22 health sub-districts were randomised in a 1:1 ratio with the intervention in 11 health areas and the other 11 serving as controls". The trial authors did not provide any further details
Allocation concealment (selection bias)	Unclear risk	The trial authors did not provide any details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Individuals who were not involved in the implementation of IPTi and who were not aware if a locality was in the intervention or non-intervention zone collected the data. Use of clusters minimizes the risk of performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Individuals who were not involved in the implementation of IPTi and who were not aware if a locality was in the intervention or non-intervention zone collected the data. Use of clusters also minimizes the risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses in intervention and control sites were less than 10%
Selective reporting (reporting bias)	Low risk	The trial authors reported the prespecified outcomes that were in the protocol
Other bias	High risk	The trial appears to have several other sources of bias Recruitment bias: individuals recruited after clusters were randomized Baseline imbalances: no report on baseline comparability of clusters Incorrect analysis: no adjustment for clustering in the analysis was reported Loss of clusters: no information was provided

Gosling 2009 TZA

Study characteristics	
Methods	**Trial design:** RCT **Trial dates:** December 2004 to May 2008 **Length of follow-up:** 24 months of age
Participants	**Number of participants:** 2419 infants **Inclusion criteria:** all infants aged 8 to 16 weeks who attended clinics for WHO's Extended Program on Immunization (EPI) at the ten study health facilities (five in each site) for DPT2 and polio vaccination were eligible for inclusion. **Exclusion criteria:** infants who had any of the following conditions: history of allergy to study drugs; history of convulsions; clinical features of severe malnutrition or chronic illness, including infants with signs of HIV/AIDS; plans to leave the study area before 12 months of age; weight less than 4.5 kg at enrolment; and no witnessed, written consent from the caretaker.

Gosling 2009 TZA *(Continued)*

Interventions	**Interventions:** IPTi with one of the following. • SP: 250 mg sulfadoxine plus 12.5 mg pyrimethamine (Fansidar, F Hoffmann-La Roche, Basel, Switzerland) • Chlorproguanil-dapsone: 15 mg chlorproguanil plus 18.75 mg dapsone (Lapdap, GlaxoSmithKline, London, UK) for 3 days • Mefloquine: 125 mg mefloquine (Lariam, F Hoff mann-La Roche, Basel, Switzerland) given with DPT and Polio 2 immunization at about 2 months of age; DPT and polio 3 at 3 months of age; and measles vaccines at 9 months of age The 1st and 2nd doses of IPTi were either: • SP: 250 mg sulfadoxine plus 12.5 mg pyrimethamine • CD: 15 mg chlorproguanil plus 18.75 mg dapsone for 3 days • MQ: 125 mg mefloquine The 3rd dose of IPTi at 9 months of age were either: • SP: 500 mg sulfadoxine plus 25 mg pyrimethamine • CD: 22.5 mg chlorproguanil plus 28.125 mg dapsone for 3 days • MQ: 250 mg mefloquine Placebo: identical placebos given at the same time points with iPTi All treatments at the health facility were observed and administered with routine immunizations. Field workers visited participants on days 2 and 3 to ensure doses were taken.
Outcomes	**Outcomes included in review** • Clinical malaria • All-cause mortality • Hospital admissions • Anaemia • Adverse events **Outcomes not included in the review:** none
Notes	**Location:** Korogwe and Same Districts, Tanzania **Malaria transmission:** moderate transmission site (Korogwe District, Tanga region) and a neighbouring low-transmission site (Same District, Kilimanjaro region). High SP resistance reported. EIR in neighbouring district (Muheza) was 148 infective bites per year (2000). **Funding:** IPTi Consortium and Gates Malaria Partnership (both supported by Bill & Melinda Gates Foundation) **Additional notes:** enrolment was prematurely suspended in the low-transmission site after interim analysis (low malaria incidence resulting in lower power) thus only data from moderate-transmission site is reported. Witnessed bed net coverage: 87% at enrolment Reported insecticide-treated net (ITN) coverage: 53% at enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used computer-generated numbers for sequence generation

Gosling 2009 TZA *(Continued)*

Allocation concealment (selection bias)	Low risk	The trial administered drugs to participants in a secluded cubicle
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both research team and child were masked to treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Both research team and child were masked to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	High risk	Percentage loss 15.3% (per protocol)
Selective reporting (reporting bias)	Low risk	The trial authors reported relevant outcomes
Other bias	Low risk	The trial appears to be free of other sources of bias

Grobusch 2007 GAB

Study characteristics	
Methods	**Trial design:** RCT **Trial dates:** December 2002 to February 2005 **Length of follow-up:** 30 months of age
Participants	**Number of participants:** 1189 infants **Inclusion criteria:** provision of parental written informed consent or witnessed oral consent in the case of illiteracy and permanent residentship in the study area. **Exclusion criteria:** known or suspected allergy to sulphonamides or pyrimethamine or signs and symptoms thereof and history of severe hepatic or renal dysfunction
Interventions	• Intervention: IPTi with SP (500 mg sulfadoxine and 25 mg pyrimethamine) given at 3, 9, and 15 months of age. 1/2 tablet at 3, 9, and 15 months of age • Placebo: identical placebos given at the same time points with iPTi
Outcomes	**Outcomes included in the review** • Clinical malaria • All-cause mortality • Anaemia • Change in haemoglobin/haematocrit • Adverse events **Outcomes not included in the review** • Aspartate transaminase level • Creatinine level • White blood cell count

Grobusch 2007 GAB *(Continued)*

Notes	**Location:** Lambaréné, Gabon **Malaria transmission:** perennial, with little seasonal variation and entomological inoculation rate of 50 infective bites/person/year. **Funding:** Bill & Melinda Gates Foundation (grant 28574), German Ministry of Education and Research (grant 01KA0202), German Academic Exchange Service

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used computer-generated numbers for sequence generation
Allocation concealment (selection bias)	Low risk	The trial used identical centrally coded drug packages
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Two copies of the code were stored separately, accessible only to the principal investigator or a delegate."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This was a placebo controlled trial and drug packages were centrally coded
Incomplete outcome data (attrition bias) All outcomes	High risk	Percentage loss was 15.5%
Selective reporting (reporting bias)	Low risk	The trial reported key outcomes
Other bias	Low risk	The trial appeared to be free of other sources of bias

Kobbe 2007 GHA

Study characteristics

Methods	**Trial design:** RCT **Trial dates:** January 2003 to September 2005 **Length of follow-up:** 24 months of age
Participants	**Number of participants:** 1070 infants (535 infants in each arm) **Inclusion criteria:** age 3 months (4 weeks tolerance accepted); permanent residence in study area **Exclusion criteria:** severe illness
Interventions	• Intervention: SP (250 mg sulfadoxine and 12.5 mg pyrimethamine) given at 3, 9, and 15 months of age: One tablet at 3, 9, and 15 months of age • Placebo: identical placebos given at the same time points with iPTi

Kobbe 2007 GHA *(Continued)*

	All participants concurrently received routine immunization with diphtheria-pertussis-tetanus (DPT) and measles vaccines
Outcomes	**Outcomes included in the review** • Clinical malaria • Anaemia • Hospital admissions • All-cause mortality • Adverse events **Outcomes not included in the review:** none
Notes	**Location:** Afigya Sekyere district, Ghana **Malaria transmission:** holoendemic, intense perennial (with seasonal peaks), EIR = 400 infective bites/person/year **Funding:** the Bundesministerium für Bildung und Forschung (grant 01KA0202) The German Academic Exchange Service La Roche (Basel, Switzerland) manufactured study drugs free of charge Sanofi-Aventis donated artesunate tablets for treatment of uncomplicated malaria episodes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used computer-generated random numbers
Allocation concealment (selection bias)	Low risk	The trial used identical and centrally coded drugs and placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A study team of 2 doctors, a nurse, a technician, and a field worker, all blinded to group assignment, was responsible for recruitment, treatment, and subsequent visits"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A study team of 2 doctors, a nurse, a technician, and a field worker, all blinded to group assignment, was responsible for recruitment, treatment, and subsequent visits"
Incomplete outcome data (attrition bias) All outcomes	High risk	Percentage loss of 18.5% (per protocol)
Selective reporting (reporting bias)	Low risk	The trial reported most of the expected outcomes
Other bias	Low risk	The trial appeared to be free of other sources of bias

Macete 2006 MOZ

Study characteristics

Macete 2006 MOZ *(Continued)*

Methods	**Trial design:** RCT **Trial dates:** September 2002 to February 2004 **Length of follow-up:** 12 months of age
Participants	**Number of participants:** 1503 infants **Inclusion criteria:** infants (age 3 months at first dose); permanent residence in study area **Exclusion criteria:** allergy to sulfa drugs; illness that required admission to hospital
Interventions	• Intervention: SP given at age 3, 4, and 9 months of age and administered according to weight): < 5 kg, 1/4 tablet; 5 to 10 kg, 1/2 tablet; > 10 kg, 1 tablet • Placebo: Identical placebos given at the same time points with iPTi All participants received routine immunization with diphtheria-pertussis-tetanus (DPT) and measles vaccines
Outcomes	**Outcomes included in the review** • Clinical malaria • Severe malaria • All-cause mortality • Anaemia • Hospital admissions • Adverse events **Outcomes not included in the review** • Serological responses to EPI vaccines
Notes	**Location:** Manhica District (Maputo Province) Mozambique **Malaria transmission:** perennial transmission with EIR of 38 infective bites/person/year **Funding:** Hoffman-La Roche provided SP (Fansidar) and placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used computer-generated random numbers
Allocation concealment (selection bias)	Low risk	The trial used identical and centrally coded drugs and placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial used placebo and centrally-coded drugs limits the chance of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"A computer-generated treatment-allocation list was used by the health assistant to ensure that subsequent doses were administered from the bottle with the same treatment identification letter as the first dose"
Incomplete outcome data (attrition bias)	Low risk	Percentage loss of 8.5%

Macete 2006 MOZ *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	The published trial report included all expected outcomes
Other bias	Low risk	The trial appeared to be free of other sources of bias

Massaga 2003 TZA

Study characteristics	
Methods	**Trial design:** RCT **Trial dates:** June 1999 to May 2000 **Length of follow-up**: 9 to 10 months of age
Participants	**Number of participants:** 291 infants **Inclusion criteria:** infants aged 12 to 16 weeks attending Maternal and Child Health (MCH) clinics for growth monitoring or to receive their third diphtheria-pertussis-tetanus (DPT) and oral poliovirus vaccine **Exclusion criteria:** congenital malformation; severe conditions that needed treatment in hospital; fever within past 2 days; packed-cell volume < 24%; taking chemoprophylaxis
Interventions	**Interventions** • Amodiaquine every 2 months and daily iron for 6 months 25 mg/kg over 3 days, with 10 mg/kg on first 2 days and 5 mg/kg on third day; 72 children • Amodiaquine and placebo; 74 children Iron and placebo: 7.5 mg elemental iron; 73 children • Placebo and placebo; 72 children Infants received 2.5 mL daily supplementation of iron (3 mg of ferric ammonium citrate mixture/mL) or placebo for 6 months. The first dose was given by the team and mothers were instructed how to administer the drug at home.
Outcomes	**Outcomes included in the review** • Clinical malaria • All-cause mortality • Hospital admissions • Anaemia • Adverse events **Outcomes not included in the review:** none
Notes	**Location:** Muheza district, north-eastern Tanzania **Malaria transmission:** perennial/Holoendemic **Funding:** Danish International Development Agency

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Massaga 2003 TZA *(Continued)*

Random sequence generation (selection bias)	Low risk	The trial used computer-generated random numbers
Allocation concealment (selection bias)	Low risk	The trial used identical and centrally coded drugs and placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"To ensure that treatment allocation was concealed from parents and the research team, and to ensure that infants received the right dose of medication, the trial drugs were coded and pre-packed."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"To ensure that treatment allocation was concealed from parents and the research team, and to ensure that infants received the right dose of medication, the trial drugs were coded and pre-packed."
Incomplete outcome data (attrition bias) All outcomes	High risk	The percentage loss was 21%
Selective reporting (reporting bias)	Low risk	The trial authors reported most expected outcomes
Other bias	Low risk	The trial appeared to be free of other sources of bias

Mockenhaupt 2007 GHA

Study characteristics	
Methods	**Trial design:** RCT **Trial dates:** March 2003 to July 2005 **Length of follow-up:** 24 months of age
Participants	**Number of participants:** 1200 infants **Inclusion criteria:** parental informed consent and permanent residence in the study area **Exclusion criteria:** conditions requiring hospital admission, signs of hepatic or renal dysfunction, and reported allergy to sulfa-containing drugs
Interventions	• Intervention: IPTi with SP at approximately 3, 9, and 15 months of age.1/2 tablet of SP (125/6.25 mg of sulfadoxine and pyrimethamine, respectively, per kg of body weight) • Placebo: identical placebos given at the same time points with iPTi All participants received routine immunization with diphtheria-pertussis-tetanus-Haemophilus influenzae type b-hepatitis B virus dose 2, measles, and yellow fever vaccinations.
Outcomes	**Outcomes included in the review** • Clincal malaria • All-cause mortality • Hospital admissions • Anaemia • Parasitaemia

Mockenhaupt 2007 GHA *(Continued)*

	Outcomes not included in the review: none
Notes	**Location:** Tamale, Ghana **Malaria transmission:** hyperendemic/perennial transmission and modest seasonal variation **Funding:** German Ministry of Education and Research (grant 01KA0202), the German Academic Exchange Service (DAAD), and Charite´—University Medicine Berlin (grant 2005-543)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used block randomization
Allocation concealment (selection bias)	Low risk	The trial used identical, centrally coded drug containers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study team and caretakers of children were blinded to the treatment regimen. The randomisation and drug code lists were kept by an individual not involved in the analysis of the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The study team and caretakers of children were blinded to the treatment regimen. The randomisation and drug code lists were kept by an individual not involved in the analysis of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no missing outcome data. The percentage loss was 5.5%
Selective reporting (reporting bias)	Low risk	The published report included key outcomes
Other bias	Low risk	The trial appears free of other sources of bias

Odhiambo 2010 KEN

Study characteristics

Methods	**Trial design:** RCT **Trial dates:** March 2004 to March 2008 **Length of follow-up:** 24 months of age
Participants	**Number of participants:** 1365 infants **Inclusion criteria:** children aged 5 to 16 weeks resident in the trial area attending clinic prior to first OPV/PENT vaccination. **Exclusion criteria:** infants with known allergy to any of the trial drugs, receiving cotrimoxazole prophylaxis for opportunistic infections, suffering concomitant illness requiring hospitalization or transfusion, or planning to be away from the study area for more than 6 months.
Interventions	**Interventions:** IPTi with one of the following.

Odhiambo 2010 KEN *(Continued)*

- SP (250 mg sulfadoxine, 12.5 mg pyrimethamine) plus 3 days of artesunate (AS3)
- 3 days of amodiaquine (AQ3)-artesunate (AS3): one paediatric amodiaquine tablet (67.5 mg), once daily for 3 days and one paediatric artesunate tablet (25 mg) once daily for 3 days
- 3 days of chlorproguanil-dapsone: one paediatric caplet (15 mg chlorproguanil and 18.75 mg of dapsone) once daily for 3 days administered at routine EPI visits -10 weeks, 14 weeks and 9 months

Placebo: 2 placebo tablets co-administered once daily for 3 days.

Treatments at the health facility were observed and administered with routine immunizations.

Supplies of iron sulphate (2 mg/kg/day) were given at the first and second IPTi courses, and 1 month later at the fourth scheduled visit to the parent/guardian of study children for home administration during a 4-month period from 2.5 to 6.5 months of age.

Outcomes

Outcomes included in the review

- Clinical malaria
- All-cause mortality
- Hospital admissions
- Anaemia
- Adverse events

Outcomes not included in the review: none

Notes

Location: Asembo, Kenya

Malaria transmission: Perennial with marked seasonal variation

Funding: Bill & Melinda Gates Foundation Global Health Program, Grant ID# 28578.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used permuted block randomization for sequence generation
Allocation concealment (selection bias)	Low risk	The trial used centrally labelled and colour coded drug containers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The colour-arm assignment of the study identification numbers remained concealed to everyone except the technician. The technician did not have access to names of participants"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The colour-arm assignment of the study identification numbers remained concealed to everyone except the technician. The technician did not have access to names of participants"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The percentage loss was 10%
Selective reporting (reporting bias)	Low risk	The trial protocol was available
Other bias	Low risk	The trial appears free of other sources of bias

Schellenberg 2001 TZA

Study characteristics	
Methods	**Trial design:** RCT **Trial dates:** August 1999 to April 2000 **Length of follow-up:** 24 months of age
Participants	**Number of participants:** 701 infants (350 versus 351) **Inclusion criteria:** infants have just received second dose of DPT and oral poliovirus vaccine **Exclusion criteria:** illness requiring hospital admission
Interventions	• Intervention: IPTi with SP (25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine) first dose at 2 months, second dose at 3 months, and third at 9 months with 1/4 tablet for children < 5 kg, 1/2 tablet for children 5 to 10 kg, or 1 tablet for children > 10 kg • Placebo: identical placebos (consisting of lactose and maize starch) were also administered according to body weight as for IPTi
Outcomes	**Outcomes included in the review** • Clinical malaria • All-cause mortality • Hospital admissions • Anaemia • Adverse events **Outcomes not included in the review** • Serological responses to EPI vaccines • Outpatient visits
Notes	**Location:** Ifakara, Tanzania **Malaria transmission:** perennial/holoendemic **Funding:** UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR); Spanish Agency for International Cooperation (AECI); Fondo de Investigaciones Sanitarias (FIS number 00/0803); Swiss Agency for Development and Cooperation; Hoffman-La Roche provided the SP and placebo, and UNICEF provided the iron syrup.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial computer-generated the sequence generation
Allocation concealment (selection bias)	Low risk	The trial used sealed, opaque envelopes and identical, centrally coded drugs and placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No other project staff had ready access to treatment allocation information besides the health assistant who was not involved in the trial.

Schellenberg 2001 TZA *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	No other project staff had ready access to treatment allocation information besides the health assistant who was not involved in the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The percentage loss was 3%
Selective reporting (reporting bias)	Low risk	The trial authors reported key outcomes
Other bias	Low risk	The trial appeared to be free of other sources of bias

Abbreviations: AIDS: acquired immunodeficiency syndrome; AQ: amodiaquine; AS: artesunate; DHAP: dihydroartemisinin-piperaquine; DPT:diphtheria-pertussis-tetanus; ECG: electrocardiogram; EIR: entomological inoculation rate; EPI: expanded programme on immunization; HIV: human immunodeficiency virus; ICC: intracluster correlation coefficient; IPTi: intermittent preventive treatment in infants; ITN: insecticide-treated net; OPV: oral poliovirus vaccine; PENT: pentavalent vaccine; RCT: randomized controlled trial; SP: sulfadoxine pyrimethamine.

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

Study	Reason for exclusion
Aponte 2009	A pooled analysis of 6 trials
Bojang 2010	Intermittent preventive treatment in children (IPTc) was the intervention studied and control arm was not randomized
Cissé 2006	IPTc was the intervention studied
Dicko 2008	IPTc was the intervention studied
Dicko 2011a	IPTc was the intervention studied
Dicko 2011b	IPTc was the intervention studied
Glinz 2015	Age of participants at enrolment was 12 to 36 months
Greenwood 1988	Chemoprophylaxis, not intermittent preventive treatment (IPT)
Konaté 2011a	IPTc was the intervention studied
Konaté 2011b	IPTc was the intervention studied
Kweku 2008	IPTc was the intervention studied
Lemnge 1997	Chemoprophylaxis (not IPT)
Liljander 2010	IPTc was the intervention studied
Menendez 1997	Chemoprophylaxis (not IPT)
Phiri 2012	IPT given to participants post discharge following recovery from malarial anaemia
Senn 2012	Study conducted outside sub-Saharan Africa

Study	Reason for exclusion
Sesay 2011	IPTc was the intervention studied
Tagbor 2011	IPTc was the intervention studied
Tine 2011	IPTc was the intervention studied
Wolde 1994	Chemoprophylaxis (not IPT)

Abbreviations: IPT: intermittent preventive treatment; IPTc: intermittent preventive treatment in children.

DATA AND ANALYSES

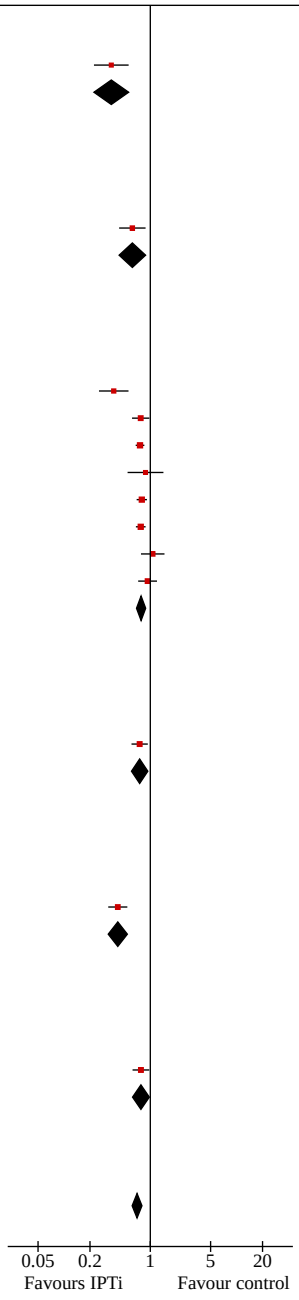
Comparison 1. IPTi versus placebo or no IPTi (by specific drug combination)

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 Clinical malaria	10	10602	Rate Ratio (IV, Random, 95% CI)	0.70 [0.62, 0.80]
1.1.1 IPTi AQ	1	146	Rate Ratio (IV, Random, 95% CI)	0.35 [0.22, 0.56]
1.1.2 IPTi MQ	1	480	Rate Ratio (IV, Random, 95% CI)	0.62 [0.44, 0.88]
1.1.3 IPTi SP	8	8774	Rate Ratio (IV, Random, 95% CI)	0.78 [0.69, 0.88]
1.1.4 IPTi AQ-AS	1	547	Rate Ratio (IV, Random, 95% CI)	0.75 [0.61, 0.94]
1.1.5 IPTi DHAP	1	147	Rate Ratio (IV, Random, 95% CI)	0.42 [0.33, 0.54]
1.1.6 IPTi SP-AS	1	508	Rate Ratio (IV, Random, 95% CI)	0.78 [0.62, 0.97]
1.2 Severe malaria	2		Rate Ratio (IV, Fixed, 95% CI)	Subtotals only
1.2.1 IPTi SP	2	1347	Rate Ratio (IV, Fixed, 95% CI)	0.92 [0.47, 1.81]
1.2.2 IPTi DHAP	1	147	Rate Ratio (IV, Fixed, 95% CI)	1.29 [0.28, 5.98]
1.3 All-cause mortality	11	16930	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.77, 1.14]
1.3.1 IPTi AQ	1	146	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.30, 5.59]
1.3.2 IPTi MQ	1	640	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.11, 3.96]
1.3.3 IPTi SP	9	14588	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.15]
1.3.4 IPTi AQ-AS	1	684	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.58, 2.55]
1.3.5 IPTi DHAP	1	196	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.08]
1.3.6 IPTi SP-AS	1	676	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.36, 1.89]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.4 Hospital admission for any reason	9		Rate Ratio (IV, Fixed, 95% CI)	Subtotals only
1.4.1 IPTi AQ	1	146	Rate Ratio (IV, Fixed, 95% CI)	0.40 [0.21, 0.77]
1.4.2 IPTi MQ	1	480	Rate Ratio (IV, Fixed, 95% CI)	0.98 [0.73, 1.31]
1.4.3 IPTi SP	7	7486	Rate Ratio (IV, Fixed, 95% CI)	0.85 [0.78, 0.93]
1.4.4 IPTi AQ-AS	1	684	Rate Ratio (IV, Fixed, 95% CI)	0.98 [0.76, 1.27]
1.4.5 IPTi DHAP	1	147	Rate Ratio (IV, Fixed, 95% CI)	1.58 [0.46, 5.42]
1.4.6 IPTi SP-AS	1	676	Rate Ratio (IV, Fixed, 95% CI)	0.92 [0.71, 1.20]
1.5 Parasitaemia	1		Rate Ratio (IV, Random, 95% CI)	Subtotals only
1.5.1 IPTi SP	1	1200	Rate Ratio (IV, Random, 95% CI)	0.66 [0.56, 0.79]
1.6 Anaemia	8		Rate Ratio (IV, Random, 95% CI)	Subtotals only
1.6.1 IPTi AQ	1	146	Rate Ratio (IV, Random, 95% CI)	0.29 [0.13, 0.63]
1.6.2 IPTi MQ	1	480	Rate Ratio (IV, Random, 95% CI)	1.06 [0.78, 1.44]
1.6.3 IPTi SP	6	7438	Rate Ratio (IV, Random, 95% CI)	0.82 [0.68, 0.98]
1.6.4 IPTi AQ-AS	1	684	Rate Ratio (IV, Random, 95% CI)	0.77 [0.53, 1.12]
1.6.5 IPTi SP-AS	1	676	Rate Ratio (IV, Random, 95% CI)	0.72 [0.49, 1.07]
1.7 Change in haemo-globin (or haemat-ocrit)	3	4295	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.43, 0.36]

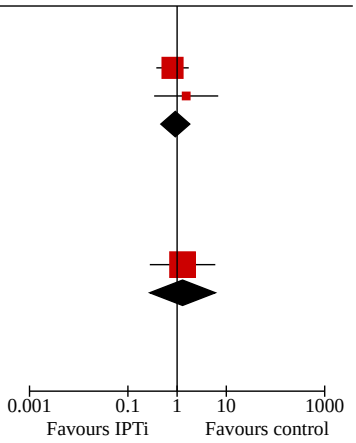
Analysis 1.1. Comparison 1: IPTi versus placebo or no IPTi (by specific drug combination), Outcome 1: Clinical malaria

Study or Subgroup	log[Rate Ratio]	SE	IPTi Total	Control Total	Weight	Rate Ratio IV, Random, 95% CI
1.1.1 IPTi AQ						
Massaga 2003 TZA	-1.041	0.236	74	72	4.7%	0.35 [0.22 , 0.56]
Subtotal (95% CI)			**74**	**72**	**4.7%**	**0.35 [0.22 , 0.56]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.41 (P < 0.0001)						
1.1.2 IPTi MQ						
Gosling 2009 TZA	-0.479	0.18	320	160	6.2%	0.62 [0.44 , 0.88]
Subtotal (95% CI)			**320**	**160**	**6.2%**	**0.62 [0.44 , 0.88]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.66 (P = 0.008)						
1.1.3 IPTi SP						
Schellenberg 2001 TZA	-0.9755	0.201	350	351	5.6%	0.38 [0.25 , 0.56]
Macete 2006 MOZ	-0.256	0.118	748	755	8.4%	0.77 [0.61 , 0.98]
Chandramohan 2005 GHA	-0.2744	0.059	1243	1242	10.4%	0.76 [0.68 , 0.85]
Grobusch 2007 GAB	-0.128	0.244	594	595	4.5%	0.88 [0.55 , 1.42]
Kobbe 2007 GHA	-0.227	0.07	535	535	10.1%	0.80 [0.69 , 0.91]
Mockenhaupt 2007 GHA	-0.255	0.066	600	600	10.2%	0.77 [0.68 , 0.88]
Gosling 2009 TZA	0.065	0.16	319	160	6.9%	1.07 [0.78 , 1.46]
Bigira 2014 UGA	-0.0726	0.128	98	49	8.0%	0.93 [0.72 , 1.20]
Subtotal (95% CI)			**4487**	**4287**	**64.0%**	**0.78 [0.69 , 0.88]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 19.35$, df = 7 (P = 0.007); $I^2 = 64\%$						
Test for overall effect: Z = 3.95 (P < 0.0001)						
1.1.4 IPTi AQ-AS						
Odhiambo 2010 KEN	-0.284	0.111	379	168	8.6%	0.75 [0.61 , 0.94]
Subtotal (95% CI)			**379**	**168**	**8.6%**	**0.75 [0.61 , 0.94]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.56 (P = 0.01)						
1.1.5 IPTi DHAP						
Bigira 2014 UGA	-0.8675	0.13	98	49	7.9%	0.42 [0.33 , 0.54]
Subtotal (95% CI)			**98**	**49**	**7.9%**	**0.42 [0.33 , 0.54]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.67 (P < 0.00001)						
1.1.6 IPTi SP-AS						
Odhiambo 2010 KEN	-0.25	0.114	339	169	8.5%	0.78 [0.62 , 0.97]
Subtotal (95% CI)			**339**	**169**	**8.5%**	**0.78 [0.62 , 0.97]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.19 (P = 0.03)						
Total (95% CI)			**5697**	**4905**	**100.0%**	**0.70 [0.62 , 0.80]**
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 52.14$, df = 12 (P < 0.00001); $I^2 = 77\%$						
Test for overall effect: Z = 5.31 (P < 0.00001)						
Test for subgroup differences: $Chi^2 = 28.78$, df = 5 (P < 0.0001), $I^2 = 82.6\%$						



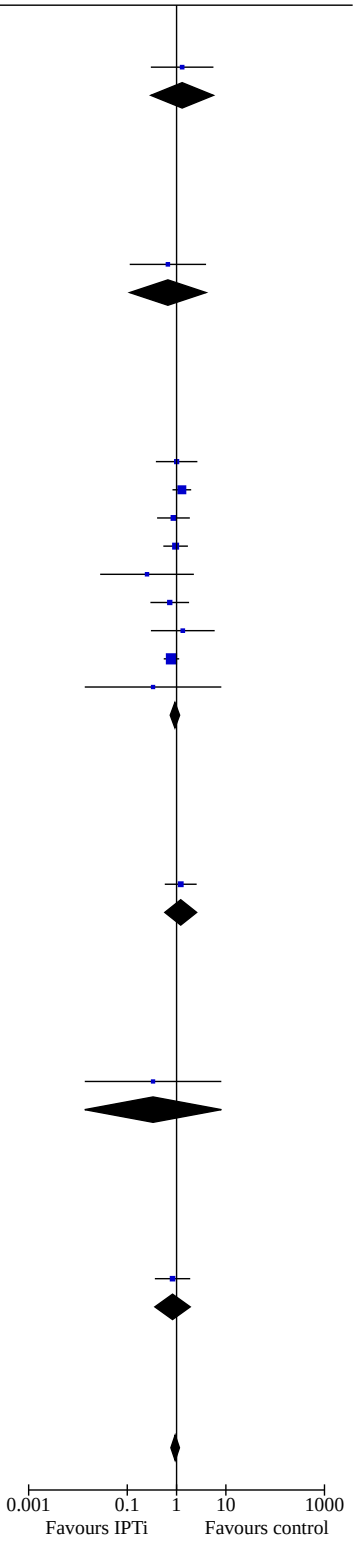
Analysis 1.2. Comparison 1: IPTi versus placebo or no IPTi (by specific drug combination), Outcome 2: Severe malaria

Study or Subgroup	log[Rate Ratio]	SE	IPTi Total	Control Total	Weight	Rate Ratio IV, Fixed, 95% CI
1.2.1 IPTi SP						
Mockenhaupt 2007 GHA	-0.214	0.387	600	600	79.6%	0.81 [0.38 , 1.72]
Bigira 2014 UGA	0.425	0.765	98	49	20.4%	1.53 [0.34 , 6.85]
Subtotal (95% CI)			**698**	**649**	**100.0%**	**0.92 [0.47 , 1.81]**
Heterogeneity: Chi² = 0.56, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
1.2.2 IPTi DHAP						
Bigira 2014 UGA	0.255	0.782	98	49	100.0%	1.29 [0.28 , 5.98]
Subtotal (95% CI)			**98**	**49**	**100.0%**	**1.29 [0.28 , 5.98]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						



Analysis 1.3. Comparison 1: IPTi versus placebo or no IPTi (by specific drug combination), Outcome 3: All-cause mortality

Study or Subgroup	IPTi Events	IPTi Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 IPTi AQ						
Massaga 2003 TZA	4	74	3	72	1.9%	1.30 [0.30 , 5.59]
Subtotal (95% CI)		**74**		**72**	**1.9%**	**1.30 [0.30 , 5.59]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.73)						
1.3.2 IPTi MQ						
Gosling 2009 TZA	2	320	3	320	1.3%	0.67 [0.11 , 3.96]
Subtotal (95% CI)		**320**		**320**	**1.3%**	**0.67 [0.11 , 3.96]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.66)						
1.3.3 IPTi SP						
Schellenberg 2001 TZA	8	350	8	351	4.3%	1.00 [0.38 , 2.64]
Chandramohan 2005 GHA (1)	44	1183	35	1203	21.0%	1.28 [0.83 , 1.98]
Macete 2006 MOZ	12	748	14	755	6.9%	0.87 [0.40 , 1.86]
Mockenhaupt 2007 GHA	22	600	23	600	12.2%	0.96 [0.54 , 1.70]
Grobusch 2007 GAB	1	504	4	507	0.8%	0.25 [0.03 , 2.24]
Kobbe 2007 GHA	8	535	11	535	4.9%	0.73 [0.29 , 1.79]
Gosling 2009 TZA	4	319	3	320	1.8%	1.34 [0.30 , 5.93]
Dicko 2012 MLI (1)	51	2869	68	3013	31.0%	0.79 [0.55 , 1.13]
Bigira 2014 UGA	0	98	1	98	0.4%	0.33 [0.01 , 8.08]
Subtotal (95% CI)		**7206**		**7382**	**83.3%**	**0.93 [0.74 , 1.15]**
Total events:	150		167			
Heterogeneity: Tau² = 0.00; Chi² = 5.21, df = 8 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
1.3.4 IPTi AQ-AS						
Odhiambo 2010 KEN	15	347	12	337	7.2%	1.21 [0.58 , 2.55]
Subtotal (95% CI)		**347**		**337**	**7.2%**	**1.21 [0.58 , 2.55]**
Total events:	15		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
1.3.5 IPTi DHAP						
Bigira 2014 UGA	0	98	1	98	0.4%	0.33 [0.01 , 8.08]
Subtotal (95% CI)		**98**		**98**	**0.4%**	**0.33 [0.01 , 8.08]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.3.6 IPTi SP-AS						
Odhiambo 2010 KEN	10	339	12	337	5.9%	0.83 [0.36 , 1.89]
Subtotal (95% CI)		**339**		**337**	**5.9%**	**0.83 [0.36 , 1.89]**
Total events:	10		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
Total (95% CI)		**8384**		**8546**	**100.0%**	**0.94 [0.77 , 1.14]**
Total events:	181		198			
Heterogeneity: Tau² = 0.00; Chi² = 6.51, df = 13 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Chi² = 1.30, df = 5 (P = 0.94), I² = 0%						



Analysis 1.3. (Continued)

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Chi² = 1.30, df = 5 (P = 0.94), I² = 0%

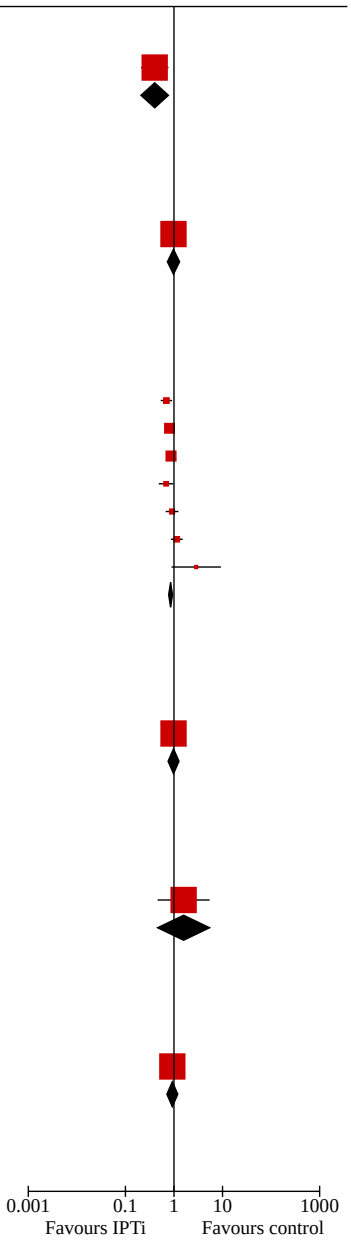
Footnotes

(1) Cluster randomised trial

Analysis 1.4. Comparison 1: IPTi versus placebo or no IPTi (by specific drug combination), Outcome 4: Hospital admission for any reason

Study or Subgroup	log[Rate Ratio]	SE	IPTi Total	Control Total	Weight	Rate Ratio IV, Fixed, 95% CI
1.4.1 IPTi AQ						
Massaga 2003 TZA	-0.914	0.333	74	72	100.0%	0.40 [0.21 , 0.77]
Subtotal (95% CI)			**74**	**72**	**100.0%**	**0.40 [0.21 , 0.77]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.74 (P = 0.006)						
1.4.2 IPTi MQ						
Gosling 2009 TZA	-0.023	0.148	320	160	100.0%	0.98 [0.73 , 1.31]
Subtotal (95% CI)			**320**	**160**	**100.0%**	**0.98 [0.73 , 1.31]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.88)						
1.4.3 IPTi SP						
Schellenberg 2001 TZA	-0.357	0.138	350	351	11.3%	0.70 [0.53 , 0.92]
Macete 2006 MOZ	-0.211	0.084	748	755	30.4%	0.81 [0.69 , 0.95]
Chandramohan 2005 GHA (1)	-0.1392	0.083	1183	1203	31.2%	0.87 [0.74 , 1.02]
Mockenhaupt 2007 GHA	-0.375	0.177	600	600	6.9%	0.69 [0.49 , 0.97]
Kobbe 2007 GHA	-0.091	0.154	535	535	9.1%	0.91 [0.68 , 1.23]
Gosling 2009 TZA	0.137	0.142	319	160	10.6%	1.15 [0.87 , 1.51]
Bigira 2014 UGA	1.054	0.597	98	49	0.6%	2.87 [0.89 , 9.25]
Subtotal (95% CI)			**3833**	**3653**	**100.0%**	**0.85 [0.78 , 0.93]**
Heterogeneity: Chi² = 12.65, df = 6 (P = 0.05); I² = 53%						
Test for overall effect: Z = 3.47 (P = 0.0005)						
1.4.4 IPTi AQ-AS						
Odhiambo 2010 KEN	-0.021	0.132	347	337	100.0%	0.98 [0.76 , 1.27]
Subtotal (95% CI)			**347**	**337**	**100.0%**	**0.98 [0.76 , 1.27]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
1.4.5 IPTi DHAP						
Bigira 2014 UGA	0.457	0.629	98	49	100.0%	1.58 [0.46 , 5.42]
Subtotal (95% CI)			**98**	**49**	**100.0%**	**1.58 [0.46 , 5.42]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.73 (P = 0.47)						
1.4.6 IPTi SP-AS						
Odhiambo 2010 KEN	-0.078	0.132	339	337	100.0%	0.92 [0.71 , 1.20]
Subtotal (95% CI)			**339**	**337**	**100.0%**	**0.92 [0.71 , 1.20]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.55)						

Test for subgroup differences: Chi² = 8.16, df = 5 (P = 0.15), I² = 38.7%

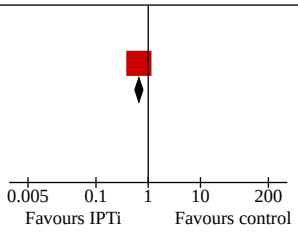


Footnotes

(1) Cluster randomised trial

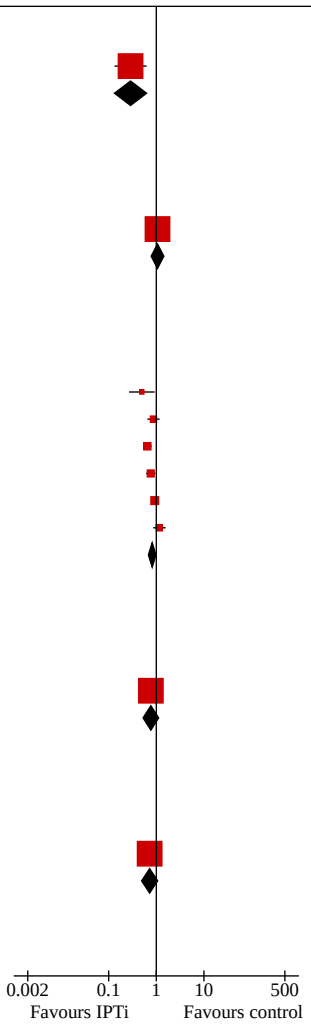
Analysis 1.5. Comparison 1: IPTi versus placebo or no IPTi (by specific drug combination), Outcome 5: Parasitaemia

Study or Subgroup	log[Rate Ratio]	SE	Experimental Total	Control Total	Weight	Rate Ratio IV, Random, 95% CI
1.5.1 IPTi SP						
Mockenhaupt 2007 GHA	-0.411	0.089	600	600	100.0%	0.66 [0.56 , 0.79]
Subtotal (95% CI)			**600**	**600**	**100.0%**	**0.66 [0.56 , 0.79]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.62 (P < 0.00001)						



Analysis 1.6. Comparison 1: IPTi versus placebo or no IPTi (by specific drug combination), Outcome 6: Anaemia

Study or Subgroup	log[Rate Ratio]	SE	IPTI Total	Control Total	Weight	Rate Ratio IV, Random, 95% CI
1.6.1 IPTi AQ						
Massaga 2003 TZA	-1.245	0.396	74	72	100.0%	0.29 [0.13 , 0.63]
Subtotal (95% CI)			**74**	**72**	**100.0%**	**0.29 [0.13 , 0.63]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.14 (P = 0.002)						
1.6.2 IPTi MQ						
Gosling 2009 TZA	0.058	0.156	320	160	100.0%	1.06 [0.78 , 1.44]
Subtotal (95% CI)			**320**	**160**	**100.0%**	**1.06 [0.78 , 1.44]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.37 (P = 0.71)						
1.6.3 IPTi SP						
Schellenberg 2001 TZA	-0.699	0.316	350	351	6.6%	0.50 [0.27 , 0.92]
Macete 2006 MOZ	-0.136	0.151	748	755	15.8%	0.87 [0.65 , 1.17]
Chandramohan 2005 GHA (1)	-0.4307	0.108	1243	1242	19.9%	0.65 [0.53 , 0.80]
Mockenhaupt 2007 GHA	-0.269	0.116	600	600	19.1%	0.76 [0.61 , 0.96]
Kobbe 2007 GHA	-0.075	0.076	535	535	23.0%	0.93 [0.80 , 1.08]
Gosling 2009 TZA	0.148	0.154	319	160	15.6%	1.16 [0.86 , 1.57]
Subtotal (95% CI)			**3795**	**3643**	**100.0%**	**0.82 [0.68 , 0.98]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 15.20$, df = 5 (P = 0.010); $I^2 = 67\%$						
Test for overall effect: Z = 2.14 (P = 0.03)						
1.6.4 IPTi AQ-AS						
Odhiambo 2010 KEN	-0.263	0.192	347	337	100.0%	0.77 [0.53 , 1.12]
Subtotal (95% CI)			**347**	**337**	**100.0%**	**0.77 [0.53 , 1.12]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.6.5 IPTi SP-AS						
Odhiambo 2010 KEN	-0.322	0.198	339	337	100.0%	0.72 [0.49 , 1.07]
Subtotal (95% CI)			**339**	**337**	**100.0%**	**0.72 [0.49 , 1.07]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						



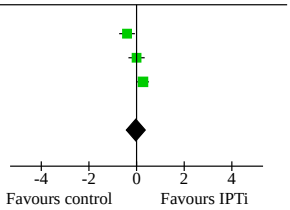
Footnotes

(1) Cluster randomised trial

Analysis 1.7. Comparison 1: IPTi versus placebo or no IPTi (by specific drug combination), Outcome 7: Change in haemoglobin (or haematocrit)

Study or Subgroup	IPTi Mean	IPTi SD	IPTi Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Chandramohan 2005 GHA (1)	31	4.2	1242	31.4	4.2	1243	32.3%	-0.40 [-0.73 , -0.07]
Grobusch 2007 GAB	30	3	594	30	3	595	31.8%	0.00 [-0.34 , 0.34]
Armstrong Schellenberg 2010 TZA (1)	9.66	1.52	347	9.39	1.6	274	35.8%	0.27 [0.02 , 0.52]
Total (95% CI)			**2183**			**2112**	**100.0%**	**-0.03 [-0.43 , 0.36]**

Heterogeneity: Tau² = 0.10; Chi² = 10.13, df = 2 (P = 0.006); I² = 80%
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable



Footnotes
(1) Cluster randomised trial

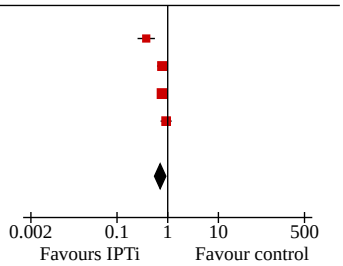
Comparison 2. Sensitivity analysis: IPTi with SP versus placebo or no IPTi

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Clinical malaria	4	3551	Rate Ratio (IV, Random, 95% CI)	0.71 [0.55, 0.92]
2.2 Anaemia	3	3404	Rate Ratio (IV, Random, 95% CI)	0.77 [0.62, 0.95]
2.3 All-cause mortality	4	3551	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.60, 1.37]
2.4 Hospital admission for any reason	4	3551	Rate Ratio (IV, Fixed, 95% CI)	0.78 [0.68, 0.88]

Analysis 2.1. Comparison 2: Sensitivity analysis: IPTi with SP versus placebo or no IPTi, Outcome 1: Clinical malaria

Study or Subgroup	log[Rate Ratio]	SE	IPTi Total	Control Total	Weight	Rate Ratio IV, Random, 95% CI
Schellenberg 2001 TZA	-0.9755	0.201	350	351	18.5%	0.38 [0.25 , 0.56]
Macete 2006 MOZ	-0.256	0.118	748	755	26.0%	0.77 [0.61 , 0.98]
Mockenhaupt 2007 GHA	-0.255	0.066	600	600	30.4%	0.77 [0.68 , 0.88]
Bigira 2014 UGA	-0.0726	0.128	98	49	25.1%	0.93 [0.72 , 1.20]
Total (95% CI)			**1796**	**1755**	**100.0%**	**0.71 [0.55 , 0.92]**

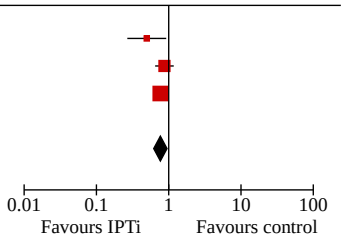
Heterogeneity: Tau² = 0.05; Chi² = 14.76, df = 3 (P = 0.002); I² = 80%
Test for overall effect: Z = 2.62 (P = 0.009)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Sensitivity analysis: IPTi with SP versus placebo or no IPTi, Outcome 2: Anaemia

Study or Subgroup	log[Rate Ratio]	SE	IPTI Total	Control Total	Weight	Rate Ratio IV, Random, 95% CI
Schellenberg 2001 TZA	-0.699	0.316	350	351	10.7%	0.50 [0.27 , 0.92]
Macete 2006 MOZ	-0.136	0.151	748	755	36.9%	0.87 [0.65 , 1.17]
Mockenhaupt 2007 GHA	-0.269	0.116	600	600	52.4%	0.76 [0.61 , 0.96]
Total (95% CI)			**1698**	**1706**	**100.0%**	**0.77 [0.62 , 0.95]**

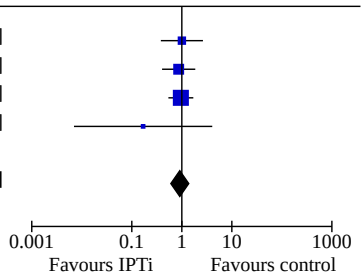
Heterogeneity: Tau² = 0.01; Chi² = 2.61, df = 2 (P = 0.27); I² = 23%
Test for overall effect: Z = 2.46 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Sensitivity analysis: IPTi with SP versus placebo or no IPTi, Outcome 3: All-cause mortality

Study or Subgroup	IPTi Events	IPTi Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Schellenberg 2001 TZA	8	350	8	351	18.0%	1.00 [0.38 , 2.64]
Macete 2006 MOZ	12	748	14	755	28.9%	0.87 [0.40 , 1.86]
Mockenhaupt 2007 GHA	22	600	23	600	51.4%	0.96 [0.54 , 1.70]
Bigira 2014 UGA	0	98	1	49	1.7%	0.17 [0.01 , 4.06]
Total (95% CI)		**1796**		**1755**	**100.0%**	**0.91 [0.60 , 1.37]**
Total events:	42		46			

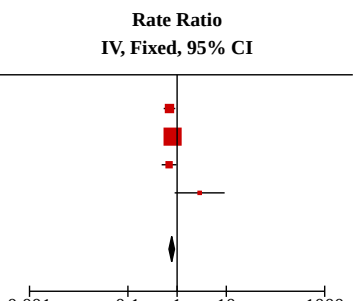
Heterogeneity: Tau² = 0.00; Chi² = 1.17, df = 3 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Sensitivity analysis: IPTi with SP versus placebo or no IPTi, Outcome 4: Hospital admission for any reason

Study or Subgroup	log[Rate Ratio]	SE	IPTi Total	Control Total	Weight	Rate Ratio IV, Fixed, 95% CI
Schellenberg 2001 TZA	-0.357	0.138	350	351	22.9%	0.70 [0.53 , 0.92]
Macete 2006 MOZ	-0.211	0.084	748	755	61.9%	0.81 [0.69 , 0.95]
Mockenhaupt 2007 GHA	-0.375	0.177	600	600	13.9%	0.69 [0.49 , 0.97]
Bigira 2014 UGA	1.054	0.597	98	49	1.2%	2.87 [0.89 , 9.25]
Total (95% CI)			**1796**	**1755**	**100.0%**	**0.78 [0.68 , 0.88]**

Heterogeneity: Chi² = 6.09, df = 3 (P = 0.11); I² = 51%
Test for overall effect: Z = 3.81 (P = 0.0001)
Test for subgroup differences: Not applicable



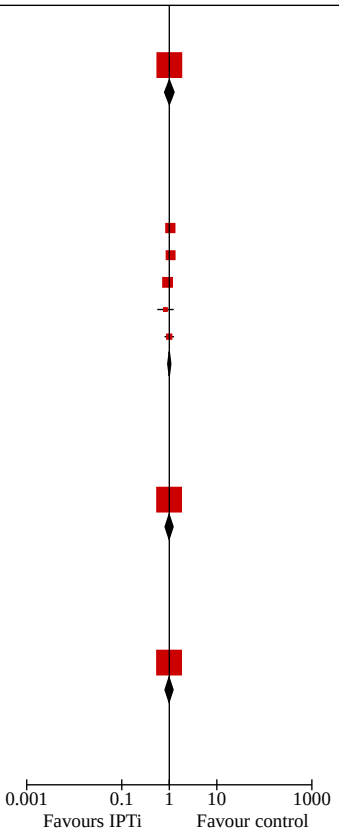
Comparison 3. IPTi versus placebo or no IPTi (post-intervention follow-up)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Clinical malaria	6		Rate Ratio (IV, Random, 95% CI)	Subtotals only
3.1.1 IPTi MQ	1	451	Rate Ratio (IV, Random, 95% CI)	1.00 [0.80, 1.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.2 IPTi SP	5	5359	Rate Ratio (IV, Random, 95% CI)	1.00 [0.93, 1.07]
3.1.3 IPTi AQ-AS	1	520	Rate Ratio (IV, Random, 95% CI)	0.99 [0.82, 1.20]
3.1.4 IPTi SP-AS	1	520	Rate Ratio (IV, Random, 95% CI)	0.99 [0.81, 1.20]
3.2 All-cause mortality	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.2.1 IPTi MQ	1	449	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.12, 2.39]
3.2.2 IPTi SP	3	2106	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.24, 1.13]
3.3 Hospital admission for any reason	2		Rate Ratio (IV, Random, 95% CI)	Subtotals only
3.3.1 IPTi MQ	1	450	Rate Ratio (IV, Random, 95% CI)	1.37 [1.01, 1.87]
3.3.2 IPTi SP	2	1337	Rate Ratio (IV, Random, 95% CI)	1.09 [0.84, 1.42]
3.4 Anaemia	4		Rate Ratio (IV, Random, 95% CI)	Subtotals only
3.4.1 IPTi MQ	1	395	Rate Ratio (IV, Random, 95% CI)	0.97 [0.68, 1.36]
3.4.2 IPTi SP	3	3479	Rate Ratio (IV, Random, 95% CI)	0.89 [0.73, 1.08]
3.4.3 IPTi AQ-AS	1	684	Rate Ratio (IV, Random, 95% CI)	0.89 [0.63, 1.26]
3.4.4 IPTi SP-AS	1	676	Rate Ratio (IV, Random, 95% CI)	0.78 [0.54, 1.12]

Analysis 3.1. Comparison 3: IPTi versus placebo or no IPTi (post-intervention follow-up), Outcome 1: Clinical malaria

Study or Subgroup	log[Rate Ratio]	SE	IPTi Total	Control Total	Weight	Rate Ratio IV, Random, 95% CI
3.1.1 IPTi MQ						
Gosling 2009 TZA	0.002	0.117	320	131	100.0%	1.00 [0.80 , 1.26]
Subtotal (95% CI)			**320**	**131**	**100.0%**	**1.00 [0.80 , 1.26]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.99)						
3.1.2 IPTi SP						
Chandramohan 2005 GHA (1)	0.05	0.07	1088	1103	28.5%	1.05 [0.92 , 1.21]
Kobbe 2007 GHA	0.064	0.072	535	535	26.9%	1.07 [0.93 , 1.23]
Mockenhaupt 2007 GHA	-0.083	0.067	520	527	31.1%	0.92 [0.81 , 1.05]
Grobusch 2007 GAB	-0.186	0.203	315	287	3.4%	0.83 [0.56 , 1.24]
Gosling 2009 TZA	-0.003	0.117	319	130	10.2%	1.00 [0.79 , 1.25]
Subtotal (95% CI)			**2777**	**2582**	**100.0%**	**1.00 [0.93 , 1.07]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.67$, df = 4 (P = 0.45); $I^2 = 0\%$						
Test for overall effect: Z = 0.03 (P = 0.98)						
3.1.3 IPTi AQ-AS						
Odhiambo 2010 KEN	-0.01	0.099	379	141	100.0%	0.99 [0.82 , 1.20]
Subtotal (95% CI)			**379**	**141**	**100.0%**	**0.99 [0.82 , 1.20]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
3.1.4 IPTi SP-AS						
Odhiambo 2010 KEN	-0.013	0.099	379	141	100.0%	0.99 [0.81 , 1.20]
Subtotal (95% CI)			**379**	**141**	**100.0%**	**0.99 [0.81 , 1.20]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						

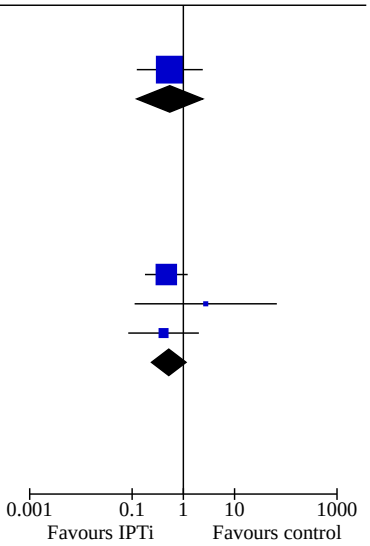


Footnotes

(1) Cluster randomised trial

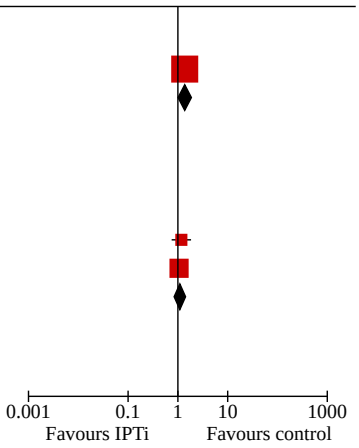
Analysis 3.2. Comparison 3: IPTi versus placebo or no IPTi (post-intervention follow-up), Outcome 2: All-cause mortality

Study or Subgroup	IPTi Events	IPTi Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 IPTi MQ						
Gosling 2009 TZA	4	319	3	130	100.0%	0.54 [0.12 , 2.39]
Subtotal (95% CI)		**319**		**130**	**100.0%**	**0.54 [0.12 , 2.39]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
3.2.2 IPTi SP						
Mockenhaupt 2007 GHA	6	525	13	529	73.1%	0.47 [0.18 , 1.21]
Grobusch 2007 GAB	1	315	0	287	3.0%	2.73 [0.11 , 66.85]
Gosling 2009 TZA	3	319	3	131	24.0%	0.41 [0.08 , 2.01]
Subtotal (95% CI)		**1159**		**947**	**100.0%**	**0.52 [0.24 , 1.13]**
Total events:	10		16			
Heterogeneity: Chi² = 1.17, df = 2 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.66 (P = 0.10)						



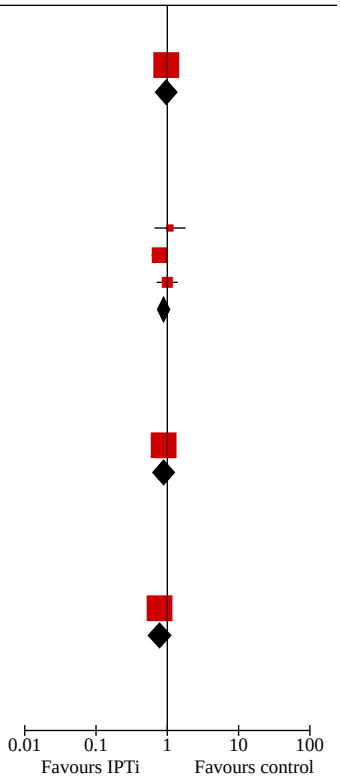
Analysis 3.3. Comparison 3: IPTi versus placebo or no IPTi (post-intervention follow-up), Outcome 3: Hospital admission for any reason

Study or Subgroup	log[Rate Ratio]	SE	IPTi Total	Control Total	Weight	Rate Ratio IV, Random, 95% CI
3.3.1 IPTi MQ						
Gosling 2009 TZA	0.316	0.157	320	130	100.0%	1.37 [1.01 , 1.87]
Subtotal (95% CI)			**320**	**130**	**100.0%**	**1.37 [1.01 , 1.87]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.01 (P = 0.04)						
3.3.2 IPTi SP						
Kobbe 2007 GHA	0.16	0.229	448	439	34.4%	1.17 [0.75 , 1.84]
Gosling 2009 TZA	0.054	0.166	319	131	65.6%	1.06 [0.76 , 1.46]
Subtotal (95% CI)			**767**	**570**	**100.0%**	**1.09 [0.84 , 1.42]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						



Analysis 3.4. Comparison 3: IPTi versus placebo or no IPTi (post-intervention follow-up), Outcome 4: Anaemia

Study or Subgroup	log[Rate Ratio]	SE	IPTi Total	Control Total	Weight	Rate Ratio IV, Random, 95% CI
3.4.1 IPTi MQ						
Gosling 2009 TZA	-0.035	0.176	265	130	100.0%	0.97 [0.68 , 1.36]
Subtotal (95% CI)			**265**	**130**	**100.0%**	**0.97 [0.68 , 1.36]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
3.4.2 IPTi SP						
Chandramohan 2005 GHA (1)	0.086	0.257	1243	1242	14.7%	1.09 [0.66 , 1.80]
Grobusch 2007 GAB	-0.248	0.133	315	287	53.6%	0.78 [0.60 , 1.01]
Gosling 2009 TZA	-0.001	0.174	261	131	31.7%	1.00 [0.71 , 1.40]
Subtotal (95% CI)			**1819**	**1660**	**100.0%**	**0.89 [0.73 , 1.08]**
Heterogeneity: Tau² = 0.00; Chi² = 2.04, df = 2 (P = 0.36); I² = 2%						
Test for overall effect: Z = 1.22 (P = 0.22)						
3.4.3 IPTi AQ-AS						
Odhiambo 2010 KEN	-0.119	0.177	347	337	100.0%	0.89 [0.63 , 1.26]
Subtotal (95% CI)			**347**	**337**	**100.0%**	**0.89 [0.63 , 1.26]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
3.4.4 IPTi SP-AS						
Odhiambo 2010 KEN	-0.251	0.185	339	337	100.0%	0.78 [0.54 , 1.12]
Subtotal (95% CI)			**339**	**337**	**100.0%**	**0.78 [0.54 , 1.12]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						



Footnotes
(1) Cluster randomised trial

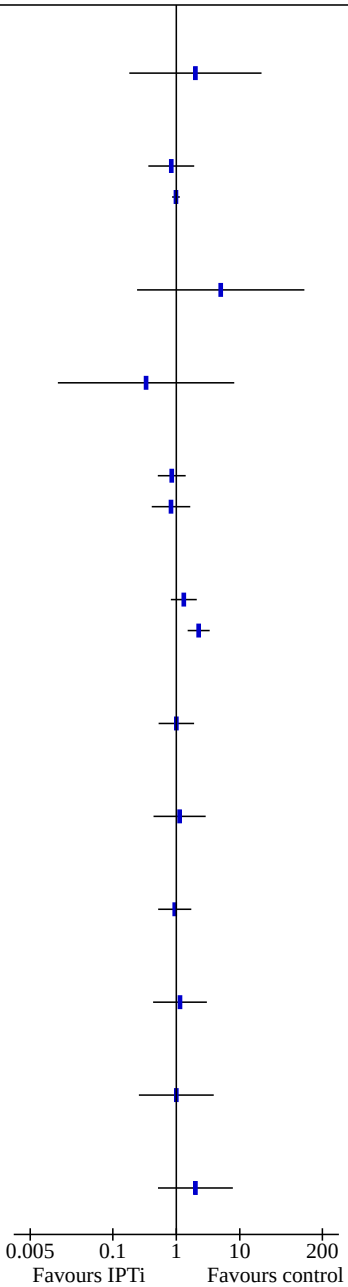
Comparison 4. IPTi versus placebo or no IPTi (adverse events)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 SP	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.1 Stevens-Johnson syndrome	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.2 Fever	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.3 Loss of appetite	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.4 Weakness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.5 Skin	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.6 Gastrointestinal	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.7 Respiratory	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.8 Laboratory abnormalities	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.9 Thrombocytopenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.10 Elevated aspartate aminotransferase	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.11 Elevated alanine aminotransferase	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1.12 Neutropenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.2 DHAP	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.2.1 Fever	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.2.2 Thrombocytopenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.2.3 Elevated aspartate aminotransferase	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.2.4 Elevated alanine aminotransferase	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.2.5 Neutropenia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: IPTi versus placebo or no IPTi (adverse events), Outcome 1: SP

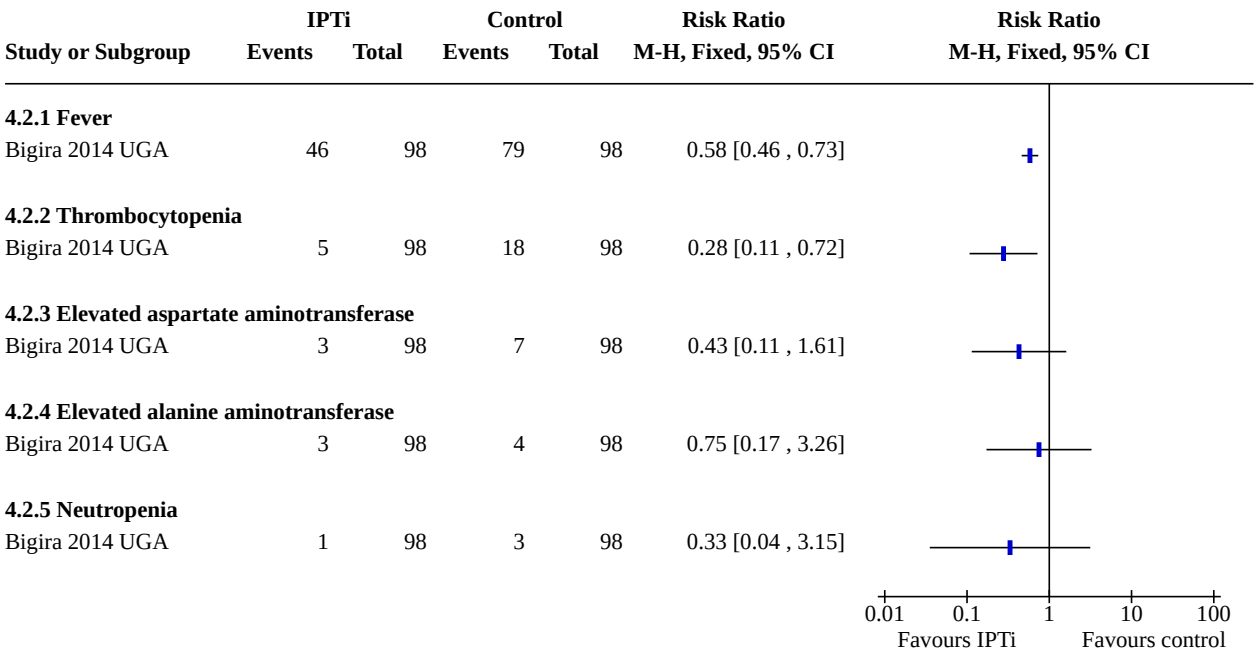
Study or Subgroup	IPTi Events	IPTi Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Stevens-Johnson syndrome					
Kobbe 2007 GHA	2	535	1	535	2.00 [0.18 , 21.99]
4.1.2 Fever					
Grobusch 2007 GAB	10	594	12	594	0.83 [0.36 , 1.91]
Bigira 2014 UGA	78	98	79	98	0.99 [0.86 , 1.14]
4.1.3 Loss of appetite					
Grobusch 2007 GAB	2	594	0	595	5.01 [0.24 , 104.10]
4.1.4 Weakness					
Grobusch 2007 GAB	0	594	1	595	0.33 [0.01 , 8.18]
4.1.5 Skin					
Chandramohan 2005 GHA (1)	27	1103	32	1108	0.85 [0.51 , 1.40]
Grobusch 2007 GAB	14	594	17	595	0.82 [0.41 , 1.66]
4.1.6 Gastrointestinal					
Grobusch 2007 GAB	38	594	29	595	1.31 [0.82 , 2.10]
Kobbe 2007 GHA	72	535	32	535	2.25 [1.51 , 3.35]
4.1.7 Respiratory					
Grobusch 2007 GAB	18	594	18	595	1.00 [0.53 , 1.91]
4.1.8 Laboratory abnormalities					
Grobusch 2007 GAB	9	594	8	595	1.13 [0.44 , 2.90]
4.1.9 Thrombocytopenia					
Bigira 2014 UGA	17	98	18	98	0.94 [0.52 , 1.72]
4.1.10 Elevated aspartate aminotransferase					
Bigira 2014 UGA	8	98	7	98	1.14 [0.43 , 3.03]
4.1.11 Elevated alanine aminotransferase					
Bigira 2014 UGA	4	98	4	98	1.00 [0.26 , 3.89]
4.1.12 Neutropenia					
Bigira 2014 UGA	6	98	3	98	2.00 [0.51 , 7.77]



Footnotes

(1) Cluster randomised trial

Analysis 4.2. Comparison 4: IPTi versus placebo or no IPTi (adverse events), Outcome 2: DHAP



ADDITIONAL TABLES

Table 1. Definitions of outcome measures used in the included trials

Trial	Clinical malaria	Anaemia
Armstrong Schellenberg 2010 TZA	Not reported	Severe anaemia defined as haemoglobin level of < 8 g/dL. Mild anaemia defined as haemoglobin level of < 11 g/dL.
Bigira 2014 UGA	Documented fever (tympanic temperature ≥ 38.0°C) or history of fever in the previous 24 hours plus parasitaemia (thick blood smear).	Moderate–severe anaemia was defined as haemoglobin level of < 8.0 g/dL.
Chandramohan 2005 GHA	Not reported	Anaemia was defined as packed-cell volume of < 24%.
Dicko 2012 MLI	Not reported	Not reported
Gosling 2009 TZA	Either a history of fever during the previous 2 days or an axillary temperature greater than 37.5°C plus parasitaemia of any density	Moderate anaemia was defined as haemoglobin level of < 8.0 g/dL
Grobusch 2007 GAB	The presence of any asexual *P falciparum* parasitaemia and either a rectal temperature of at least 38.5°C or a history of fever during the last 48 hours reported by the mother.	Anemia was defined as a haemoglobin level of < 8.0 g/dL.
Kobbe 2007 GHA	A malaria episode was defined as fever (temperature 38.0°C or fever during the preceding 48 hours reported by mothers without being	Anemia was defined as haemoglobin level of < 7.5 g/dL.

Table 1. Definitions of outcome measures used in the included trials *(Continued)*

	asked), accompanied by asexual *P falciparum* parasitaemia of 1500 parasites/mL.	
Macete 2006 MOZ	An episode of clinical malaria was defined as an axillary temperature of ≥ 37.5°C together with asexual *P falciparum* parasitaemia of any density.	Severe anaemia was defined as a packed-cell volume of < 25%.
Massaga 2003 TZA	A febrile malarial episode was diagnosed in infants with a reported history of fever within the last 24 to 72 hours or a measured temperature of 37.5°C or greater (or both), who had a positive blood slide with asexual forms of *P falciparum* at any level of parasite density at time of contact with Maternal and Child Health clinic.	Anaemia was defined as packed-cell volume of < 24%.
Mockenhaupt 2007 GHA	Malaria was defined as parasitaemia of any density plus fever (axillary temperature, ≥ 37.5°C) or a voluntarily reported history of fever within 48 hours of presentation to the clinic.	Severe anaemia was defined as haemoglobin level of < 7.0 g/dL.
Odhiambo 2010 KEN	An episode of clinical malaria was defined as an axillary temperature of at least 37.5°C or history of fever in the preceding 48 hours together with asexual *P falciparum* parasitaemia of any density.	Moderate-to-severe anaemia defined as haemoglobin level of < 8 g/dL.
Schellenberg 2001 TZA	A clinical malaria episode was defined as an axillary temperature of at least 37.5°C together with asexual *P falciparum* parasitaemia of any density.	Severe anaemia was defined as a packed-cell volume of < 25%.

Table 2. Additional data: IPTi versus placebo or no IPTi

Prespecified outcome	Trial-reported outcome	Trial	Number of participants	IPTi	Placebo or no IPTi	Comparative results reported in article
Anaemia	Mild anaemia (< 11 g/dL)	Armstrong Schellenberg 2010 TZA	620	277/346 (80%)	241/274 (88%)	P = 0.02
	Severe anaemia (< 8 g/dL)		620	40/346 (12%)	44/274 (16%)	P = 0.19
	Moderate-to-severe anaemia (< 8 g/dL)	Bigira 2014 UGA IPTi SP	196	145/1113 (13%)	66/1112 (6%)	P = 0.04
		Bigira 2014 UGA IPTi DHAP	196	25/899 (3%)	66/1112 (6%)	P = 0.04
	Moderate anaemia (at least one episode)	Grobusch 2007 GAB IPTI SP	1011	65/504 (13%)	88/507 (17%)	P = 0.05
Severe malaria	Severe malaria (WHO definition)	Macete 2006 MOZ	1503	26/748 (4%)	29/755 (4%)	P = 0.66
Parasitaemia	Asymptomatic parasitaemia	Bigira 2014 UGA	196	59/500	60/528	P = 0.89

Table 2. Additional data: IPTi versus placebo or no IPTi *(Continued)*

IPTi SP		(12%)	(11%)	
Bigira 2014 UGA	196	24/849	60/528	P < 0.001
IPTi DHAP		(3%)	(11%)	

Abbreviations: IPTi: intermittent preventive treatment in infants.

Table 3. Adverse event information not appropriate for meta-analysis

Type of antimalarial drug	Trial	Adverse event	Comments
Sulfadoxine-pyrimethamine (SP)	Macete 2006 MOZ	Chest indrawing	RR 0.57, 95% CI 0.34 to 0.94, P = 0.025
		Splenomegaly	RR 0.06, 95% CI 0.01 to 0.47, P < 0.001
		Diarrhoea	RR 0.09, 95% CI 0.01 to 0.69, P = 0.002
		Skin	No severe cutaneous reactions
	Schellenberg 2001 TZA	Fever	PE 13%, 95% CI 0.1 to 24.3, P = 0.048
		Vomiting	"The frequency of vomiting after each dose was low (1%) and similar in each group."
		Skin	"No severe skin reactions were reported in any child at any stage."
	Armstrong Schellenberg 2010 TZA	Skin	"No children aged 2–11 months were admitted because of a rash associated with SP in either IPTi or comparison divisions."
		Fever	"Fever in the 2 weeks before the survey was similar in the two groups, being reported for 38% children in the intervention areas and 41% children in comparison areas (P = 0.24)."
	Chandramohan 2005 GHA	Vomiting	"The proportions of children who vomited after administration of drugs was similar between the two groups (0.4% in the placebo group versus 0.3% in the sulfadoxine-pyrimethamine group)"
Amodiaquine + artesunate	Odhiambo 2010 KEN	Skin and haematological	"No serious cutaneous adverse events were noted, and no cases of severe haemolysis were recorded."
SP in combination	Odhiambo 2010 KEN	Skin and haematological	
Amodiaquine	Massaga 2003 TZA	Haematological	“No clinical adverse effects such as sore throat or agranulocytosis were reported or observed during the study.” “No significant difference in mean leucocyte counts between the groups.”

Abbreviations: CI: confidence interval; PE: protective efficacy; SP: sulfadoxine-pyrimethamine. RR: risk ratio; IPTi: intermittent preventive treatment in infants.

APPENDICES

Appendix 1. Search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	Embase[b]	LILACS[b]
1	malaria	Malaria [Mesh, ti, ab]	Malaria [Mesh, ti, ab]	Malaria (Emtree, ti,ab)	malaria
2	prophylaxis	Prophylaxis ti,ab	Prophylaxis ti,ab	Prophylaxis ti,ab	prophylaxis
3	intermittent treatment	intermittent treatment ti, ab	Chemoprophylaxis ti,ab	Chemoprophylaxis ti,ab	intermittent treatment
4	IPT*	Prevention ti, ab	Prevention ti, ab	Prevention ti, ab	IPT$
5	Infant* OR newborn* OR neonatal	presumptive treatment ti, ab	intermittent treatment ti,ab	intermittent treatment ti,ab	Infant$ OR newborn$ OR neonatal
6	2 or 3 or 4	IPT* ti, ab	presumptive treatment ti, ab	presumptive treatment ti, ab	2 or 3 or 4
7	1 and 5 and 6	Infant* OR newborn* OR neonatal ti,ab	IPT* ti, ab	IPT* ti, ab	1 and 5 and 6
8	—	2 or 3 or 4 or 5 or 6	2 or 3 or 4 or 5 or 6 or 7	2 or 3 or 4 or 5 or 6 or 7	—
9	—	1 and 7 and 8	Infant* OR newborn* OR neonatal ti,ab	Infant* OR newborn* OR neonatal ti,ab	—
10	—	—	1 and 8 and 9	1 and 8 and 9	—

[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 (Lefebvre 2011).

WHAT'S NEW

Date	Event	Description
7 July 2021	New citation required but conclusions have not changed	Author team addressed minor comments submitted via Cochrane Comments system
7 July 2021	Amended	Feedback incorporated into the review to clarify methods used to assess heterogeneity, and correct minor inconsistencies between sections.

HISTORY

Protocol first published: Issue 2, 2015
Review first published: Issue 12, 2019

CONTRIBUTIONS OF AUTHORS

Martin Meremikwu (MM) conceived the idea for the review. Ekpereonne Esu (EE) assessed the eligibility of trials. Chioma Oringanje (CO) and EE extracted data and assessed the methodological quality of eligible trials. EE entered data into Review Manager 5 (Review Manager 2014). EE prepared the 'Summary of findings tables' and GRADE assessments. All review authors read, provided input, and approved the final version.

DECLARATIONS OF INTEREST

Ekpereonne Esu has no known conflicts of interest.

Chioma Oringanje has no known conflicts of interest.

Martin Meremikwu has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- University Of Calabar, Nigeria
- Liverpool School Of Tropical Medicine, UK

External sources

- Department for International Development, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no differences between the protocol and the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Africa South of the Sahara; Amodiaquine [therapeutic use]; Antimalarials [*therapeutic use]; Artemisinins [therapeutic use]; Bias; Confidence Intervals; Disease Eradication; Drug Combinations; Endemic Diseases [*prevention & control]; Hospitalization [statistics & numerical data]; Malaria [*prevention & control]; Parasitemia [drug therapy]; Pyrimethamine [therapeutic use]; Quinolines [therapeutic use]; Randomized Controlled Trials as Topic; Sulfadoxine [therapeutic use]

MeSH check words

Humans; Infant